Advanced Drug Delivery Reviews 143 (2019) 37–67

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Intratumoral fate of functional nanoparticles in response to microenvironment factor: Implications on cancer diagnosis and therapy

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ARTICLE INFO

Article history:
Received 29 October 2018
Received in revised form 4 June 2019
Accepted 24 June 2019
Available online 2 July 2019

Keywords:
Functional nanoparticles
Intratumoral fate
Tumor microenvironment
Cancer diagnosis
Cancer therapy

ABSTRACT

The extraordinary growth and progression of tumor require enormous nutrient and energy. Unregulated behaviors of cancer cell progressing and persistently change of tumor microenvironment (TME) which acts as the soil for cancer growth and metastasis are the ubiquitous features. The tumor microenvironment exhibits some unique features which differ with the normal tissues. While the nanoparticles get through the blood vessel leakage, they encounter immediately and interact directly with these microenvironment factors. These factors may inhibit the diffusion of nanoparticles from penetrating through the tumor, or induce the dissociation of nanoparticles. Different nanoparticles encountered with different intratumoral microenvironment factors end up in different way. Therefore, in this review, we first briefly introduced the formations, distributions, features of some intratumoral microenvironment, and their effects on the tumor progression. They include extracellular matrix (ECM), matrix metalloproteinases (MMPs), acidic/hypoxia environment, redox environment, and tumor associated macrophages (TAMs). We then exemplified how these factors interact with nanoparticles and emphasized the potentials and challenges of nanoparticle-based strategies facing in enhancing intratumoral penetration and tumor microenvironment remodeling. We hope to give a simple understanding of the interaction between these microenvironment factors and the nanoparticles, thus, favors the designing and constructing of more ideal functional nanoparticles.

Contents

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https://doi.org/10.1016/j.addr.2019.06.007
0169-409X/

1. Introduction

It has been >20 years since the first nanoparticle drug – Doxil had been approved by the U.S. Food & Drug Administration (FDA) at 1990s when had pasted >30 years from the first paper on liposomes published in mid-1960s. During this period, which ranges more than half century, either the scale of clinical translational nanomedicines or the research depth of the biological and multi-disciplinary basic theory of nanomedicine has been greatly developed. It has been reported that >700 open or active clinical trials have been undergoing (search results from ClinicalTrials.gov). Meanwhile, in fundamental research fields, the uncovering of enhanced permeability and retention (EPR) effect and its prevailing have promoted the development nanosystems [1,2], although its extent and homogeneity as well as susceptibility still need to be further validated [3]; the heterogeneity of cancer which mainly accounted for the poor therapeutic outcome of chemotherapy or immunotherapy, etc. has also been identified [4,5]; rethinking and further development of tumor microenvironment (TME) have provided more biological information on its effect on nanomedicine-based tumor therapy [6,7]; active tumor-targeting has been rendered and proved to be a more efficient strategy for nanomedicine accumulation in tumor site; then, "protein corona" has been identified as the "prime culprit" caused the failure of active tumor-targeting [8,9], while the active tumor targeting can also be further realized by controlling the surficial physical and chemical properties of the nanoparticles; the concept of nanotheranostics has also been proposed for the capacity of nanoparticle in therapeutics or diagnostic agents delivering [10]; and the nano- biological effects, e.g. biocatalysis (Fenton reaction, etc.), immune stimulation, etc. have also been emphasized and highlighted as promising strategies for cancer inhibition and TME regulation [11,12]. The progresses obtained in tumor biological structures and functions plus in nanomedicine design and construction further stimulate the development of more suitable nanomedicines [13,14].

Even though, some critical challenges are still impeding the development of nanomedicine, which pull us back to the reality: there is a long road to get through before we get the ideal nanomedicines with expected tumor-targeting and therapeutic outcome. One of these challenges is the delivery efficiency of nanomedicines to cancer cells. A recently report has pointed out that the nanoparticles ended up in a solid tumor was estimated as only 0.7% of an injected dose of nanoparticles [15]. With active tumor-targeting ligand modification, the median delivery efficiency is just increased to 0.9%. And the number of the nanoparticles directly interacted with cancer cells is as low as 0.0014% [16]. Although some drug developers point out that the free drug molecules accumulate with efficiencies are just one-tenth to one one-hundredth the median efficiencies of the nanoparticle-based formulations (nanomedicines) and the debates about the controversial low delivery efficiency is still ongoing, the uncovered intratumoral biological barriers actually indicate a bumpy road while the nanoparticles enter into the tumor tissues to directly interact with cancer cells.

The extraordinary growth of tumor requires enormous nutrient and energy. Unregulated behaviors of cancer cell progressing and persistently change of tumor microenvironment (TME) which acts as the soil for cancer growth and metastasis are the ubiquitous features [17]. It forces the cancer to alter their metabolic behaviors and adapt to the upregulated glucose metabolism which promoting the cancer cells transforming to more invasive subtype [18]. The expanding neoplastic mass and disorganized tumor vasculature lead to the formation of physiological environment of tumor microenvironment with ubiquitous features.

After the nanoparticles get through the endothelial cell layer by EPR effect or transcytosis, they will firstly encounter the basement membrane-a type of extracellular matrix (ECM), and then the interstitial ECM, which all have crosslinked hydrogel network structure of collagens, proteoglycans (PGs), hyaluronic acid (HA), elastin, etc. and service as reservoir of enzymes, cytokines, chemokines, and growth factor, etc. Nanoparticles can be physically trapped or chemically degraded in the ECM regions. Meanwhile, monocytes can also be found in the ECM, which can further eliminate the nanoparticles via endocytosis. Besides, inside the TME, plenty of environmental factors related with tumor cells metabolism are secreted, which are also critical for tumor proliferation and metastasis. These environmental factors include physiological factors (proton, ROS, or GSH, etc.), and protein-based factors (MMP etc.), which are localized intracellularly or extracellularly or both. The concentration or activity or expression level of these factors in TME are significant different with normal tissues and normal cells. They form a complex and dynamic TME to promote cancer progression. Beside serving as the targets for enhancing the therapeutic outcome of

nanomedicines, they also play critical roles in the intratumoral fate of nanoparticles. The formation and biological functions of each of these factors has been reviewed somewhere [19–22], most of these reviews, however, just focus on one or two of these factors, and lack the co-discussion of the interaction with nanoparticle which determines the fate of nanoparticle and therapeutic outcome of nanomedicines consequently. Therefore, in here, we are going to first systematically review the intratumoral biological barriers that the nanoparticle will encounter after entering into the tumor, and present the up-to-date findings about the formation, features, and distribution of these barriers, and summarize the interactions between these barriers and the nanoparticles as well as the existing strategies for functional nanoparticle construction to utilize the barriers to fight against themselves, and figure out the challenges and opportunities in nanomedicine-based cancer diagnosis and therapy. As the underlying mechanism of EPR effect has been deeply studied, which is mainly influencing the enrichment of nanoparticles in the tumor site but not the intratumoral fate, and extensive reviews have been reported, the EPR effect is exclusive in the review. Besides, the high interstitial pressure of tumor is just pressing the nanoparticles back to the circulation system, it will not be discussed either. We mainly focus on the effects of ECM, matrix metalloproteinases (MMPs) and related enzymes, acidosis and hypoxia, redox environment, and monocytes etc. onto the intratumoral fate of nanoparticles, and hope to figure out the implications on cancer diagnosis and therapy (Fig. 1). We presume all the discussions are based on systematic administration, but we will also give a brief introduction of the intratumoral fate of nanoparticles via intratumoral injection route due to the recent findings in nanoparticle-based local cancer treatment and immunotherapy. In sum, we hope this review can provide some guidelines for the design and construction of stimuli-responsive nanoparticles to enhance the precision in cancer diagnosis and the therapeutic outcome in cancer therapy.

2. Big picture of tumor microenvironment factors

Tumor microenvironment (TME) is generally defined as the cellular environment supporting the tumorigenesis. It includes surrounding blood vessels, immune cells (tumor-infiltrating lymphocytes (TILs), tumor-associated macrophages (TAMs), fibroblast (which is cancer-associated fibroblasts (CAFs) in cancer), bone marrow-derived inflammatory cells, etc.), molecules for cellular signaling (enzymes, cytokines, chemokines, growth factors (GFs), etc.) and the extracellular matrix (ECM). All the cell types involved in TME can influence the microenvironment by releasing extracellular signals, such as cytokines, chemokines, growth factors, and even metabolites, to direct the tumor growth and evolution. Because of the aberrant growth of tumor cells and excessive demand of nutrients, most of the tumors (which most of them are carcinomas), exhibit dysregulated angiogenesis with leakage vascular structure (which also is the main biological foundation of EPR effect), increased stiffness and interstitial pressure (as the results of over-deposited of extracellular matrix (ECM) and angiogenesis), immunosuppression (as the results of polarization of monocytes (macrophages) or fibroblast and activation of regulator T cells (Treg)), overexpression of enzymes, acidic and hypoxic environments, and overactivated redox environment, etc. All these abnormal features in tumor tissue form a complex intratumoral microenvironment promoting the proliferation and progression of tumor (Fig. 2).

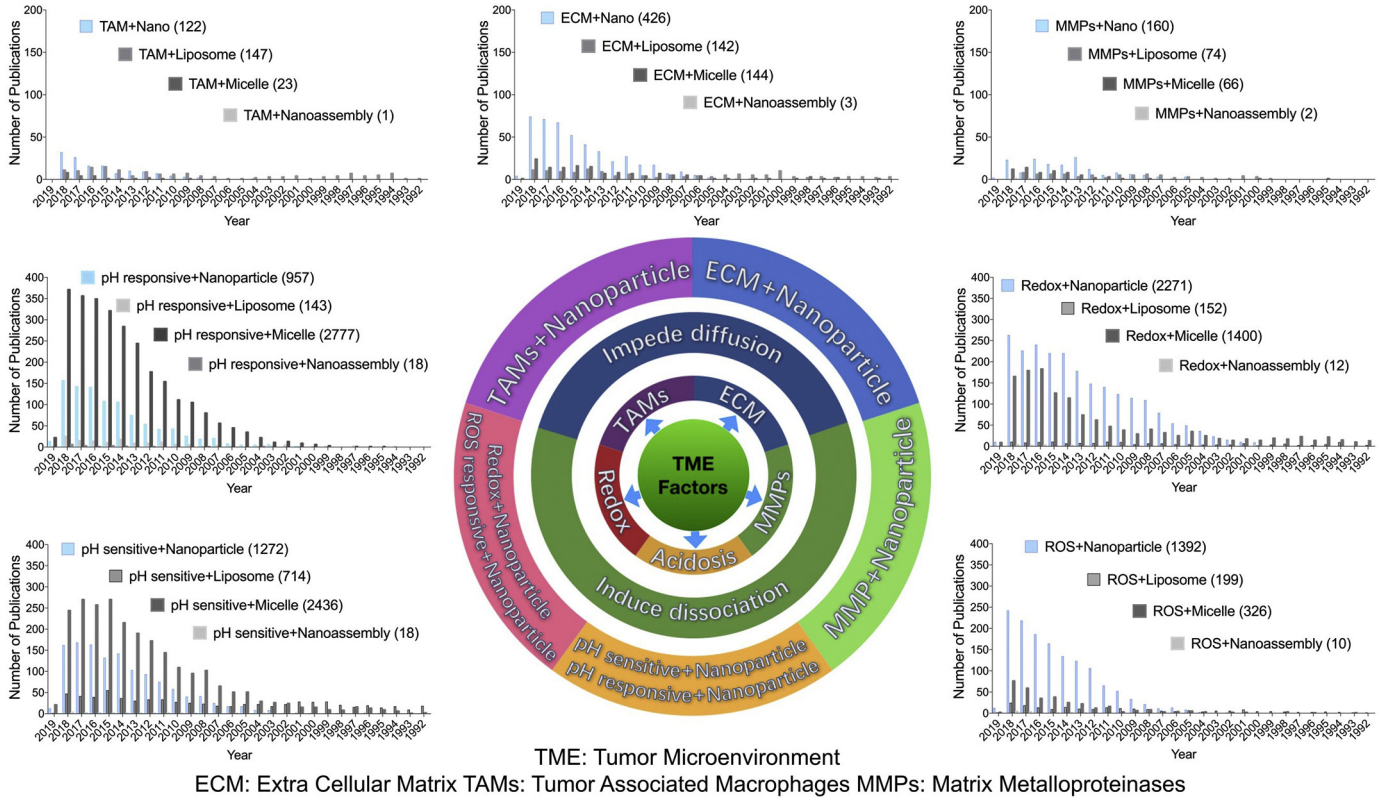


Fig. 1. Tumor microenvironment factors and the publications about each tumor microenvironment factor plus nanoparticle or liposome or micelle or nanoassembly in the past two decades. We used Web of Science database, and the search terms were "extracellular matrix" + "nanoparticle" (or + "liposome", or + "micelle", or + "nanoassembly"), "matrix metalloproteinase" + "nanoparticle" (or + "liposome", or + "micelle", or + "nanoassembly"), "pH responsive" + "nanoparticle" (or + "liposome", or + "micelle", or + "nanoassembly"), "pH sensitive" + "nanoparticle" (or + "liposome", or + "micelle", or + "nanoassembly"), "redox" + "nanoparticle" (or + "liposome", or + "micelle", or + "nanoassembly"), "reactive oxygen species" + "nanoparticle" (or + "liposome", or + "micelle", or + "nanoassembly"), and "tumor associated macrophage" + "nanoparticle" (or + "liposome", or + "micelle", or + "nanoassembly"), respectively.

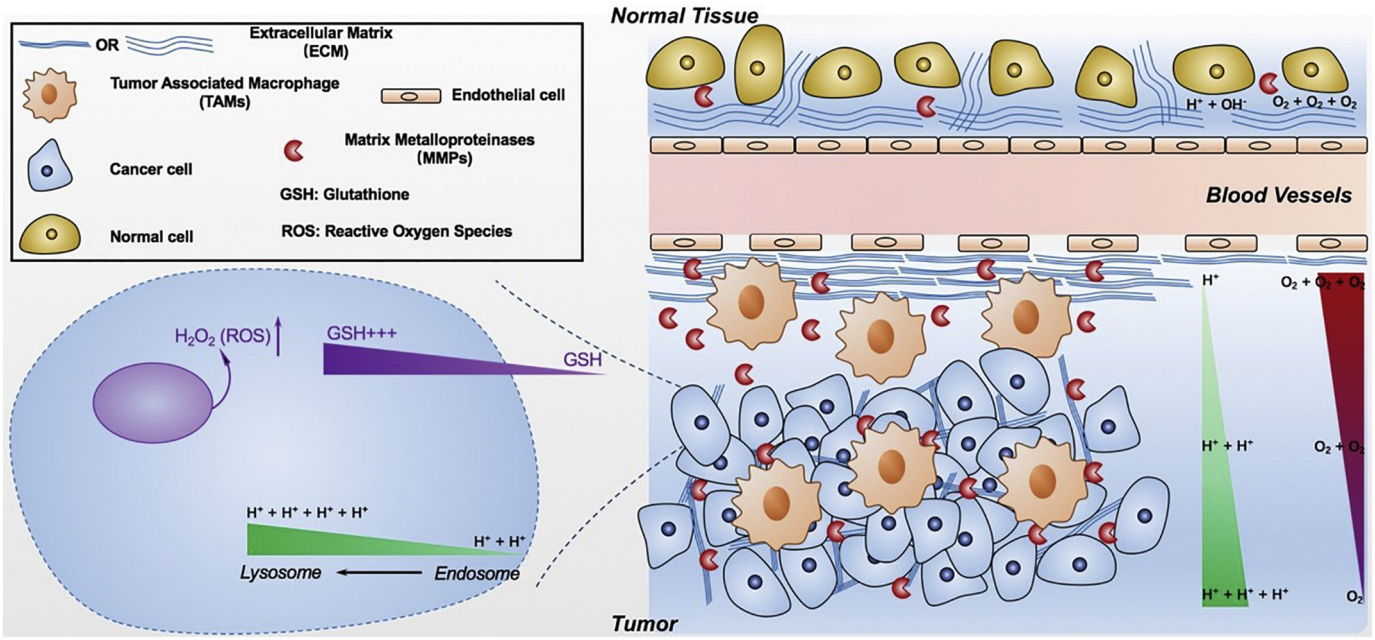


Fig. 2. Big picture of intratumoral microenvironment factors. In normal tissues: the ECM is loose and elastic; pH is maintained in 7.3–7.4; MMPs activity is neglectable; oxygen is sufficient, redox environment is homeostasis; the concentration of GSH is low; macrophages are acting as immune cells to keep immunohomeostasis. In tumor tissues: basement membrane is thicker and ECM is highly cross-linked; the stiffness of ECM is much higher than (6 times of) normal tissues; hypoxia and acidity are the prevailing features; redox environment is harsh; macrophages are differentiated to M2-type tumor-associated macrophages (TAMs). These factors will trap or degrade the functional nanoparticles entered into the tumor tissues. They provide biological barriers or stimuli for impeding the diffusion of nanoparticles or accelerating the cargo release.

Aberrant deposition of ECM is ubiquitous in many diseases, including inflammation and cancer. The ECM in tumor exhibits different physical and chemical structures while compare with that in normal tissues. The main factor caused the aberrant ECM is the over-activation of MMPs and their natural inhibitors-TIMPs. Various cell types in TME express kinds of MMPs, which favoring the remodeling of ECM for tumor progression and invasion. Beyond aberrant ECM, the levels and diversity of enzymes are critical for tumor progression. All the cellular behaviors are not capable to process without the involvement of enzymes. The degradation or formation or regeneration of the biomolecules are mediated by enzymes. Moreover, acidic environment is one of the key microenvironmental factors that connect with the growth, proliferation and development of tumor [23]. The formation of acidic environment in tumor is used to be considered as the result of hypoxia, another key microenvironmental factor regulating the progress of tumor growth or metastasis [24]. The hypothesis seems solid. And most of the aggressive solid tumors are all containing hypoxic core. In order to obtain enough ATP and biosynthetic precursors and to counterbalance the over-generated lactic acids or carbonic acids during tumor proliferation, the cancers rely on exacerbated glycolysis as well as robust pH-regulating systems. And the location and distribution of acidosis region and hypoxia region are often overlapped. But the recent results indicate that the hypoxia and acidosis have different pathway in the regulation of tumor proliferation and metastasis, although they interplay with each other [25]. Beyond acidic characteristic, reactive oxygen species (ROSs) are the other kind of important environmental factors which form redox environment with glutathione (GSH) system. ROSs are generated during the process of aerobic metabolism. And mitochondrial respiration is responsible for the generation of majority of the accidental ROSs which are involved in regulating kinds of cellular functions. The ROSs can be divided to several subtypes according to their activities and chemical properties, which including the oxygen singlet, the superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^{\bullet -}$). Different species of ROS have different concentration levels and lifetimes. Meanwhile, GSH is another factor involved in the redox-dependent regulation during energy metabolism. GSH is an important antioxidant which is capable of protecting important cellular components from ROSs-caused damage. It also serves as endogenic reducer to cleave the disulfide bonds which are normally formed in cytoplasmic proteins to generate cysteines. Its intracellular concentration is of 2–20 mM (in normal cells: <10 mM; in cancer cells: 10–20 mM). Beyond all these above environmental factors, monocytes, especially the macrophages, form another kind of biological barrier inhibiting the penetration of nanoparticles inside the tumor. Most of the macrophages in tumor tissues are polarized to M2-type TAMs, which promote the tumor growth and metastasis. In normal tissues, all these microenvironmental factors are maintained a kind of balance to provide a suitable environment to regulate the metabolism. However, the tumor proliferation and progression are far more different with normal tissues, this balance has been broken, and a different microenvironment are formed by these environmental factors, which favors the formation a tumor cells adaptive microenvironment.

Although these factors promote the progress and metastasis of tumor by providing an adaptive metabolic environment, thoroughly understanding of these factors is critical for nanomedicine development and favors the uncovering of the intratumoral fate of nanomedicines, e.g. ECM is a potential target for enhancing the diffusion of nanoparticles as well as the physical barrier impeding the penetration (via systematic administration) or spreading (via intratumoral administration) of nanoparticle; other environmental factors, such as enzymes, acidic, GSH, and ROS, they also can be used as the stimuli for triggering drug release, which can improve the therapeutic outcome. They also are of the biological foundations for prodrugs and functional nanoparticles-based medicines which are designed and constructed to benefit from these ubiquitous metabolic-related environmental factors. Meanwhile, the factors can be served as the promotors to degrade or dissociate the nanoparticles they encountered and end the intratumoral journey of nanoparticle inside tumor. Up to now, numerous nanosystems have been developed, including pH-sensitive, redox-responsive, ROS-cleavages, or enzyme-responsive, etc. However, to our knowledge, the

formation, distribution (localization) etc. of the stimuli inside tumor (including extracellular and intracellular) and their effects onto the intratumoral fate of nanoparticles still need to be systematically reorganized because of the important roles they playing in the trapping or degradation of nanoparticles in tumor as well as in promoting tumor progression and invasion. Therefore, this review first summarizes the recent findings of the formation mechanism, distribution (localization and concentration) of these microenvironmental factors in tumor, and the interactions between these factors and the nanoparticles and the effects on the intratumoral fate of nanoparticles, and then listed some of the state-of-the-art nanoparticle-based strategies which have used these stimuli for precise tumor diagnosis and therapy (or theranostics), especially the nanoparticles which can further enhance the precision or efficiency in tumor diagnosis and therapy activated by stimuli. Furthermore, the nanoparticles administrated either systematically or intratumorally (local delivery) are facing all these factors during their penetrating or spreading inside tumor, thus, we will fist discuss all these factors and the interactions between these factors and the nanoparticles based on the systematically administrating routes, and then list some of the recent findings in local delivery of nanoparticles and their combinations with other cancer treatments, such as immunotherapy, radiotherapy, etc.

3. Extracellular matrix (ECM) and ECM-nanoparticle interactions

3.1. Formation and features

3.1.1. Location of ECM

The first intratumoral tissue that the nanoparticles encounter after extravasation from blood vessel is extracellular matrix (ECM). Normally, ECM is a vital noncellular structure located in all tissues and organs. Its fundamental functions are providing essential physical scaffolding for the integrity and elasticity and triggering multiple essential biological activities to promote the development of normal organ and maintain tissue homeostasis. The ECM can be divided to two main classes according to the location and composition. One type is the interstitial connective tissue matrix. This type of ECM locates around the cells and acts as scaffold for tissue supporting. And the other type of ECM is the basement membrane. It locates between the epithelium or endothelium and the surrounding stroma.

3.1.2. The components and compositions of ECM

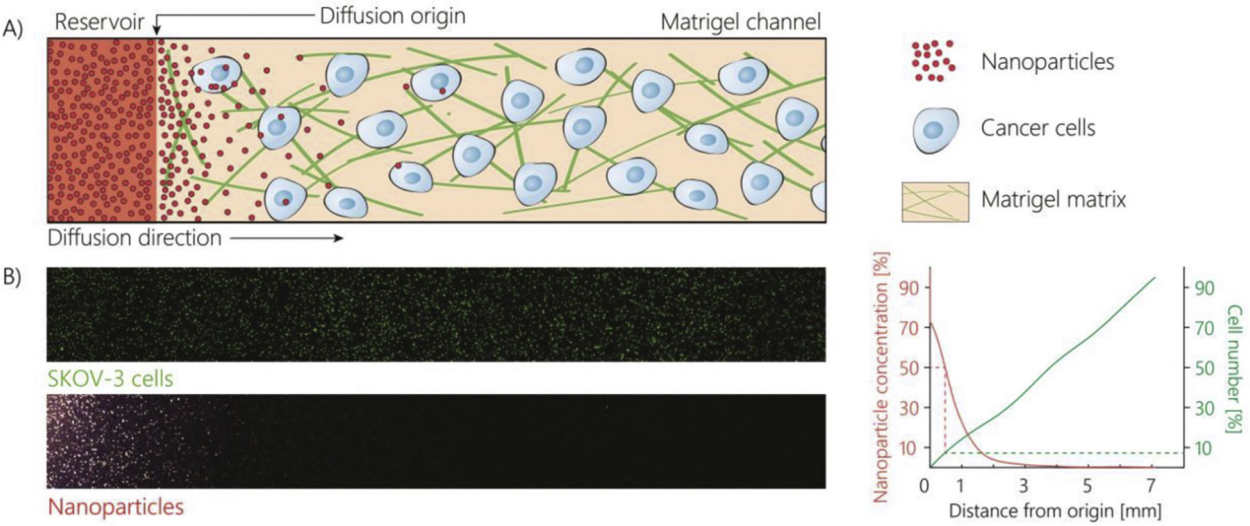
Although the expression levels or accumulations of the ECM components in tumor tissues may differ from the normal tissues, they both share the similar ECM components and compositions. In general, two important kinds of biomacromolecules, which are proteoglycans (PGs) and fibrous proteins, have constructed the foundational structure of the ECM [26,27]. PGs are existing as hydrogel filling most of the interstitial space. Because of their structural characteristics, PGs have distinguished performance in regulating the changes of the chemical or physical environment by buffering, hydration, specifically binding and structural stabilization. Collagens, elastins, fibronectins and laminins have constructed the majority of the fibrous proteins in ECM [28]. They together with other around 300 proteins which containing collagen subunits, PGs and hundreds of complex glycoproteins form the core matrisome [29]. These various proteins together with water compose a hydrogel-like ECM structure. There are three main proteins constructing the fibrous structure of the ECM, which including collagens, elastin and fibronectin (FN). And in multicellular animals, 30% (*w*/w) of the proteins are collagens. The collagens are essential in regulating the physiochemical properties of the ECM, thus, to regulate the cell behaviors inside the ECM [30]. Most of the collagens are generated or secreted by the fibroblasts. And the fibroblasts mainly distribute or may be recruited in the stroma, resulting in much thicker collagen layer in the stroma. In response to the external force, the orientation of the collagen fibers can be adjusted by the fibroblasts. While the orientation of the collagen fiber has been transformed, the cell behaviors including adhesion, differentiation, and migration will be changed [31]. As another major component involved in the formation of ECM fibrous structure, elastin allows the tissues to reversely stretch and shrink, which is the basic biological structure for tissue elasticity. The tissues are not directly secreting elastin. Tropoelastin is first generated. Then, under the catalytic properties of lysyl oxidase (LOX) and lysyl oxidase monolog (LOXL), the tropoelastins are highly cross-linked to form elastin with high elasticity. The final type of proteins that constructing the fibrous structure of the ECM is fibronectin (FN). The main functions of FN are controlling and maintaining the main structure of the ECM, and regulating the attachment of the cell in ECM, thus, regulate the functions of the attached cells, due to the encoding of the ECM receptors, e.g. integrin, syndecans, etc. in these proteins [33].

Furthermore, a more important feature of the ECM structure is the dynamic and persistent remodeling via either the enzymatic or non-enzymatic reconstruction. The stored proteins used to form fibrous structure and the PGs (including hyaluronan and decorin) have benefit to maintain the homeostasis and integrity of the ECM structure by forming a complicate and an easy-practical hydrogel-like network structure with versatile properties [34].

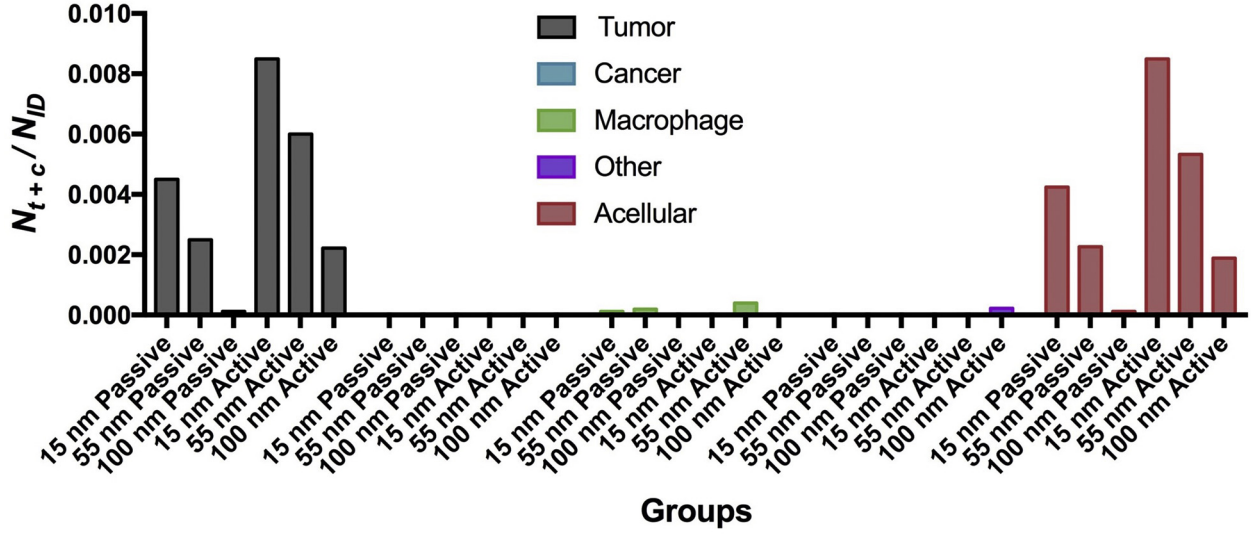
3.1.3. Dysregulation of ECM and out-of-balance of ECM homeostasis in tumor

In generally, the homeostasis of the ECM is maintained by persistently rebuilding and remodeling resulting from numerous cellular functions, such as biosynthesis, biodegradation, reassembly and chemical modification [35]. Proteolysis is the first step during ECM remodeling. MMPs-secreted by fibroblast mediate and promote this process [36]. In order to prevent the over-activation of MMPs which may cause uncontrollable degradation of ECM and maintain the integrity of the tissues, relevant inhibitors have to be secreted by the tissues to counterbalance the over-activity of MMPs [37]. This inhibitor family is named as tissue inhibitor of metalloproteinase (TIMP). While compare with the MMPs which have been identified 24 members, there are only four TIMPs have been identified (TIMP1-TIMP4). TIMPs not only selectively restrain the activity of MMPs, but also the activity of the ADAMs (a disintegrin and metalloproteases) as well as the ADAMTs (a disintegrin and metalloproteinase with a thrombospondin type I motif). The homeostasis of the ECM can be controlled by maintaining the ratios of MMP and TIMP. For example, TIMP3 together with membrane-associated reversion-inducing Cys-rich protein with Kazal Motifs (RECK) can regulate the activity of MMPs and ADAMs as well as ADAMTs, while the TIMP3 is acting as the inhibitor of ADAMs and ADAMTs. Different from the other TIMPs which are soluble in vivo, TIMP3 is anchoring on the surface of the backbone structure of the ECM. Besides, the involvement of some other enzymes, such as LOX and transglutaminases, are essential for the further crosslinking of ECM [32]. A plenty of ECM-associated proteins are nonetheless important and directing the ECM remodeling. These proteins include including growth factors (GF), cytokines, Ser proteases, cathepsins (found both extracellularly and intracellularly in lysosomes), heparanases, and sulphatases, etc. These versatile proteins with different properties in the modulation of cell growth and migration which are stored in the ECM by anchoring onto the structure of ECM are essential in maintaining the homeostasis of normal tissue [38]. By a complex regulation process, the ECM homeostasis can be maintained in normal tissue.

In the cases of diseases, such as osteoarthritis, fibrosis or cancer, persistently dysregulated composition, structure, stiffness and abundance of ECM were observed during ECM remodeling. Because of the inherent structure and location of the ECM, it should favor the suppression of the malignant tumor by stabilizing the tumor cells inside the ECM [39]. By in vivo evaluation in rat model, it found out that the hyaluronan with high molecular weight which is by a factor of 6 of the hyaluronan in human or mouse can efficiently inhibit the tumor growth [40]. It demonstrates the potential of ECM, which containing hyaluronan as a


A)
Reservoir
Diffusion origin
Matrigel channel
Diffusion direction
Nanoparticles
Cancer cells
Matrigel matrix
B)
SKOV-3 cells
Nanoparticles
Nanoparticle concentration [%]
Cell number [%]
Distance from origin [mm]

C)


N_{t+c}/N_{ID}
Tumor
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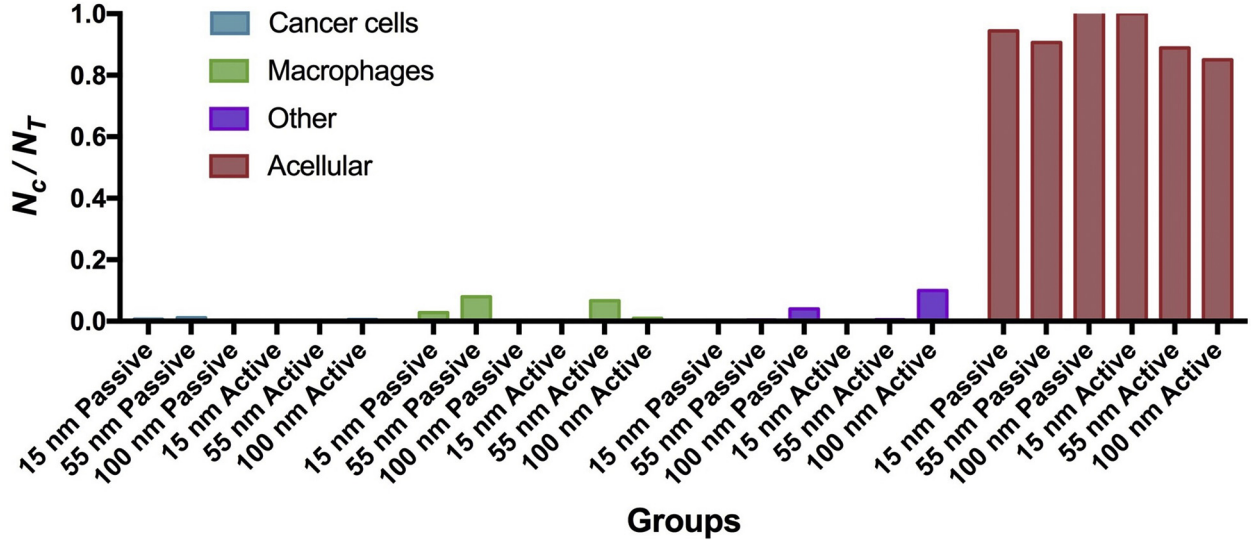
N_c/N_T
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main component, in inhibiting cancer progression. The balance activity between the MMPs and TIMPs maintains the stabilization of ECM structures (homeostasis), while the activity of these active proteinases, particular the MMPs, is low in normal conditions. However, during disease formation, such as aging, fibrosis, inflammation or cancer, the activation of stromal fibroblasts and their induced-transdifferentiation into myofibroblast, the activity of MMPs increased. It directs the progress of ECM dysregulation. Moreover, ECM appears to evolve during tumor growth. The thickness and length trend to be reduced, as the tumor growing. And a loss in structure of ECM was also observed. It further demonstrates that dynamically changing is an essential feature of ECM. And it is persistently remodeled, particular in the tumor tissues.

3.1.3.1. Abnormal stiffness. In the tumor case, abnormal deposition and enhanced stiffness of ECM are the obvious features while comparing with the surrounding tissues [41]. In tumor tissues, inflammation is prevailing, which is induced by chemokines and GFs [42,43]. Inflammation favors the activation of stromal fibroblast then induces their transdifferentiation into myofibroblasts [31]. A plenty of ECM proteins have been deposited by myofibroblasts. They further generate numerous types of GFs by enzyme-degradation, which results in the promotion of ECM contraction. And what's worst is the formation of desmoplasia. After the release of cleaved GFs, the remained ECM proteins, which including collagen and elastin, will be further crosslinked by the enzymes. It causes the enhancement of the stiffness of the ECM. The expressions of LOX and LOXL enzymes, which both of them are normally overexpressed in kinds of cancer (even in the metastatic sites), are negatively correlated with survival of the patients [44]. As results, a larger and more-rigid and stiff fibrous crosslinking structure is obtained [45–47]. The stiffness of surrounding normal tissues is around 500 Pa, while in the tumor tissue, this value can be increased by 6-folds to around 3000 Pa. Besides, MMPs, as the crucial enzymes involved in ECM remodeling, secreted and activated by tumor cells and by myofibroblasts can remodel the basement membrane (BM) and release various GFs by cleaving the ECM-associated proteins [48]. Vascular endothelial growth factor (VEGF) is one of the cleaved GFs that regulating the bio-microenvironment surrounding tumor, favors the angiogenesis and enhances the vascular permeability. The newly formed vascular structure further presses the inter-vascular ECM then generates interstitial tissue pressure. Thus, an amplifying stiffening is added to the ECM.

3.1.3.2. Effects of ECM stiffness on tumor progression. ECM itself has the potential to promote tumor progression [49]. It has been revealed that the overexpressed collagen IV has the potential to promote the progression of lung cancer cells during metastasis in the liver [50]. The tumor highly expressing protease inhibitors indicates relative good prognosis, while many types of MMPs overexpressing in tumor may connect with the poor prognosis, meanwhile, promote the further progression or metastasis of cancer cells [51]. Collagen existing in the tumor tissues can also be acted as signals to promote epithelial-mesenchymal transition (EMT) and tumor progression by interacting with the Tyr kinases discoidin domain-containing receptor (DDR).

As the consequence of ECM remodeling in tumor tissues, the ECM stiffening has been proved to disrupt tissues morphogenesis and contribute to malignant progression [52]. During the ECM stiffening, as a critical enzyme for collagen crosslinking, LOX can also cluster the β1 integrin, signal the PI3K and induce the focal adhesion. The results reveal that the LOX may trigger the tumor cells to be more invasive and aggressive [53]. It makes the LOX a potential target for cancer therapy. And the introduction of LOX inhibitor has positive effect on the suppression of fibrosis and stabilizing the tumor during development [47]. Besides, the stiffened ECM structure can recruit tumor-promoting immune cells, e.g. tumor-associated macrophages, to secrete signaling molecules (miR-18a, targeting to tumor suppressor phosphatase and tensin homologue (PTEN)) to promote tumor progress and the development of metastasis [54].

Moreover, the fiber structure of the ECM can induce and regulate the migrating behavior of the immune cells. In ECM, the fiber structure is mainly formed by fibronectin and collagen. Apparently, the loose fiber structure favors the penetration of T cell through the ECM, conversely, the migration of the immune cells in ECM can be restricted by the dense fiber structure, as a result, controlling the interaction between the immune cells and the cancer cells [55]. It has been proved that the deconstruction of the collagens in the ECM structure by the administration of collagenase enhances the penetration of T cells in the tumor tissues. It indicates that ECM geometric remodeling can be a promising strategy to improve immunotherapy. Beyond fibronectin and collagen which formed the fiber structure, some other ECM component can also recruit various types of immune cells and induce the activation and differentiation or suppression of these immune cells, and in the case of tumor,to aggregate the inflammation and metastasis [56].

During cell migration, the migrating behavior of the cells passing through the ECM is determined by the ECM geometry, and cells can also reshape itself to fit the porous structure of the ECM [57]. Around the tumor margins, because of the enhanced stiffness of the ECM, it may force the cells to alter their shape, surface proteins, and to detach from the original site to escape from the confinement of the ECM, and results in metastasis [58].

3.2. Fate of nanoparticle in ECM

The ECM are observed to encapsulate the tumor blood vessels, and it services as a basal support for blood vessels and the primary barrier impeding the further penetration of nanoparticles into the tumor compartments. Diffusion imparts the driving force to nanoparticles to enter into the interior cancer cells. However, the diffusion of nanoparticles from the capillary into the interior cells has impeded by the presence of ECM. In most of the solid tumors, the mesh size of the matrix is generally ranging between 20 and 40 nm. While the particle size of the nanoparticles is larger than the mesh size, they will be completely trapped in the ECM and entirely prevented from further diffusion. Even the particle size is equal to the mish size, the diffusion will also be hindered. Only the particles smaller than the mesh size can penetrate the ECM freely. Although the ECM in tumor tissues exhibits highly heterogeneous which determines the different diffusion paths of nanoparticle, the density and the stiffness of the collagen as well as the cross-linking percentage of tumor ECM are generally high. It indicates a highly impeded diffusion pattern in the case of nanoparticles pass though the ECM and get contact with cancer cells. Besides, while the nanoparticles enter the ECM after extravasation, the nanoparticles unavoidably interact with the ECM components more or less, which further impedes the diffusion of nanoparticles to get through ECM. Being trapped and prolonged retention present the fate of nanoparticles in ECM.

It has been uncovered recently that 88.2–99.9% of active targeting nanoparticles enriched in tumor site were retained in acellular regions after systemic administration [16]. And the particle size ranges from 15 nm to 100 nm. The ECM has been identified as the major barriers inhibiting the transportation of the nanoparticles inside the tumor tissues. Besides, the diffusion of nanoparticles in ECM is size-dependent (Fig. 3). In an in vitro assay, Matrigel was used to simulate the ECM structure, the distance of the nanoparticles diffused in the Matrigel was evaluated and recorded. The results demonstrated that as the

Fig. 3. The ECM structure impedes the diffusion of nanoparticle entry into the tumor tissues. A) The scheme of the nanoparticle diffusing in the ECM structure. B) The diffusion of gold nanoparticles in the Matrigel in vitro. C) Accumulation of the gold nanoparticles with different sizes in tumor. D) the intratumoral distribution of gold nanoparticles entered into tumor tissues. Reproduced with permission from (ACS nano, 2018, 12(8), 8423–8435.). Copyright (2018) American Chemical Society.

increasing of the particle size of the active targeting nanoparticles (from 55 nm to 100 nm), the diffusion distance was dramatically decreased from ~200 μm to 0 μm. While the particle size decreased from 55 nm to 15 nm, the distance was increased from ~200 μm to ~400 μm. Similar results were obtained in the case of passive targeting nanoparticles.

Moreover, the interaction between the nanoparticles and the ECM may affect the compositions of the ECM then further affect the diffusion of nanoparticles. It has revealed that nanoparticles can significantly increase the production of LOX [19,59], which is a copper-dependent amine oxidase and favors the stability of the elastic matrix. It can catalyze the crosslinking of tropoelastin and turn it into mature elastic fibers [60]. The increase in LOX production is consistent with desmosine crosslinking of elastin [61]. The over-crosslinked elastin aggregates the deposition of elastic matrix, which will further increase the thickness of ECM and further impedes the diffusion of nanoparticles.

3.3. Implications on nanomedicine-based cancer diagnosis and therapy

The ECM is a biological barrier which inhibiting the penetration of nanoparticles entry into the tumor tissues. In order to enhance the therapeutic outcome of nanomedicines in solid tumors, more active strategies need to be developed beyond fine-tuning the sizes or the shapes or the surface coatings of the nanoparticles, although the size is critical in determining the diffusion of nanoparticles in the fibrous ECM structure. The introduction of recombinant human IGF-1 and combining with chemotherapy drug can obtain a IGF-1R targeted nanoparticle delivery system for cancer theranostics. Repeated systemic administrations of this nanoparticle favored the breaking of the tumor stromal barrier and improved the therapeutic effect. The expression of IGF1R is positive in active stromal fibroblast cells (CAFs or myofibroblasts) and macrophages in tumor tissues (TAMs). CAFs and TAMs play critical roles in collagen production and deposition during ECM remodeling. The repeated administrations of the IGF1-modified chemodrug-loaded nanoparticles may inhibit the growth of CAFs and TAMs, thereafter, the ECM structure has been remodeling [62,63]. Moreover, in a more directly way, after administration of hyaluronidase (HAase), an enzyme can break down hyaluronan, increased tumor vessel densities and effective vascular area as well as improved EPR effect can be achieved, resulting in the increase of tumor uptake of nanomedicines. It favors the enrichment of nanomedicines in the tumor site and enhancement of photodynamic therapy [64]. Beside the proteinases which can degrade the ECM structure (which including collagenases, hyaluronidases, or MMPs), several antifibrotic agents are also developed, which including losartan, candesartan and metformin. These small molecules can also be used to modulate the ECM.

Furthermore, beyond the drug-based strategies, some physical approaches are found to be of the effective way to deconstruct the ECM structure and enhance the permeation of nanoparticles passing through the ECM (Fig. 4). It has been revealed that hypothermia has the potential to reorganize the collagen fibers after the irreversible denaturation of the proteins. After heating, the native triple helical structure of collagen fiber transforms into random coiled structure (Fig. 4A and B). It has

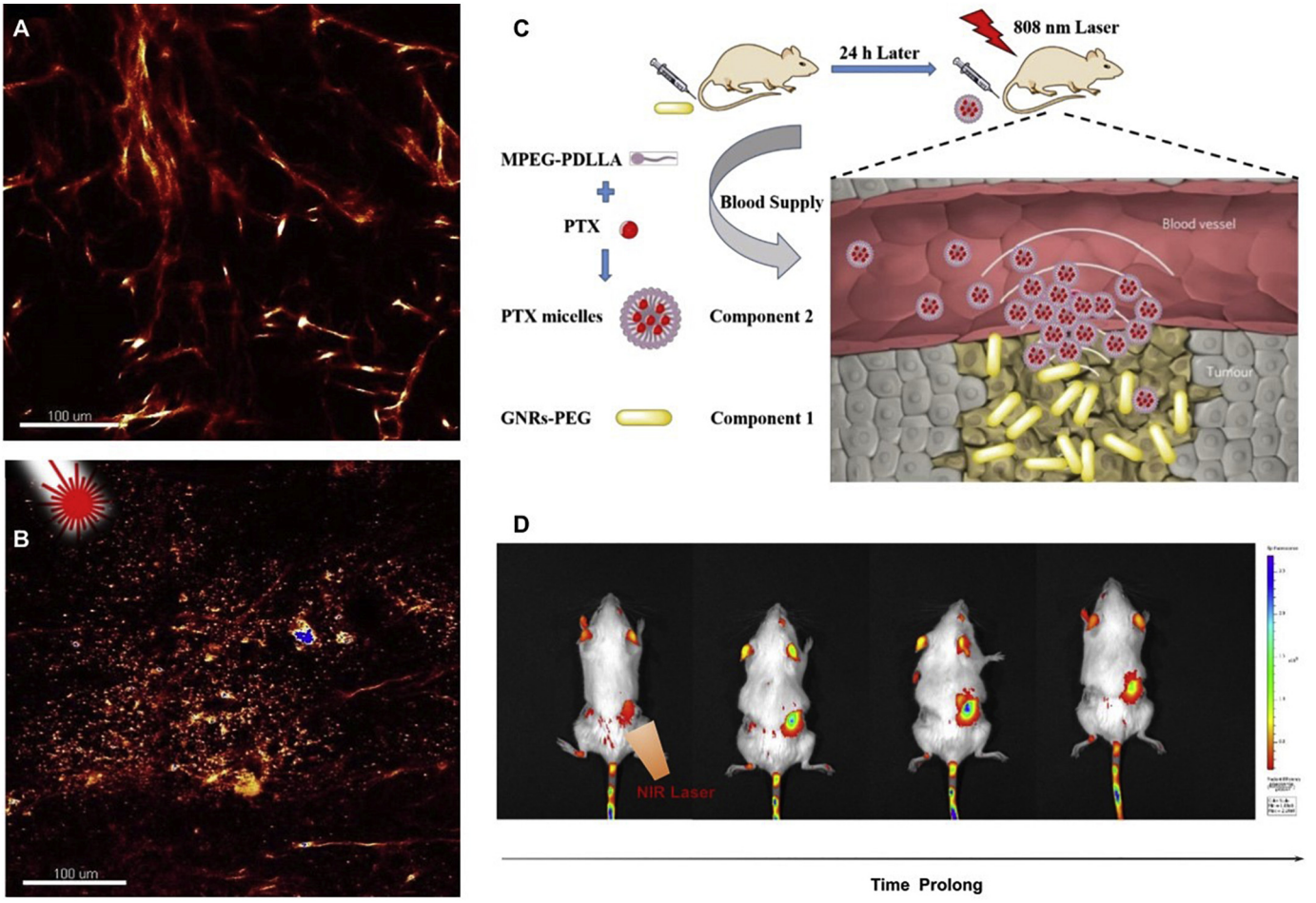


Fig. 4. PTT-induced derangement of ECM in tumor tissue and enhance accumulation of nanomedicines in tumor site. The collagen fibers organization in the tumors A) non-treated with PTT and B) treated with PTT observed by two photon microscopy through the second harmonic generation signal. C) An assay we conducted to study the effect of PTT on the accumulation of nanoparticles in tumor site. D) the fluorescence imaging of the dual-tumor-bearing mice which the right flange was pretreated with gold nanorod-mediated PTT. A) and B) Adapted with permission from (*Pharmacol. Res.*, 2017, 126, 123–137). Copyright (2017), with permission from Elsevier.

been revealed that the average diffusivity of 50 nm and 120 nm nanoparticles in denatured collagen (I) has been increased by ~14 and ~21 fold of those in intact untreated collagen matrix, respectively [65]. It indicates that the denaturation of collagen improves the diffusion of nanoparticle. Moreover, after hypothermia by gold-mediated photothermal therapy (PTT), the doses of chemotherapeutics targeted to the tumors can be increased >40 times [66]. The experiment we have conducted has come out with similar results (Fig. 4C and D). The effect of nanoparticle-based hyperthermia onto the tumor extracellular matrix remodeling has been reviewed by Kolosnjaj-Tabi, et al. They conclude that the hypothermia has altered the mechanical properties of the tumor. It favors the improvement of the therapeutic outcome of conventional anticancer drugs by allowing better penetration of drug molecules or nanoparticles passing through the altered ECM structure [67]. In recent years, nanoparticle-based hypothermia, such as photothermal therapy (PTT) or alternate magnetic field triggered thermal therapy, has been getting enormous attentions for their efficiency in eliminating the in situ tumors, some of them can even trigger the immune response for cancer immunotherapy [68–71]. But their specific advantages are not dug out thoroughly. Their potential in ECM remodeling and further altering the diffusion behavior of nanomedicines during penetrating through the ECM will provide the new opportunities and challenges in the development of novel anticancer strategies.

4. Metalloproteinases (enzymes) and MMP-responsive nanoparticles

As mentioned in Section 3, MMPs are the critical enzymes involved in the remodeling of the ECM. Their basic functions are enzymatically cleaving and degrading the collagen fibers and triggering the release of the small fragments as the peptide- or protein-based cytokines or GFs. Up to date, peptide- or protein-based nanoparticles have been emerging and exhibiting unique disadvantages, which can function as the cytokines or GFs to realize disease-targeting or stimulate immune response. Beside as tumor targeting ligands, peptides or proteins are providing enzyme-responsive motif to achieve active biological functions. Because MMPs are overactivated in the tumor tissues, and activating various biological signaling, and can be served as stimuli for cleavage of nanoparticles, thus, we are going to briefly introduce their basic chemical structures, classifications, distributions, and their effects on the tumor progression and invasion.

4.1. MMPs (enzymes): basic structure and classifications

MMPs are a subtype of the metzincin superfamily of metalloproteinases (Fig. 5). The activity of metalloproteinases was first discovered by Gloss and Lapiere in 1962 in the assay of tadpole tail fin tissue implants

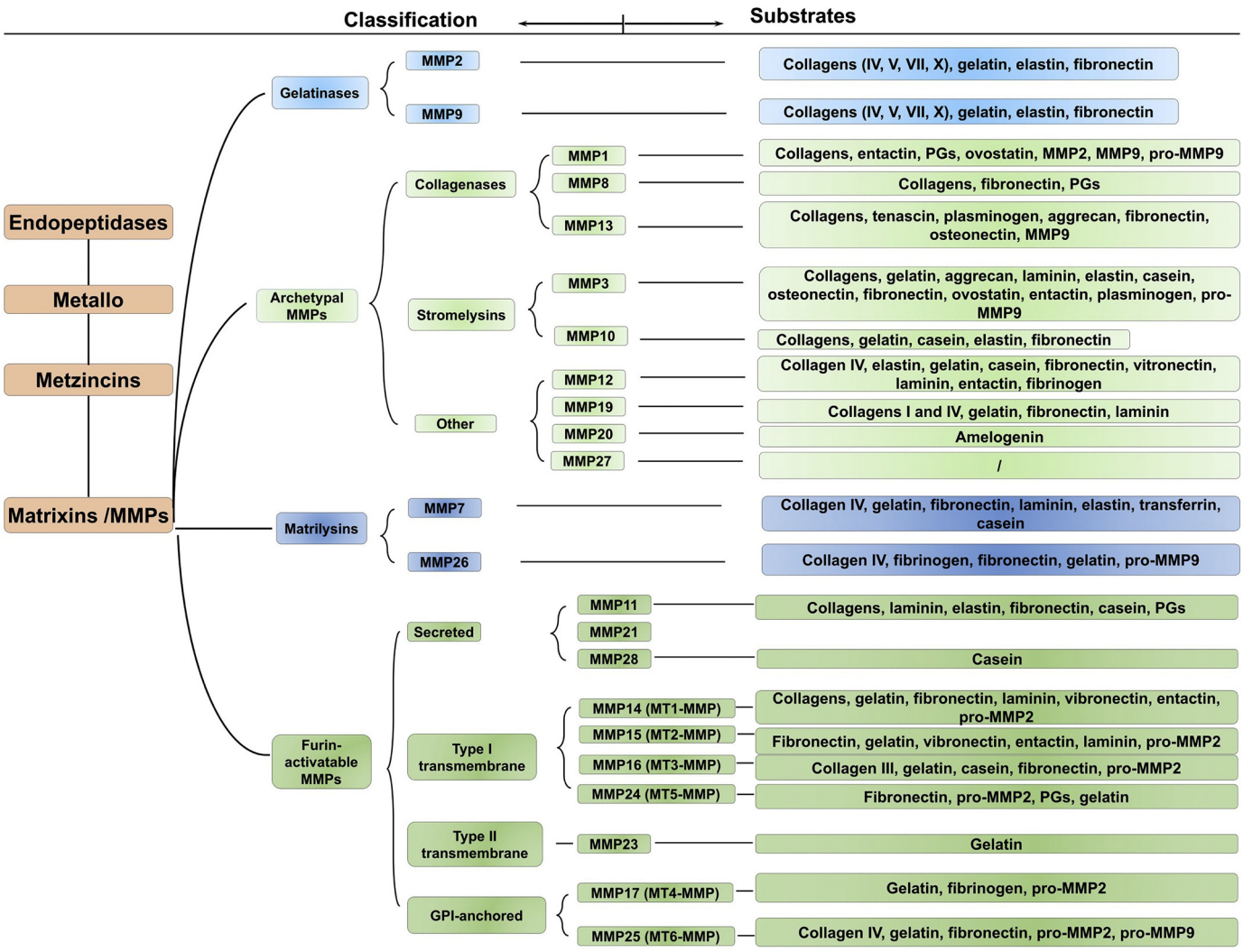


Fig. 5. Classification of MMPs and their substrates in the ECM. There are 23 types of MMPs.

[72]. Since then, the metalloproteinases have gaining enormous attention for their modeling or degrading properties to ECM proteins. 23 types of MMP proteins have been identified, they were encoded from 24 MMP gene, respectively, while there are a pair of duplicated gene encoding a same type of MMP. In the aspect of protein structure, because of their different biological functions as catalytic enzymes, the structures of the MMPs are different with each other, but they all share a globular catalytic domain with the length of approximately 130–260 residues. Moreover, all the MMPs are containing a zinc-biding motif (with the sequence of HEXXHXXGXX(HD)) as well as a methionine containing Met-turn.

The MMPs can be classified in several patterns according to their structures or functions. A traditional classification is based on the substrate specificity and cellular localization of the MMPs. However, this classification still needs to be improved due to the exception of some MMPs which cannot be classified.

Another classification which is based on the domain organization is divided the MMPs as archetypal MMPs, matrilysins, gelatinases or furin-activated MMPs. And the archetypal MMPs are including collagenases, stromelysins and "other". This classification mainly bases on the substrate specificity of the MMPs. Several MMPs which including MMP1, MMP8, MMP13 and MMP18 in Xenopus spp. belong to collagenases, they all contain the similar properties in processing of the collagen triple helix. Because MMP3 and MMP10 can activate some pro-MMPs but cannot degrade native collagen, they were classified as stromelysis, although they have the same structural design as collagenases. The other archetypal MMPs are including MMP12, MMP19, MMP20, and MMP27. The matrilysins are just containing two MMP members, which are MMP7 and MMP26. They both lack a haemopexin domain. The number of MMPs in gelatinases groups are similar with matrilysins. The gelatinases include MMP2 and MMP9. Either MMP2 or MMP9 contains a fibronectin type II motif in the catalytic domain, which give the catalytic potential in gelatin degradation. In the case of furin-activatable MMPs, they are all containing a furin recognition motif connecting the propeptide and the domain for the realization of catalytic functions. The Furin-activatable MMPs can also be classified into two different groups according to their existence forms, one is the free forms of Furin-activatable MMPs, and the other is the membrane-anchoring types, which is also named as MT-MMPs. MMP11, MMP21, and MMP28 are belonged to the free forms of furin-activatable MMPs, meanwhile, MMP14, MMP16, MMP17, MMP24 and MMP25 are assigned to the membrane-anchoring types of MMPs with different names as MT(1–6)-MMP, respectively. MT-MMPs are all anchoring onto the cell surface to regulate the pericellular environment. At last, there are two MMPs, which including the MMP23A and MMP23B (MMP22), cannot be classified into all the above groups due to their unique features, and they are classified as the "others" MMPs. Their structural characteristics make the "others" MMPs so different with the other types of MMPs. In fact, what we known about the functions of each MMP are still limited. The uncovering of the structure and the functions of the MMPs provides guidelines for the design and construction of MMP-responsive nanostructures.

4.2. Functions and expressions of MMPs

4.2.1. Basic functions

The basic function of MMPs is the selectively degradation of the structural components of the ECM. MMPs combining with ADAMs and meprins persistently remodel the environment of the substrates. By this way, they can modify the extracellularly soluble or the membrane-bound proteins prost-translationally and control their delivery and activation. Control The bioactive state and local delivery of kinds of proteins including cytokines, chemokines, and growth factors, etc. are controlled by MMPs via clipping a short fragment from these proteins after activation [74–76]. Apparently, the responsiveness of the receptor distributed on the cell surface to extracellular signals an also be regulated by the shedding properties of MMPs. The cleavage activity of MMPs provides an alternative and unique posttranslational regulation option for the transmission of crucial signals.

Thereby the MMPs are involving in regulation of kinds physiological functions, including regeneration, embryogenesis, angiogenesis and ECM remodeling which has been discussed in the previous section. Moreover, the activation of some signaling molecules, e.g. tumor necrosis factor (TNF), etc. are directly mediated by the MMPs [73].

4.2.2. Secretion or expression

In generally, the activity of MMP is low in normally physiological conditions and become detectable in some biological processes, e.g. angiogenesis, bone development, wound healing, mammary involution, and cancer [29]. And the MMP activities are also tightly regulated by tissue inhibitor of metalloproteinases (TIMPs) and some other regulation ways (transcriptional regulation) to maintain tissue homeostasis [77]. The expressions of MMPs and TIMPs can be induced by various external stimuli, such as phorbol ester, intergrin-driven signals, ECM fragments, GFs, cytokines, pathogen- or danger-associated molecular patterns. All this MMP promoters are containing *cis* elements which can bind several transcription factors restricted by cell type and depended on stimuli, then trigger the expressions of MMPs and TIMPs [77].

Moreover, the expressions of MMPs are various in different organ or cell types. In organ level, during embryogenesis, placenta, uterus, and decidua are expressing almost all kinds of MMPs, ADAMs and TIMPs genes. They play critical and specific roles in the generation and remodeling of the tissues [78]. In the case of the distribution of the MMPs and the ADAMPs as well as the TIMPs in vivo, up-to-now, we have identified that several kinds of MMPs (including MMP2, MMP14, etc.) and ADAMs (ADAM15, ADAM17, ADAM19, etc.) and TIMPs (TIMP2, TIMP3, etc.) all exhibit high expression during the developing of lungs and kidneys. Meanwhile, the MMP14, MMP19 and ADAM10 as well as TIMP2 have also been identified in the fatal spleen and liver, indicating the functions of these proteins may relate with the haematopoiesis.

In cellular level, the expressions of MMPs in many immune cells are maintained low in the resting state. The expressions of several MMPs, including MMP2, and MMP9 (which are known as gelatinase A and gelatinase B, respectively) are low in mouse splenic CD4+ T cells while only other two metalloproteinases (ADAM10 and ADAM17) are highly expressed [13]. Meanwhile, during inflammation, the overproduced cytokines and chemokines in inflammatory environment promote the immune cells to generate and activate MMPs. Moreover, MMP9 is stored in the tertiary granules of neutrophils which lack the expression of TIMP [79]. It can achieve rapidly release after the stimulation of several cytokines [80]. This MMP distributing pattern and the impaired TIMP-mediated inhibition favor the early response of neutrophils to infection or to tissue damage. Meanwhile, in unstimulated state, TIMPs are expressed in a steady state in B cell and T cells. Different from B cells which highly expressing TIMP3, monocytes, which can be differentiated to macrophages or dendritic cells, are exhibiting higher levels of TIMP1 and TIMP2 as well as TIMP4 expression [81,82].

4.2.3. Effects of MMPs on tumor progression and invasion

In the case of cancer, inflammation, especially persistent inflammation has critical role in cancer progression. Meanwhile, the expression of MMPs is also intimately associated with cancer progression and with persistent inflammation [82]. And about 20 years ago, MMPs were known as playing an important role in promoting cancer progression. They favor the degradation of connective tissues and thus promote the escape of tumor cells from the originate site and the formation of metastasis. Among the host organ microenvironments, the expression of MMPs are different, and metastasis can be promoted by the combinational functions of a group of expressed MMPs [83]. Some clinical results have revealed that kinds of MMPs are detected or overexpressed in both

primary tumors and metastases of the cancer patients. They include MMP1, MMP2, MMP3, MMP7, MMP9, MMP13, and MMP14. And the expression levels of these MMPs can also be served as the indicators for the identification of tumor progression. It has also been revealed that the MMP9 in tumors is mainly produced by some of the stromal cells, such as CAFs (myofibroblasts), and inflammatory cells. They are the prevailing cell types in tumor microenvironment. However, beyond the MMPs which are serving as the positive indicators for evaluation of cancer progression, the expressions of MMP8 and MMP3 are negatively associated with the cancer progression. The expression of MMP8 in the non-metastatic breast tumor cells are significantly higher than in those acquired the ability to metastasize [84]. Meanwhile, the genetic deficiency in MMP8 and the absence of MMP3 are all promoting the development of skin tumors [85,86]. It indicates that MMPs are not all promoting the progression of cancer, some of which may serve as negative regulators to counterbalance the overactivation of the others. It may be the main reason that why >50 MMPs inhibitors used as anticancer drugs were all fail in clinical trials. They may non-targetingly inhibit the activities of all the MMPs.

Besides, while the MMPs are overexpressing, the expression of their natural inhibitors-TIMPs is also correspondently increased. For example, increased productions of both MMP9 and TIMP1 are observed in the serum of the patients with lung carcinomas. Interestingly, the expression of TIMPs is also critical in cancer progression. Beside reducing tumorigenesis and inhibiting the activities of gelatinases, overexpression of TIMPs not only has little effect on the alleviation of metastasis, but also more likely promotes the development of skin carcinogenesis [87–90].

Moreover, from the results of animal model, the expression of MMPs in primary tumor generally differs from that in metastatic site. While comparing with the primary tumors established in murine model, elevated expression of MT1-MMP, MMP2, and MMP9 are detected in lymph node and metastatic site [91]. Similar results have been obtained in numerous animal experiments. These results demonstrate that the expression of MMP2, or MMP7, or MMP9, or MT1-MMP is significantly higher in the carcinomas with more invasive and metastatic potential than that in benign tumors or in situ carcinomas [92–95]. It indicates that some of the MMPs are positively expressed with the progression of melanoma or carcinomas. The more danger the tumor is, the higher expression of these MMPs is.

Furthermore, the functions of the MMPs in tumor microenvironment seem to be confined within the tumor microenvironment. MMP9, a common MMPs which can be produced by perivascular cells and inflammatory cells and is overexpressing in kinds of invasive tumors, favor the tumor-induced angiogenesis and the development and invasion and metastasis of tumor cells [96,97]. However, these functions of MMP9 appear to be confined within the tumor microenvironment. Because the deficiency of MMP9 in mice dose not exhibit any obvious abnormalities [98].

Therefore, in summary, the only function we are sure about the MMPs is the enzymic cleavage properties to numerous proteins, which is critical important in ECM remodeling and intracellular signaling. However, the effects of the expression of MMPs on the tumor progression, especially on the metastasis are still remaining complexity to be solved due to the ambiguous variation of MMPs expression and functions during tumor progression [99]. Fortunately, some specific MMPs are identified as overexpression in the primary tumor and metastatic site. Because of their effective enzymatic cleavage to kinds of proteins, the overexpressed MMPs can be served as the very stimuli for triggering the dissociation of peptide- or protein-based or grafted nanoparticles [100].

4.3. Cleavage sequences for MMPs

The basic function of MMPs is their cleavage properties to kinds of proteins. The MMPs and their ECM substrates for cleavage are listed in Fig. 5. Notably, the MMPs are not randomly cleaving the proteins. Even in the case of same protein, different MMP types have different cleavage sites. MMPs preferentially cleaved the specific peptide sequences of the targeting proteins. Table 1 has listed the MMP cleavage site which has been identified as well as the predicted sites which can be cleaved by MMP [101].

Normally, there are existing some cleavage site motifs in the structure of targeting proteins. They are sharing some structural features which can be summarized to guide the designing of MMP responsive peptide sequences. We can define the cleavage sequence for MMPs as "… P3-P2-P1-P1′-P2′-P3′ …", and the bond between the P1 and P1′ is scissile bond for cleavage [102]. There are some requirements for the chemical structure of the motif containing in the targeting proteins for the selectively cleaving by MMPs. Generally, the amino acids at P1′ are

Table 1
The MMP cleavage site which has been identified as well as the predicted sites which can be cleaved by MMP. A) the cleavage site (amine acid sequences embedded in the natural proteins which can be cleaved by MMPs. B) the potential amine acid sequences which can be cleaved by MMP2 and the constructed MMP2 cleavable sequences. C) the existing MMP-cleavable sequences in different proteins and their corresponding MMPs. Reproduced from (Nat. Biotechnol., 2001, 19, 661). Copyright (2001), with permission from Springer Nature.

A

Protein	Cleavage site
Aggrecan (bovine)	IPEN-FFGV
Big endothelin-1	VPYG-LGSP
Brevican/BEHAB (rat)	HPSA-FSEA
Collagen-α_1 (I) (bovine)	GPQG-IAGQ
Collagen-α_2 (I) (bovine)	GPQG-LLGA
Collagen-α_1 (X)	GPAG-LSVL
Collagen-α_1 (X)	GPAG-IVTK
Decorin	DAAS-LLGL
FGFR-1	RPAV-MTSP
Galectin-3	PPGA-YHGA
IGFBP-3	LRAY-LLPA
IL-1β	GPYE-LKAL
Laminin-5 γ2-chain (rat)	TAAA-LTSC
α_2-Macroglobulin	GPEG-LRVG
α_2-Macroglobulin	GHAR-LVHV
MCP-3	QPVG-INTS
Pregnancy zone protein	ELGT-YNVI
Pro-MMP1	DVAQ-FVLY
Pro-MMP2	DVAN-YNFF
SPARC	HPVG-LLAR
Substance P	KPQQ-FFGL

B

MMP2 motif	P4	P3	P2	P1	P1'	P2'	P3'
Protein substrates	G (7) D (3) H (2)	P (14) V (2) A (2)	A (9) Q (3) V (2) E (2) Y (2) G (2)	G (8) A (3) Q (2) N (2)	L (10) F (4) I (3) Y (3)	L (4) V (3) N (3)	G (6) S (3) V (3) A (2)
Peptide libraries	I V	P V I	V A	S G A E	L M I Y	R K Y M	S A G

C

Protein	Site	Likely protease
Betaglycan (rat)	HVLN-LRST	MMP2, MMP7, MMP9
Dentin	DPES-IRSE	MMP1, MT1-MMP
Integrin-αv	DPLE-FKSH	MMP2, MMP3
Integrin-α6	RPIP-ITAS	MMP7, MMP9
Integrin-αx	RVLG-LKAH	MMP3, MMP7
Integrin-α9	KVLN-LTDN	MMP7, MMP9
NG2 proteoglycan (rat)	PPEA-LRGI	MMP1, MMP2
Neurocan (rat)	IVAM-LRAP	MMP2, MMP3
PAI-3 (mouse)	TAAA-ITGA)	MMP2

required for hydrophobic amino acids (all enzymes prefer aliphatic amino acids at this position, and phenylalanine and tyrosine are the other two alternative choices for MMP2, MMP3, MMP9, and MT1-MMP), while amino acid at P2′ can preferentially be either hydrophobic or basic. At P3′ position, different MMPs have different preferences. For example, the amino acids with small molecules, such as alanine, glycine, or serine, favor the cleavage activity of MMP1, MMP2, and MMP9. Meanwhile, methionine is preferred at P3′ for the selectively cleaving by MMP3, MMP7, and MT1-MMP (Fig. 6). Furthermore, if the amino acids at P1′ are aromatic, MMPs exhibit diverse but distinguished cleavage activities. By identifying the cleavage site at the targeting proteins for the MMPs and uncovering the underlying mechanism of the compositions of the cleavage site motif, a library of MMPs-cleavable peptides sequences can be constructed.

4.4. MMPs responsive nanomedicines: now and future

In the past decade, peptide-based or protein-based nanostructures have emerged and been exhibiting unique advantages in activated drug delivery, in situ assembling, and immunomodulating, etc. In tumor case, although various types of MMP types are positive associated with the progression of cancer, MMP2 and MMP9 are the only two MMPs which have been identified as overexpressing in kinds of tumors. Therefore, most of the functional nanoparticles constructed for MMP responsive are mainly based on the peptide-sequences which can be cleaved by MMP2 or MMP9, especially by the MMP2 [103–105]. Two peptide sequence, which have the amino acid sequences as PLGVRG and PLGLAG, respectively, are MMP2 cleavable (Fig. 7). Beyond the construction of MMP-responsive drug delivery nanosystems, PLGVRG has been used to connect the porphyrin and RGD as targeting ligand to obtain a purpurin-peptide conjugates. After the targeting delivery to tumor sites, these conjugates can be cleaved by MMP2 and the residues containing purpurin are responsively self-assembled into nanofibers in situ. It enhances the retention of therapeutic and imaging agent in tumor sites [106]).

Moreover, PLGLAG peptide or PLGC(Me)AG peptide or gelatin, which is the primary target protein for MMP2 and MMP9, can also be used to construct MMP responsive nanoparticles to enhance the efficiency in therapeutic agents or imaging agents delivering [107,108]. Besides, as the distinguished therapeutic outcome of immune checkpoint blockage strategies in tumor therapy, MMP responsive peptides can also be served as building blocks for the construction of multifunctional nanoparticles (DEAP-DPPA-1) to co-deliver IDO inhibitor (NLG919) and peptide-based PD-1/PD-L1 agonist (DPPA-1). DEAP-DPPA-1 are formed by 3-diethylaminopropyl isothiocyanate and DPPA-1 with the connection of PLGLAG. DEAP-DPPA-1 s can co-assemble with NLG919 to form multifunctional nanoparticles. The obtained drug-loaded nanoparticle can be dissociated in the tumor site by the enzymatic activity of MMP, not only accelerates the release of DPPA-1, but also triggers the release of NLG919 to further downregulate the activity of regulatory T cells [109]. Furthermore, the cleavage activity of MMPs can further improve the tumor targeting efficiency of nanoparticles to tumor cells. By MMPs-responsive peptide modification, a protective coating can be introduced to avoid the degradation of the active tumor targeting ligands during circulation. In tumor site, after the cleavage of MMPs, the ligands re-exposure, which enhances the opportunity of the ligands recognized by the receptors. By this way, active tumor targeting can be achieved [110,111]. Moreover, by introducing the tumor targeting ligands into the terminal of the MMP-responsive peptide, tumor-targeting combining with MMP-responsive drug delivery and controlled release behavior can be also achieved [112–114]. These strategies form the main streams of the construction of MMPs-responsive nanosystems. We can also conclude that the intratumoral fate of the MMPs-responsive nanoparticle is but not limited in structural dissociation, degradation and promoting the reassembling of the remains. It favors the realization of actively accelerated drug release or active tumor-targeting and tumor microenvironment remodeling.

In fact, the MMPs are just only one kind of enzymes that can be used to construct enzyme responsive nanostructures. The enzymes which can be used as the stimuli are extensively and systematically reviewed in some other reports [115]. These enzymes include acid phosphatase (AP), protein kinase A and MMPs, etc. Besides, another enzyme named as legumain which is mainly distributing in lysosomes can also be used to cleave some specific peptide sequences. Legumain can hydrolysis the –Asn-Xaa-bonds in proteins and small molecules. By fine designing, the legumain responsive peptides modified gold nanoparticles can take place aggregation in the enzymatically catalyzation of legumain, thus, increase the retention of gold nanoparticles in brain tumor sites [116–118].

The constructions and applications of enzyme-responsive nanoparticles have been extensively reviewed. Most of these reviews are not reviewing from the aspect of the biological functions, secretion, distribution of these enzymes as well as their effects on the progression of the diseases. It may lead to a limited conception for the design and construction of functional nanoparticles. That is why we pay so much attention on the biological functions of MMPs in this section.

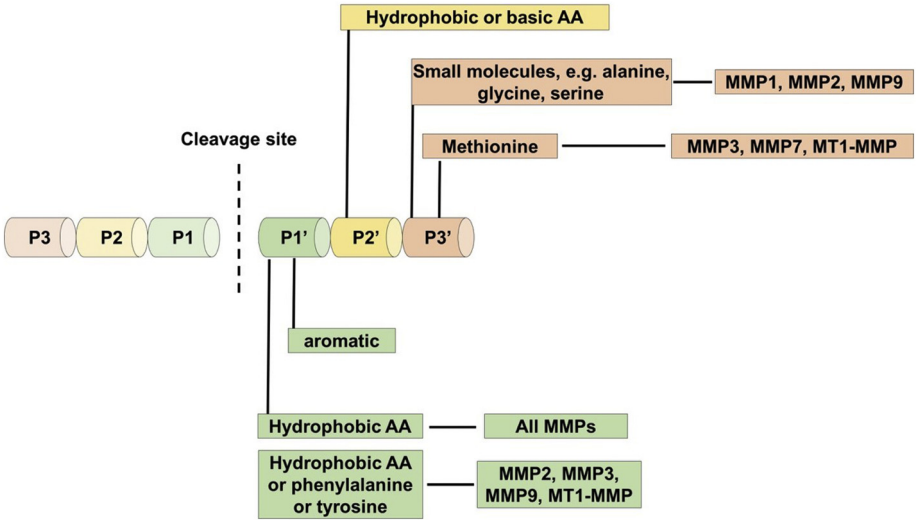


Fig. 6. Some of the requirements for the amino acid (AA) structure around the cleavage site.

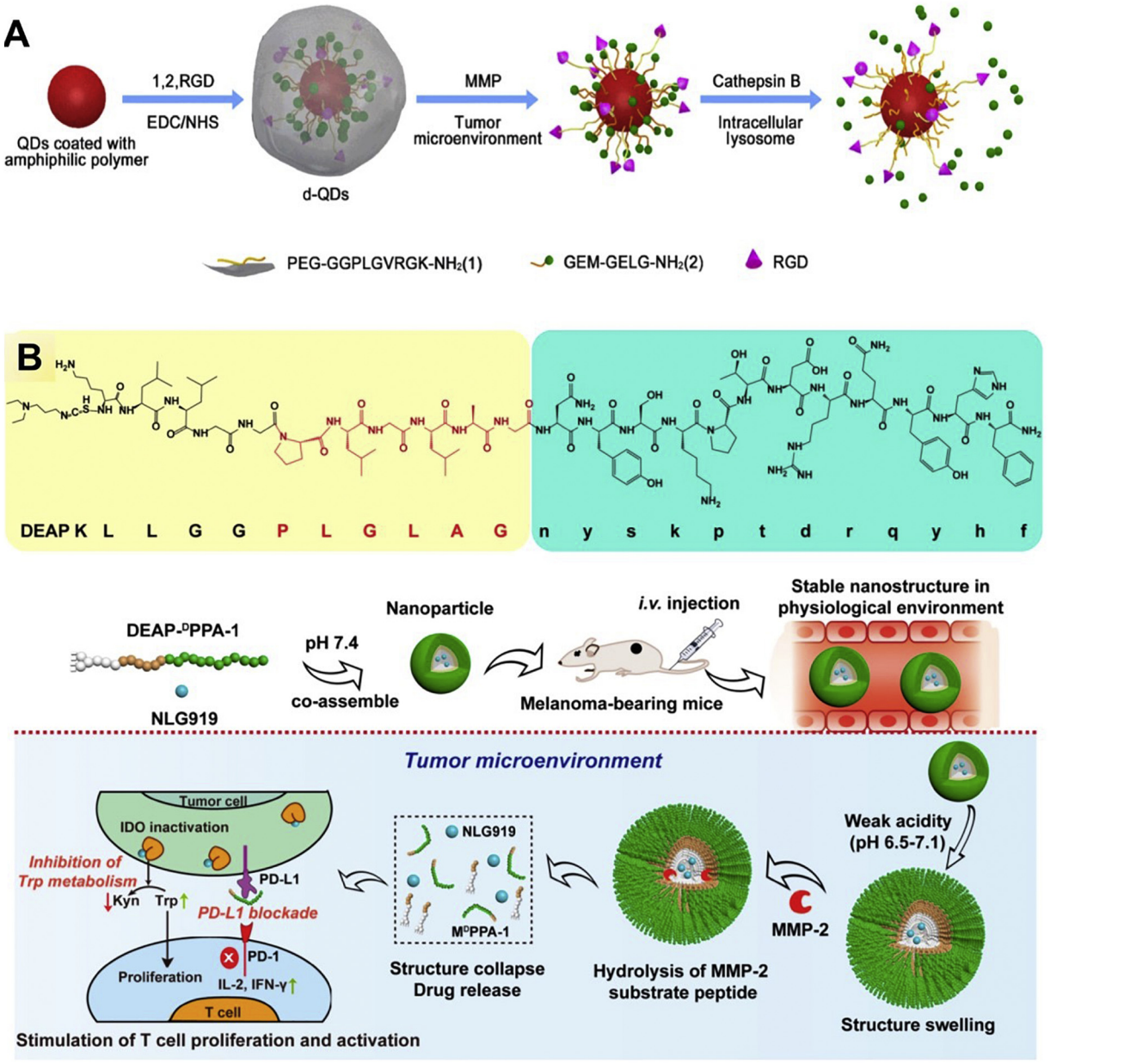


Fig. 7. The applications of MMP2 responsive peptide motif for the construction of MMP2 responsive nanoparticles. Two peptide motifs were exemplified: A) PLGVRG and B) PLGLAG. A) Adapted from (*ACS nano*, 2017, 11, 1281–1291.) Copyright (2017) American Chemical Society. B) Adapted from (*Nano Lett.*, 2018, 18, 3250–3258). Copyright (2018) American Chemical Society.

In summary, from the above discussion, we can conclude that the MMPs not only cleave the scissile peptides to dissociate the structure then accelerate the release of therapeutic or imaging agents, but also induce the aggregation of the residues cleaved by MMPs to form fibrous structure or gel structure to regulate the cellular functions in situ. Structural reconfiguration is the main effect that the MMPs interact with MMP responsive nanoparticles. Although progresses have been achieved in the development of MMP responsive nanoparticles, some challenges are still remained to be solved. First, thoroughly understanding of the biological functions of MMPs and their development during the progression of the diseases is foremost important as it provides the basic biological foundation for the design and construction of nanoparticles. Second, the effect of the architecture and configuration of the MMP responsive motifs in the constructed nanoparticles on the cleavage activity of MMPs remains unclear. If the MMP responsive motif locates in the core of the nanoparticles, could the MMPs access into the core and do their cleaving job?

5. Tumor acidity and pH-responsive nanomaterials for tumor diagnosis and therapy

5.1. Formation and distribution of tumor acidity

Tumor acidosis is a ubiquitous feature of the tumor microenvironment (TME) in solid tumors, which is extensively studied by far [119]. It is related with tumor hypoxia and extracellular lactic acid accumulation. It uses to be considered the tumor acidity is result of hypoxia. The recent findings reveal that the tumor acidity is the result of a complex metabolism process which including the response of tumor to hypoxia, H^+ and HCO_3^- transportation, tumor respiration, and extracellular H^+ venting. The hypoxia induces HIF1α, a transcription factor, to further increase the generation of pyruvate [120]. It promotes the cancer cells to change their glucose metabolism way to adapt the hypoxic environment. Meanwhile, energy and biosynthetic intermediates were also generated to tumor cells in the environment with limited O_2

supplement. And in hypoxia environment, the glycolytic flux will be further aggregated due to the overexpressed HIF-α may further upregulate the transcription and expression of lactate dehydrogenase A (LDHA) and the monocarboxylate transporter 4 (MCT4), which are all critical in H+ generation and transportation. LDHA can convert the pyruvate into lactate, consequently, the MCT4 help to transport the lactate out of the cells. It is a lactate/H+ symporter. However, the driving force of the MCT4 in lactate transportation is concentration gradient dependent. If the concentration of lactate in extracellular TME raise, the MCT4 mediated lactate transportation will be attenuated. Therefore, it needs the help of other pathway to co-transport the H^+ out of the cells. It has uncovered that the H+-ATPases and Na^+/H^+ exchangers (NHEs) are also acting the role of transporter to maintain the H^+ efflux from the hypoxia-bearing cancer cells. The H^+ transportation mediated by these extruders are energy-dependence. This is a depicted model for H^+ generation in the deep hypoxia (MCT4 and NHE1) and normoxic region (MCT1, ATPase and NHE1) of the tumor. It seems that the deep hypoxic and normoxic regions are all acidic. However, in actually, the normoxic region is near-neutral. Because the normoxic regions are near to tumor blood vessels, the released H^+ ions into the extracellular medium of the normoxic region can be washed out by venting into the bloodstream. Therefore, the extracellular pH (*p*He) value of the normoxic region is higher than 7.0 (7.0–7.4). In the deep hypoxic region, the detected *p*He is about 6.7–6.9, and some studies also report that the deep hypoxic region is not the most acidic or hostile environment in the surrounding microenvironment of a tumor, but the region under mediate hypoxia is. Because under the condition of moderate hypoxia, the mitochondria-mediated pyruvate oxidation is co-occurring with the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). By combining with the cristae remodeling, the efficiency of respiration of the cancer cell is optimized to adapt the moderate hypoxic condition. During the respiration, the production of CO_2 (two CO_2 molecules can be generated by each acetyl-CoA) further increase the acid production of oxidative cancer cells. And the nonpolar CO_2 can freely diffuse to the external environment, which also favor the increase of the extracellular concentration of CO_2 to further accelerate the hydration of CO_2 to HCO_3^- and H^+. At the same time, the produced extracellular HCO_3^- can be transported into the cells to titrate the excess intracellular H^+ ions by hypoxia-independent transporters – the Na^+/HCO_3^- co-transporters (NBCs). According to this mechanism, the region under the condition of moderate hypoxia is expected to be highly acidic [25]. However, the measured *p*He of these region is about 6.9, and relative stable even the distance from the nearest blood vessel increases. The mechanism of how the physiological system to regulate the *p*He of this region remains unknown. But by combining with the measured data, we can get a relative detailed distribution or value of the tumor acidosis. It is the foundation for pH-responsive nanoparticles design and construction. We have depicted the recent findings about tumor acidosis in Fig. 8 for better understanding.

Besides, the intracellular pH (*p*Hi) value of the cancer cells is different with that of the normal cells. The *p*Hi of cancer cells is a little alkaline (pH > 7.4) and higher than the normal cells (~7.2), while the *p*He of cancer cells is acidic (6.5–7.0) and lower than the normal cells (~7.4) [121]. This is the results of a complicate metabolic mechanism that the tumor cells used to adapt the hostile extracellular environment. The alkaline intracellular condition favors the promotion of the proliferation of cancer cells and prevents the cancer cells from apoptosis [122]. Moreover, the *p*Hi we discussed here represent the pH value of cytosol. Inside the tumor cells, the pH of different subcellular compartments or organelles is different with each other.

Although the *p*Hi or *p*He of tumor cells are different with normal cells, and some proteins, such as $2Cl^-/^1H^+$ exchanger Cl^- channel 5 (CLCN5), CLCN6, CLCN7, etc. in cancer cells take place mutations, the pH gradient or distribution of the subcellular compartments inside tumor cells are surprisingly not perturbed and similar with normal cells (the underlying mechanistic basis still need to be further investigated). The most alkaline organelle is mitochondria (pH~8.0), while the most acidic subcellular compartment is lysosome (pH~4.7). And what's more important in drug delivering is the pH continuous changes during endocytosis: ~6.3 in early endosome, ~5.5 in late endosome, and ~4.7 in lysosome (Fig. 9). This progressive luminal acidification plays a key role in realizing the functions of endocytosis and

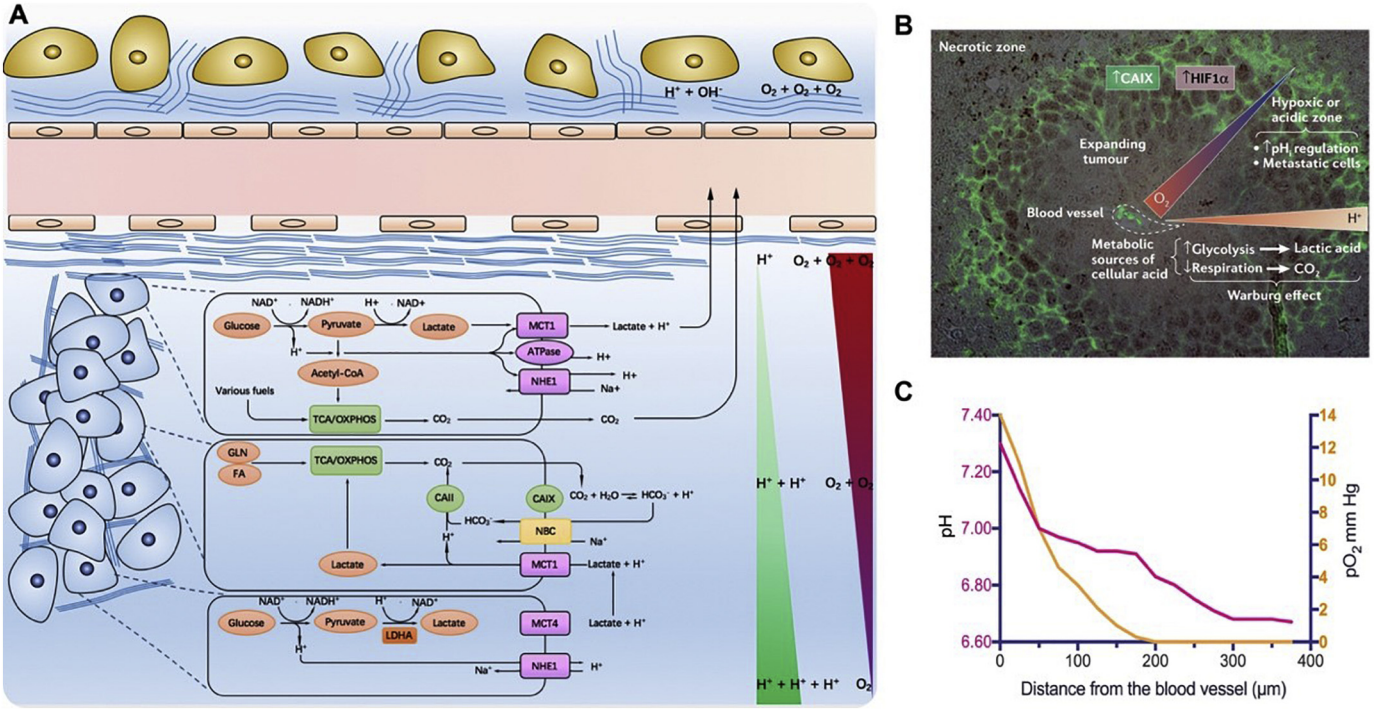


Fig. 8. The intratumoral pH features: acidity. A) The metabolic mechanism inside tumor. B) An image of a xenograft tumor which has been revealing the variation of protein expression that is driven by O_2 and H^+ gradients. C) the pH and pO_2 value vs distance from blood vessel in the tumor tissue. B was adapted from (*Nat. Rev. Cancer*, 2013, 13, 611–623), Copyright (2013), with the permission from Springer Nature. C was reproduced from (*Nat. Med.*, 1997, 3, 177–182). Copyright (1997), with the permission from Springer Nature.

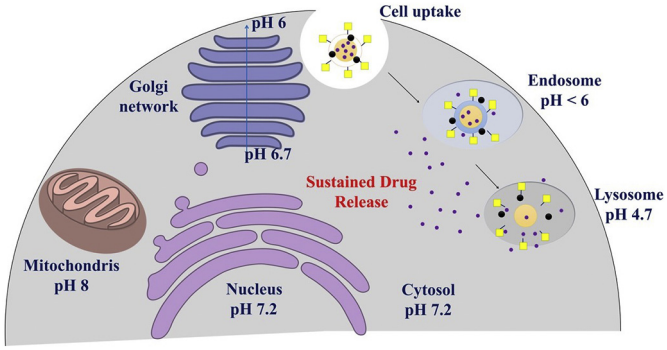


Fig. 9. The intracellular pH environment. The pH gradient or distribution of the subcellular compartments inside tumor cells are similar with normal cells.

phagocytosis, which including uncoupling of ligands and receptors, protonation of microbicidal factors, and activation of proteases, etc. It is noteworthy to mention that the delivery systems need to have the ability of endosomal escape to avoid the degradation of cargos in lysosome in biomacromolecules delivery [123].

Now, we have depicted an outline of the formation and distribution of tumor acidity, including extracellular pH gradients and intracellular pH gradients, respectively. Apparent, the gradient differences among different regions of the tumor or the subcellular compartments are subtle. And these little differences have significantly changed the metabolic pathway and the related cellular functions of tumor cells and their surrounding microenvironments. According to this outline, we can design and construct more suitable pH-responsive nanoparticles to deliver the cargos to the tissues or cells or organelles with much more precise cargo release behavior, which can enhance the outcome of diagnosis or therapy with minimum cargo dose, although there is still a long way to go and numerous obstacles need to be overcome. Meanwhile, as the accompanist of acidity, hypoxia is also a unique and ubiquitous feature in tumor. Some hypoxia-responsive molecules have been reported, such as tirapazamine (TPZ), or the AQ4N [124,125]. These molecules, however, are utilized as drugs but not as the building blocks of hypoxia-responsive nanoparticles. To our best knowledge, no hypoxia-responsive nanoparticle has been reported. Therefore, we will pay less attention on the development of hypoxia-responsive nanoparticle.

5.2. pH-responsive units for the construction of pH-responsive nanocarriers

In the following, we are going to discuss some of the most recently findings in the construction and application of pH-responsive nanoparticles in cancer diagnosis and therapy. Before this, we first list some of the pH-responsive bonds or groups used to construct the nanoparticles for cargos delivery (Table 2). The groups or bonds are listed according to the descending order of *p*Ka, because the *p*Ka represents the critical transition of the groups. It exhibits that not only the groups or bonds those used to synthesize polymer can be used to construct pH-responsive nanocarriers, but also the inorganic structure, e.g. calcium-based salts, etc. All these groups or nanosystems and their applications in diseases diagnosis, therapy or theranostics have been systematically reviewed in some other articles [126]. In here, we are going to add the responsive pH spans of some groups, and help the readers to define and find which groups are ultrasensitive. It can provide some guidelines for the selection of responsive groups to prepare nanoparticles to target specific environment with subtle pH gradients. Furthermore, the pH-responsive mechanisms of the groups include ionization (hydrophobic-hydrophilic transition), bond-cleavage, and dissociation. It provides diversity for the construction of pH-responsive nanoparticles for cargos delivery in tumor diagnosis and therapy.

5.3. pH-responsive nanomaterials for tumor diagnosis and therapy

The application of pH responsive nanoparticles in tumor diagnosis and therapy have been highlighted since the emerging of functional nanoparticle due to the unique and ubiquitous features of tumor acidity. The main action of pH responsive unit-constructed functional nanopartilces is cleavage or protonation [168,169]. Cleavage normally happens in pH sensitive covalent bonds. And protonation is the main force driving the dissociation of assembled pH responsive nanosystems. Because of their various compositions and responsive mechanism, we are going to first exemplifying some of the recently developed nanostructures and their applications in sensitive tumor diagnosis and therapy, and then find out how these nanostructures end up intratumorally. It may help us figuring out what the challenges are still impeding their application in ultrasensitive diagnosis and activated therapy.

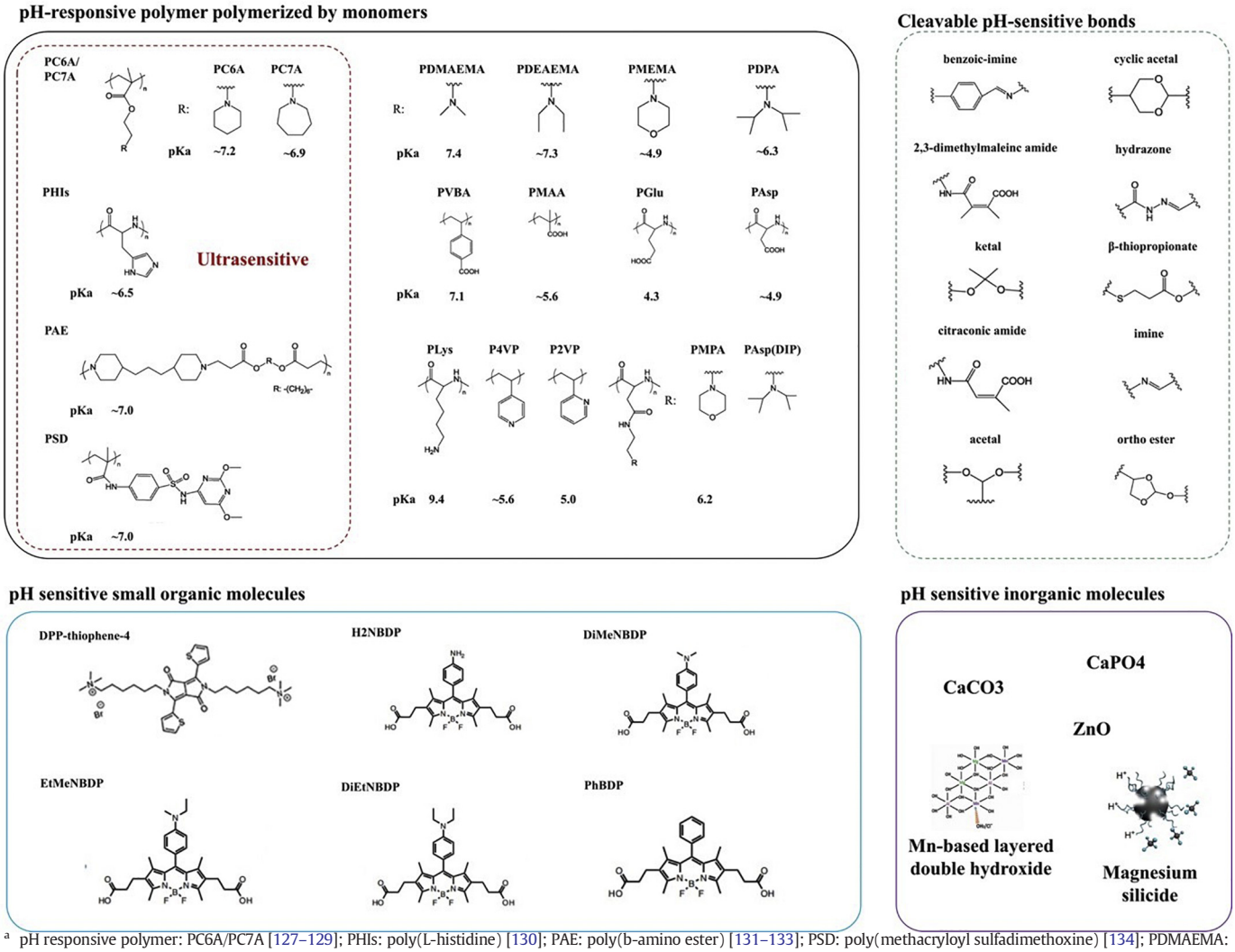
Heterogeneity is a ubiquitous feature of malignant cancer, which makes not only the intratumoral microenvironment much more complicated, but also the intertumoral characters of different types of cancers more distinguished [170]. As a result of heterogeneity, it is hard to establish a therapeutic strategy which is suitable for all type of cancers. Although by introducing active tumor-targeting ligands (peptide or antibody, etc.) which indeed enhanced the inhibition of the tumor progression in vivo, more ideal and more ubiquitous strategies still need to be developed. However, before we construct the strategies, we need to identify the features shared by different types of cancer. The founding from tumor microenvironment has indicated that acidity is a hallmark of cancers. Acidity is the result of dysregulated glycolysis, can promote the proliferation, evasion, invasion and metastasis of cancer cells [171]. It can be a target while constructing diagnostic and therapeutic strategies for cancer.

Numerous pH responsive nanomaterials have been developed for tumor diagnosis and therapy. But we are not going to list all of these nanosystems. In here, we are going to discuss some of the nanomaterials which can be used to enhance the accuracy or significantly amplify the signals and be used to enhance the therapeutic outcome with minimum adverse effects while activated by the change of pH gradients in tumor diagnosis and therapy. Therefore, some of the imaging technique are not exemplified for their signal intensity is mainly depended on the contrast agent themselves instead of the involvement of pH stimulation. Take positron emission tomography (PET) imaging technique for example. The signal intensity of PET is mainly depended on the concentration of radioactive elements, which is the accumulation of radioactive elements in tumor site for tumor diagnosis. And the accumulation of radioactive elements is controlled by the delivery efficacy which is not depended on the concentrations or compositions of the environmental factors. The pH gradients cannot help to enhance the signal intensity of PET, even the radioactive elements are delivered by the pH-ultrasensitive nanoparticles, such as ferritin (which has a pKa~6.8, a highly symmetric nanoparticle with the hydrodynamic diameter of 12 nm can be formed by 12 ferritin). And in the case of tumor therapy, all the responsive nanomaterials are designed to optimize the cargos delivering efficacy and attenuate the side-effects of some anti-cancer drugs. It is different with tumor diagnosis. Therefore, we will first simply illustrate some of the pH responsive nanoparticles used to enhance the anti-cancer properties via activated drug release, then we will mainly focus on some of the interesting therapeutic strategies developed recently.

5.3.1. Precise and activated tumor diagnosis

5.3.1.1. Magnetic resonance imaging (MRI). Different molecules or molecular complexes have different MRI signals (which are also defined as relaxation rates). And the relaxation rates of some molecules can take place dramatic change after reacted with other molecules. Manganese (Mn) is one of these molecules. Itself or its ionic isoform has relative low relaxation time in T1 mode MRI. When its ionic isoform combines

Table 2
pH responsive units for the construction of pH responsive nanoparticles[a]



[a] pH responsive polymer: PC6A/PC7A [127–129]; PHIs: poly(L-histidine) [130]; PAE: poly(b-amino ester) [131–133]; PSD: poly(methacryloyl sulfadimethoxine) [134]; PDMAEMA: poly(2-(dimethylamino)ethyl methacrylate) [135,136]; PDEAEMA [137,138]. PMEMA & PVBA: poly(2-N-(morpholine)ethyl methacrylate) & poly-(4-vinylbenzoic acid) [139]; PDPA [140,141]; PMAA: polymethacrylic acid [142,143]; PGlu: poly(glutamic acid) [144]; PAsp: poly(aspartic acid) [145]; PLys: poly(L-lysine) [145–147]; P2VP: poly(2-vinylpyridine) [148]; P4VP: poly(4-vinylphenyl phosphate) [149]; PMPA: poly((3-morpholinopropyl)-aspartamine) [146]; PAsp(DIP): poly(N-(N0,N0-diisopropyl-aminoethyl)aspartamide) [150]; pH cleavable units: Benzoic-imine [151]; 2,3-dimethylmaleic amide[152]; Ketal [153]; Citraconic amide [154]; Acetal [155]; Cyclic acetal [156]; Hydrazine [157–159]; β-thiopropionate [160]; Imine [161]; Ortho ester [162]; pH responsive small molecules: DPP-thiophene-4 [163]; NBDPs [164]; pH responsive inorganic materials: $CaPO_4$ [165]; Mn-based layered double hydroxide [166]; Magnesium silicide [167].

with the proteins, e.g. albumin, the relaxivity of the formed Mn-protein complexes significantly increase which enhance the contrast in T1 MRI. Different with some other engineered nanoparticles developed as contrast agents which has stimuli-responsiveness, stimuli-sensing MRI contrast agents with signal nonlinearly amplification are also desirable. Based on this mechanism, the nanoparticles which can deliver Mn^{+} or its precursors with activated release switch have been designed to amplify the MRI signal. Because the ionic isoform of Mn (Mn^{2+}) is water soluble, it is an obstacle to efficient deliver it to the disease site. Fortunately, Mn^{2+} can conjugated with kinds of groups, including carboxyl groups, porphyrin, etc. It can be confined within calcium phosphate (CaP) nanoparticles to obtain PEGMnCaP. Inside the chemical structure of PEGMnCaP, CaP is pH sensitive and can disintegrate, poly(glutamic acid) is used as the matrix for Ca^{2+} or Mn^{2+} confinement, while PEG is used to stabilize the hybrid nanosystems. At a low pH, pH~6.5–6.7 for example (which is the *p*He range in solid tumor), the disintegration of CaP triggers the release of Mn^{2+} which can bind to albumin then amplify the MRI signals. The T1 relaxivity coefficient (r_1) of PEGMnCaP in the environment at pH 7.4 with the absence of protein is 2.57 ± 1.8 $mM^{-1}\ s^{-1}$, which has no significant difference with in a protein-rich environment at pH 7.4 (4.96 ± 2.8 $mM^{-1}\ s^{-1}$). Oppositely, in acidic environments (pH ranges at 6.5–6.7), remarkable increases of r_1 were observed from 4.27 $mM^{-1}\ s^{-1}$ to 15.26 $mM^{-1}\ s^{-1}$ and from 4.73 $mM^{-1}\ s^{-1}$ to 19.96 $mM^{-1}\ s^{-1}$ after the PEGMnCaP were exposed to proteins at pH 6.7 and at pH 6.5, respectively [165].

Although the PEGMnCaP provides a comprehensive and effective strategy for enhancing the contrast signals and the results are significant and profound, the enhancement is mainly ascribed to the binding of Mn^{2+} with proteins, and the pH gradients are just accelerating the release rate of Mn^{2+} from the nanoparticles. In this aspect, the pH gradients are not enhancing the MRI signals of contrast agents directly. Recently, a kind of Mn-based layered double hydroxide (Mn-LDH) nanoparticles have been developed. It has a narrow pH-responsive range (pH 6.5–7.0). The longitudinal relaxivities (r_1) were 1.16 $mM^{-1}\ s^{-1}$ at pH 7.4, 6.82 $mM^{-1}\ s^{-1}$ at pH 7.0, 7.60 $mM^{-1}\ s^{-1}$ at pH 6.5, 8.24 $mM^{-1}\ s^{-1}$ at pH 6.0, and 9.48 $mM^{-1}\ s^{-1}$ at pH 5.0, respectively [166]. This system is designed to directly use the pH gradient to enhance the signal intensity of the contrast agent. It is a promising

candidate for specific sensing of tissues with pH gradients (tumor tissue, or tumor cells, even the intracellular pH detection, etc.), although whether the MRI signal variation is reversible or not still need to be further evaluated.

5.3.1.2. Fluorescent imaging probes. Another technique which is promising in activated tumor diagnosis is fluorescent imaging. Kinds of agents have been developed and used to detect tumors, including dyes, quantum dots, carbon dots, etc. Although there are still some obstacles need to be solved before its clinical translation, such as low quantum yield, low penetration in tissues, low resolution, and low precise in 3D localization which is also hard to be reconstructed the signal source, etc. some strategies developed to achieve tumor diagnosis with sufficient sensitivity and specificity and minimize the background signal original from non-target tissues provide some valuable guidelines for the designs and applications of the probes for precise tumor diagnosis. Different from the conventional strategies those used the nanoparticles to passively deliver fluorescent probe to the tumor site then detect the fluorescent signals directly, the strategies used the probes with the properties of actively enhancing fluorescent intensity attract more attention in precise detection of tumor localization.

Homo-fluorescence resonance energy transfer (homoFRET)-induced fluorescence quenching can dramatically attenuate the fluorescent signal of dyes. In the opposite way, when the dye molecules disintegrate from compacted aggregation to separated molecules dispersion, the enlarged distance among the molecules can eliminate the homoFRET-induced fluorescence quenching, which can result in a dramatic increase of the fluorescent signal intensity. It is the basic mechanism that used to guild the construction and development of pH-activated fluorescent nanoprobes for tumor activated diagnosis. And kinds of nanosystems have been developed to fulfill the requirement for precise tumor diagnosis in vivo. A series of copolymers which compose with tertiary amine containing groups and poly(ethylene oxide) segment as the backbone of the polymer chain, and tetramethyl rhodamine (TMR), was also introduced into the polymer chains as side groups, which also serve as model fluorophore and imaging beacon. By adjusting the chemical structure of tertiary amine containing segments (PR segments), we can adjust the fluorescence transition pH values (pH_t). For example, when the side groups of the tertiary amine containing segments are linear dialkyl, change the chain length from methyl to butyl, the pH_t are changed from no pH response to 7.3 (ethyl), 6.3 (isopropyl), 5.4 (butyl), with the ΔpH 10–90% (the range of pH values in which the normalized fluorescence intensity (NFI) varies from 10 to 90%) changed from no pH response to ~2.5 (ethyl), 0.24 (isopropyl), 0.21 (butyl), respectively. The small ΔpH 10–90% values indicate the remarkable pH sensitivity. Besides, when the side groups of the tertiary amine containing segments are cyclic, by changing the ring size, the pH_t change from ~8.5 (five-membered rings) to 7.2 (six-membered rings), and 6.8 (seven-membered rings), with the ΔpH 10–90% values change from ~2.3 (five-membered rings) to 0.23 (six-membered rings), and 0.20 (seven-membered rings), respectively. While the pH values higher than the pH_t, the neutral PR segments are nonionic and become the hydrophobic core of the micelles, which quenches the fluorescent signals as a result of fluorophores aggregation via homo-FRET between the fluorophores molecules.

Numerous results have demonstrated the potential of pH-sensitive nanoparticles in drug delivery applications [172–176]. However, responsiveness still needs to be further improved, not only the responsive pH range, but also the responsive time. And some of the pH sensitive dyes are also facing the same problem as well as the broad ΔpH [164]. In opposite, the copolymer micelles formed by PEG-PR not only have narrow sharpness values and large ratios of Fmax and Fmin (Fmax, the maximum fluorescent signal intensity, Fmin, the minimum fluorescent signal intensity), but also have a shorter lifetime of the fluorophores in excited state (0.44 ns for nanoprobe (isopropyl); 1.97 ns for free fluorophores, at pH 7.4) and very fast fluorescence activation (shorter then 5 ms at the pH value lower than the pKa values [127]. They are suitable for tumor diagnosis for their controllable pKa and responsive time and ability of signal enhancement. In the later research, the results reveal that the nanoprobes exhibited rapidly activation in response to the low extracellular pH in tumors with the signal intensity being enhanced by >300 folds, although the physiological pH transitions (or gradients) are subtle. And a wide range of mouse cancer models can also be detected by using these nanoprobes. By combining with their low-toxic, these fluorescent nanoprobes can be severed as the ideal reporters for tumor microenvironment detection due to their nonlinear signal amplification in response to tumor microenvironment (Fig. 10) [177].

Moreover, imaging-guided surgery is an effect manner to eliminate the tumor margins remained during the surgical resection. However, most of the tumor margins are invisible and hard to eviscerate entirely, such as mammectomy, which lead to the unnecessary resection of the tissues around the tumors. The lack of imaging technique with high specificity and resolution is the main obstacle which impede the precise resection, although some ingenious strategies have been developed [178]. The tumor remains after surgical excision maintain the microenvironments which are similar with the tumor mass, in solid tumor, for example, are also acidic. The PEG-PR copolymer micelles can also be used to guild the surgical excision of the tumor margins. Used the PEG-PR with the pHt = 6.9, the fluorescence signal in the tumor over that in the surrounding normal tissues can be nonlinearly amplified. And the output signals are discretized and binary with a spatial resolution smaller than 1 mm. It provides an efficient probe not only able to image a broad range of tumors in mouse models under the visualization of a variety of clinical cameras, but also able to perform real-time tumor acidity-guided detection and surgery excision of occult nodules (<1 mm3) in head and neck or breast tumor-bearing mice [179].

Beyond the polymer-based pH-responsive fluorescent nanomaterials, supramolecular systems also have the potential to realize the goal of extremely sharp responsiveness to pH gradients. A homoFRET-induced quenching nano-assembly formed by A small molecule (DPP-thiophene-4) has been reported recently. When the pH is higher than 7.0, the nano-assembly maintained its assembled form to quench the fluorescence, while the pH is lower than 6.8, the nano-assembly disassemble back to DPP-thiophene-4 monomers and simultaneously amplify the fluorescent signals. It is similar with the PEG-PR micelles. The transition pH of DPP-thiophene-4 is ~6.9, with a ΔpH 10–90% of 0.2 (6.8 to 7.0). Within a 0.2 pH unit gradient (7.0 to 6.8), the fluorescence signal intensity increases by 10-fold, which is also a nonlinear amplification. Although it may be lack of the research results of the tumor-targeting diagnosis by intravenous administration, the mechanism of pH gradient induced self-assembling and primary biosafety have been clarified and evaluated. More important, it provides a promising choice for the construction of pH ultrasensitive probes beyond polymer-based or inorganic based nanomaterials (Fig. 11) [163].

5.3.2. Precise and activated tumor therapy

Since the emergence of activated therapy, kinds of drug containing nanoparticles have been fabricated to achieve activated drug release with the activation of pH gradients. The construction strategies include being physically encapsulated into the pH response nanocarriers, or being chemically conjugated into the active groups of the nanocarriers with pH sensitive bonds (which can be broken at acidic environment). And numerous anticancer drugs have specific targets, which means they have to be delivered to the desired sites. For examples, DOX or CPT or cisplatin etc. activate the anti-cancer properties while being embedded into the DNA sequences during transcription (which mainly happen in the nucleus), meanwhile, the PTX or DTX take action in the cytosol by interacting with the tubulins to inhibit the proliferation of tumor cells. Therefore, it requires the delivery systems have the precisely controllable drug release. We have known that the pHe and pHi

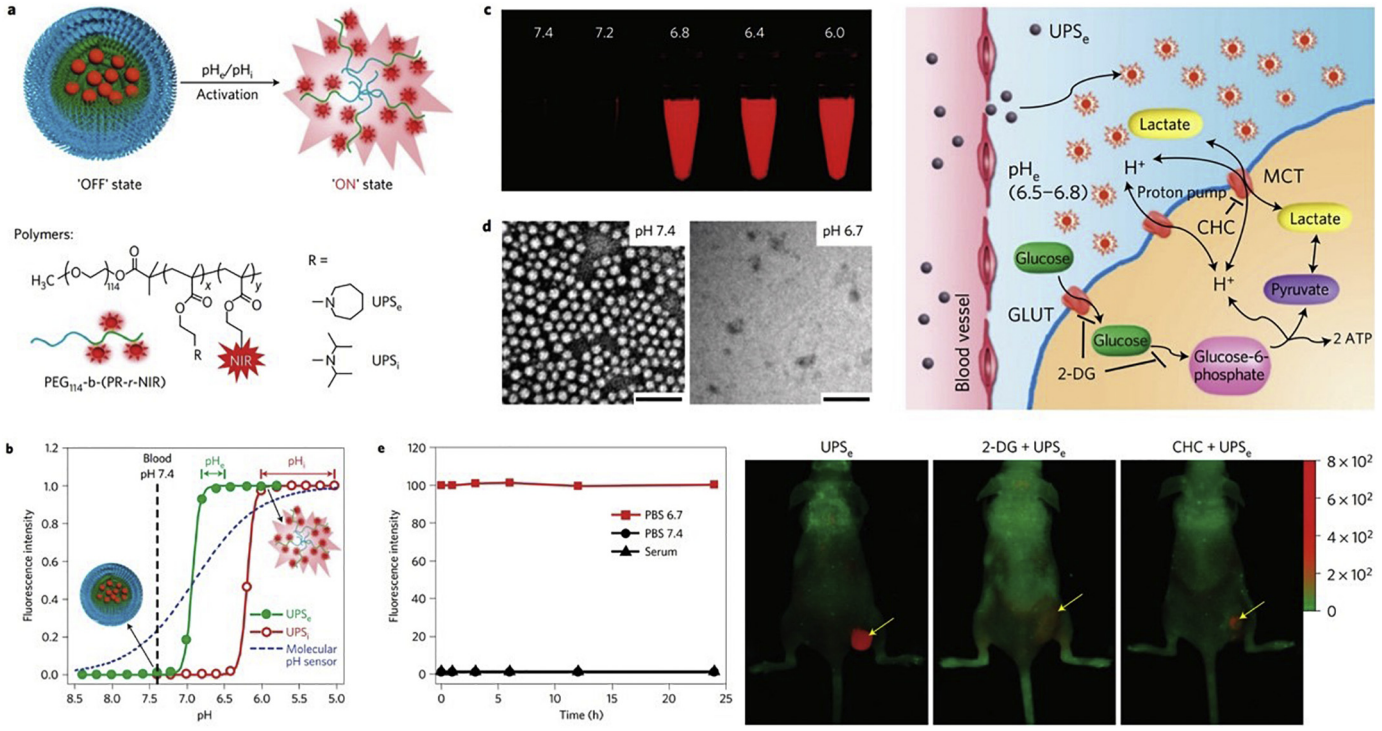


Fig. 10. The ultrasensitive PEG-PR nanoparticles for non-invasive molecular imaging of cancer. Adapted from (Nat. Mater., 2013, 3, 204). Copyright (2013), with permission from Springer Nature.

of the tumor have different pH gradients, e.g. 6.5–7.0 for pHe, 4.5–6.3 for endosome process, etc. The goal of pH responsive drug nanocarriers is of precisely delivering the cargos to the expected site and releasing at the specific pH environments. Besides, in situ formation of materials after the activation of pH gradients is also a promising therapeutic manner for cancer treatment, it includes blood vessels blocking, in situ gelation, etc. Moreover, some molecules have the properties that are not toxic in neutral environments, but become high cellular toxic after the activation in acidic environment. And by blocking the tumor-targeting ligands with pH activated bond which can take place cleavage, activated tumor targeting can also be achieved. It improves the low enrichment of some ligands modified nanomedicines in tumor site, even they have favorably active tumor cell-targeting in vitro.

5.3.2.1. Drug delivery. pH responsive nanomaterials have been widely used to deliver anticancer drugs to achieve activated drug release in specific site. Physically encapsulation and chemically conjugation by pH responsive nanomaterials are the two main manners used for nanomedicines construction. In the case of physically encapsulation, the pH sensitivity for activated drug release mainly base on the inherent pH sensitive of the materials of nanocarriers. These nanomaterials have the features of bulk structure variation (including expansion and shrinkage) to accelerate the diffusion of drugs or systemic disintegration to expose all the drugs in the mediums. In the case of chemical conjugation, unlike to the bulk structure variation, the drug release is controlled by the cleavage of the bonds formed between drugs and the backbone of the nanomaterials. The integrate structure of the nanomaterials is generally remained [180]. Either by physical encapsulation or chemical conjugation, the activation of drug release depends on the sensitivity of the bonds which are used to build the nanomaterials or to conjugate drug molecules into the nanomaterials. Kinds of pH sensitive bonds have been used to construct pH sensitive nanomedicines, some of the most widely used are listed in Table 2. We are not going to discuss which strategy is better, because the underlying mechanism is similar, which the differences are the types of bonds, the methods of synthesis, and the types of anticancer drugs. What noteworthy to be further discussed are the controlling of bonds cleavage or structural disintegration at subtle pH gradients. We know that there are existing a series of pH gradients inside tumor tissues and in tumor cells. And the difference of pH between adjacent tissues or subcellular compartment is very tiny. How to further narrow the ΔpH and shorten the responsive time is the main problem. Some ultra-pH-sensitive bonds are used to conjugate anticancer drugs. The cleavage pH is at 6.8. When these nanomedicines enter into the pH 6.8 environment, the drugs are released. It may favor the enhancement of the anticancer outcome of chemotherapy. However, if the drugs are DNA damagers, the pH 6.8 is the extracellular pH, the drugs are released in the extracellular environment, they still face the obstacles of endocytosis and drug resistance mediated by P-glycoprotein as well as the further pump back to the circulation under the high pressure of tumor tissues. During the drug release process, the cleavage of bonds is also a time-consuming process. It indeed enhances the accumulation of drugs in tumor and reduces drug-induced adverse effects. Even though, we still cannot find a series of drug containing nanomaterials which are build up by pH sensitive groups similar with the PEG-PR described above to precisely control the cleavage pH via the same preparation procedure. The main reason for this is the insufficiency of pH ultrasensitive bonds for pH sensitive nanomedicines construction. Meanwhile, while the pursuing of pH ultrasensitive bonds is still struggled ongoing, some strategies beyond conventional drug delivery by nanomaterials for cancer therapy have been invented by using the pH gradients of tumor tissues or tumor cells.

5.3.2.2. Vascular blocking. Vascular blocking is an effective way for tumor growth inhibition. It blocks the transportation of oxygen and nutrients from being received by highly proliferated and grown tumor mass. Although some latest researches have indicated that the vascular blocking may further promote the metastasis, vascular blocking is still the main treatment for cancer therapy. Most of the vascular blocking manners focus on the regulation of some vascular structure formation related growth factors or receptors, which including VEGF, EGF, EGFR, PDGF, etc. physically directly vascular blocking is only performed in embolotherapy of some cancer types, e.g. hepatoma, by being minimally

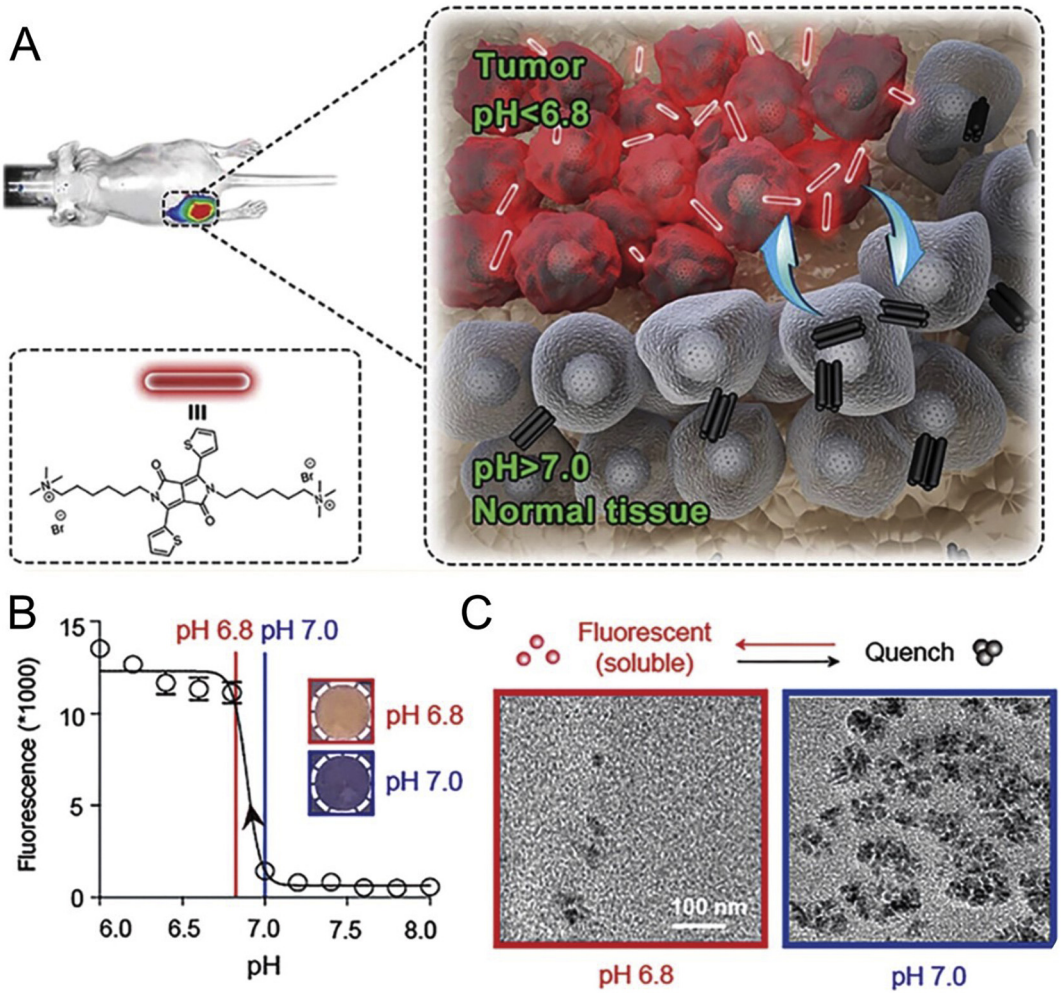


Fig. 11. pH responsive nanostructure form by the pH ultrasensitive small molecules. DPP-thiophene-4 can self-quench in the pH environment higher than 7.0, but dissociate while pH is lower than 7.0. A) Scheme for the in vivo tumor imaging mediated by DPP-thiophene-4 assemblies. B) the transition pH of DPP-thiophene-4. C) the morphological change of DPP-thiopheen-4 assembles in different pH environment. Adapted from (ACS nano, 11 (2017) 12446–12452). Copyright (2017), American Chemical Society.

invasive injected of microspheres which can deposit in the vascular structure of the tumors and impede the nutrient transportation between the tumor tissues and blood vessels. Nanoparticles are hard to be deposited in the vascular network inside tumor to block the flowing of blood for their small sizes. pH responsive nanoparticles provide an available option for activated vascular blocking. Magnesium silicide (Mg_2Si) nanoparticle has been used as an oxygen eliminator or deoxygenation agent (DOA) to consume the intratumoural oxygen to starve tumors (Fig. 12). In the acidic tumor microenvironment, the Mg_2Si can release silane to reacts with oxygen dissolved in the tissues or bound to the haemoglobin, then to form silicon oxide (SiO_2) aggregates. The formed SiO_2 aggregates further block the intratumor vascular networks, for example, the blood capillaries, which can prevent tumors to obtain new supplies of oxygen and nutrients. The silane or the SiO_2 aggregates are the by-products of Mg_2Si. And this nanoparticle can be intravenously injected and enriched in the tumor site via EPR effect. It provides a new indirect strategy to use the pH gradients of tumor tissues to achieve effective vascular blocking [181].

5.3.2.3. Activated targeting and non-toxic-to-toxic transformation. Beside activated vascular blocking, the tumor targeting (or tumor enrichment) is another challenge that we face in chemotherapy. Kinds of peptides, such as RGD, Lyp-1, R8, etc. have been used for surface modification of the nanoparticles to target the receptors expressed on the cell membrane surface. Although they exhibit high specific tumor targeting in vitro, the tumor enrichment is still low in vivo because of the protein corona coating and rapid clearance by RES (reticuloendothelial system) or protease. In the case of cell penetration peptides (CPPs), e.g. R8, they can penetrate kinds of cell membrane, however, most of them are formed with positive chemical units, which makes the CPPs-modified nanoparticles with positive charge. Positive charge aggravates the clearance of the NPs in vivo, which further attenuates the accumulation of the NPs in tumor site. To further enhance the low accumulation of NPs in tumor site, some interesting strategies have been invented. In order to achieve the prolonging of the circulation time of NPs in vivo (which will enhance the tumor enrichment of NPs via EPR effect), the positive charge of CPPs (TAT in this case) is neutralized by grafting with succinic anhydride (SA) or 2, 3-dimethylmaleic anhydride (DA). After the grafting with SA or DA, the zeta potentials of TAT-grafted poly(2-hexoxy-2-oxo-1, 3, 2-dioxaphospholane) (TAT-PHEP) are changed from +5 mV to -10 mV, which favor the reduction of the recognition by immune clearance and prolong the circulation time. Indeed, the enrichment of NPs in tumor site has been enhanced after the surface grafting of SA, however, the SA-modified TAT-PHEP cannot regain the ability of cell penetration. The bonds form between SA and TAT hardly degrade or degrade slowly. In the opposite, the bonds formed between DA and TAT can rapidly degrade in weak acidic environment. In pH 6.5 environment, the zeta potential of DA-TAT-PHEP reversed from ~ −10 mV to ~+2.5 mV in 30 mins. And the cellular uptake tumor targeting is further enhanced while compare with DA-TAT-PHEP NPs. It indicates the regain of the ability of CPPs after the DA-TAT-PHEP NPs enter the acidic environment. The protection of TAT from clearance

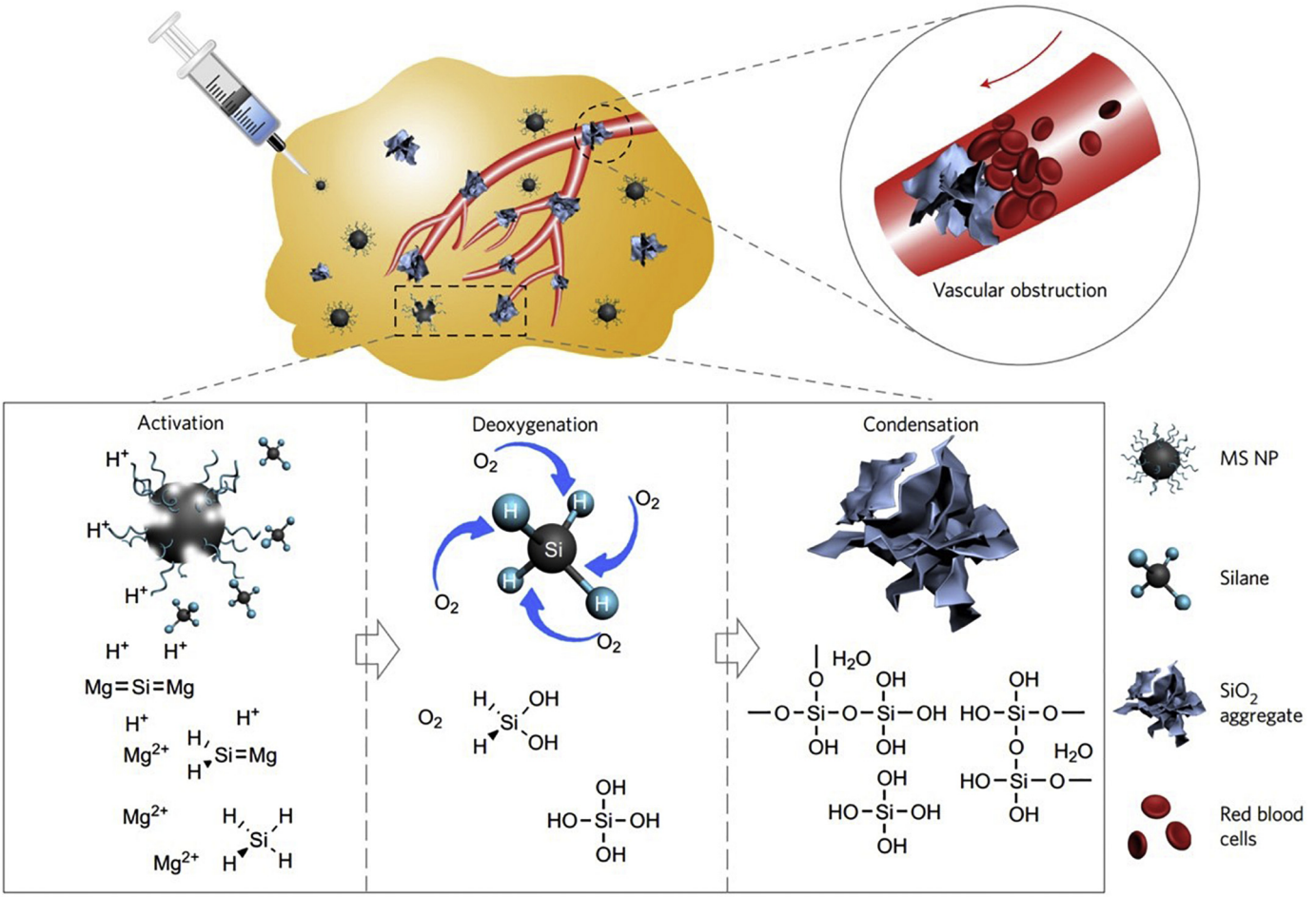


Fig. 12. In situ acid-induced SiO_2 formation. Magnesium silicide nanoparticles were used as pH sensitive precursor. In acidic environment, the Magnesium silicide degrades to release silane then to form silicon oxide (SiO_2) and aggregate to blockade the blood vessels. Reproduced from (*Nat. Nanotechnol.*, 2017, 12, 378). Copyright (2017), with the permission form Springer Nature.

in circulation by DA grafting is a pH gradient activated strategy. While in pH 7.4 physiological environment (blood, extracellular environment of normal tissues, etc.), the TAT grafted on PHEP nanoparticles are covered by DA with pH sensitive bonds. When the DA-TAT-PHEP nanoparticles enter into the extracellular microenvironment of the tumor, the pH sensitive bonds take place cleavage, and TAT are exposed again, and help the nanoparticles penetrate the cell membrane. It provides a new way to control the interaction between the nanoparticles and the biological components after the administration in vivo [182]. With the same strategy, another poly(ethylene glycol)-poly(e-caprolactone) (PEG-PCL) copolymer-based micellar nanoparticle loaded with camptothecin dimer has been developed. The circulation time of DA-TAT-PEG-PCL micelles in the physiological condition has been prolonged under the shielding of DA groups and the accumulation of NPs at the tumor site has also been enhanced after the DA groups have been removed in acidic tumor extracellular microenvironment [183].

5.3.3. pH-responsive nanotheranostics

Because of the loading capacity and diversity of the nanoparticles, not only can the therapeutics be loaded by nanoparticles, imaging agents can also be encapsulated into the nanoparticles. Nanotheranostics can be achieved. By reasonable combination of the strategies used for cancer diagnosis and therapy, pH-responsive nanotheranostics can also be achieved. Extensive studies have been done in this area. And kinds of biomaterials can be used as the carriers. But what interesting is the $CaCO_3$-based nanoparticles. Normally, the $CaCO_3$-based nanoparticles can take place degradation in acidic environment. But the degradation process is often slow, which limits the applications of $CaCO_3$-based nanoparticles in the construction of ultrasensitive nanosystems for nanotheranostics. In a recent study, a form of polydopamine hybrid $CaCO_3$ ($CaCO_3$-PDA) nanoparticles prepared via a one-pot, gas diffusion procedure has been reported to have high sensitivity to pH gradient [184]. It took place rapid degradation under a slightly acidic environment. And it can effectively load photosensitizer, i.e., chlorin e6 (Ce6) which can be used for photodynamic therapy, and bind with kinds of metal ions due to the existing of PDA which has strong affinity with metal ions. The $CaCO_3$ in hybrid nanoparticles favors the construction of high pH-sensitive nanosystems for nanotheranostics [185]. By fine tuning of the synthetic procedure, different $CaCO_3$ with varied structures can be achieved. It has provided a novel strategy and candidate for the construction of pH-sensitive nanoparticle for nanotheranostics.

5.4. Beyond the fate of dissociation of the intratumoral nanoparticles in acidic environment

Although we have known so much about the pH distribution of tumor tissues and developed numerous pH sensitive nanoparticles to enhance the accuracy or specify of tumor diagnosis and therapy, we still know little about the intratumoral fate of these nanoparticle, particular their exact location. Will they remain in the action site? Does the variation of the signal in detection positively associate with the change of the environment surrounding the nanoparticles? What is the metabolic path after they entry into the tumor? Moreover, will the

introduction of these pH responsive nanoparticles disturb the pH balance in the microenvironment of the action site?

Beside the examples introduced briefly above, there are still many nanoparticle-based strategies have been developed (>2000 papers were found under the topic combination of pH + nanoparticle + cancer) to utilize the pH gradients formed between the normal tissues and tumor tissues to further enhance the therapeutic outcome in cancer therapy. The differences between these strategies include raw materials, construction methods, transition pH, or responsive time, etc. But most of the strategies mainly focus on further improving the precisely detecting the pH gradients, the therapeutic outcome via activated drug release, the targeting efficiency via pH controlled interaction between nanoparticle and biological system. Strategies are developed more and more faster, however, clinical applications are still rare. There are still many obstacles need to be solved.

6. Redox environment

6.1. Components and features

Reactive oxygen species (ROS) include kinds of O_2-derived free radicals (Fig. 13) [1]. Compared with normal cells, many types of cancer cell are proved to produce increased levels of ROS, because the increase of ROS may play an important role in the initiation and progression of cancer [186,187]. To balance the ROS generation, cancer cells also recruit nonenzyme ROS scavengers including glutathione (GSH) and vitamins C and E to adapt to oxidative stress. GSH is the most abundant nonprotein thiolated tripeptide with highly reductive ability. As the most important and protective compounds of intracellular ROS-scavenging systems, GSH exists at concentrations of 10–20 mM in cancer cells, compared of 0.5–10 mM in normal human cells [188]. Although elevated GSH and ROS levels formed the characteristic of cancer cell make the neoplastic tissues more resistant to chemotherapy, the high redox status represent an opportunity for improving the redox environment-responsive therapeutic efficacy. On the other hand, numerous evidence suggested cancer cells with increased oxidative stress are inclined to be more sensitive to damage by further ROS introduction generated after the treatments of exogenetic agents, as the excessive generation of ROS can also be toxic to the cells [189]. Based on the biological roles of ROS, common approach in cancer therapies, such as chemotherapy, photodynamic therapy (PDT), and radiation therapy (RT), rely on inducing ROS overproduction to damage and eventually kill cancer cells [190]. Mitochondria is the generator of major intracellular ROSs. Among kinds of ROSs existed in the biological environment, H_2O_2 exhibits the lowest reactivity and the highest stability as well as the highest intracellular concentration. Recent findings demonstrate that a specialized enzyme-produced H_2O_2 was helpful in the ROS-induced cancer therapy [191]. However, as the "two-faced" molecules, ROS are involved in various of alleviating detrimental effects during cancer therapy because of their complex signaling pathways. As a result, the controversial therapeutic effects of ROS are still under re-investigation.

6.2. GSH responsive units and ROS responsive units

Various bonds have been uncovered to response to the redox environment, especially to the GSH and ROS. In the following, we will list some of the bonds used to construct GSH responsive and ROS responsive nanoparticles, respectively. In generally, the GSH responsive bonds are reversible and the bond types are limited (disulfide bonds and some metal oxides), while the ROS responsive bonds are irreversible. However, either the GSH-responsive nanoparticles or the ROS-responsive nanoparticles shares the similarly intratumoral fate: degradation accompanying with dissociation. It triggers the release of the cargos, and turns the nanoparticles into pieces.

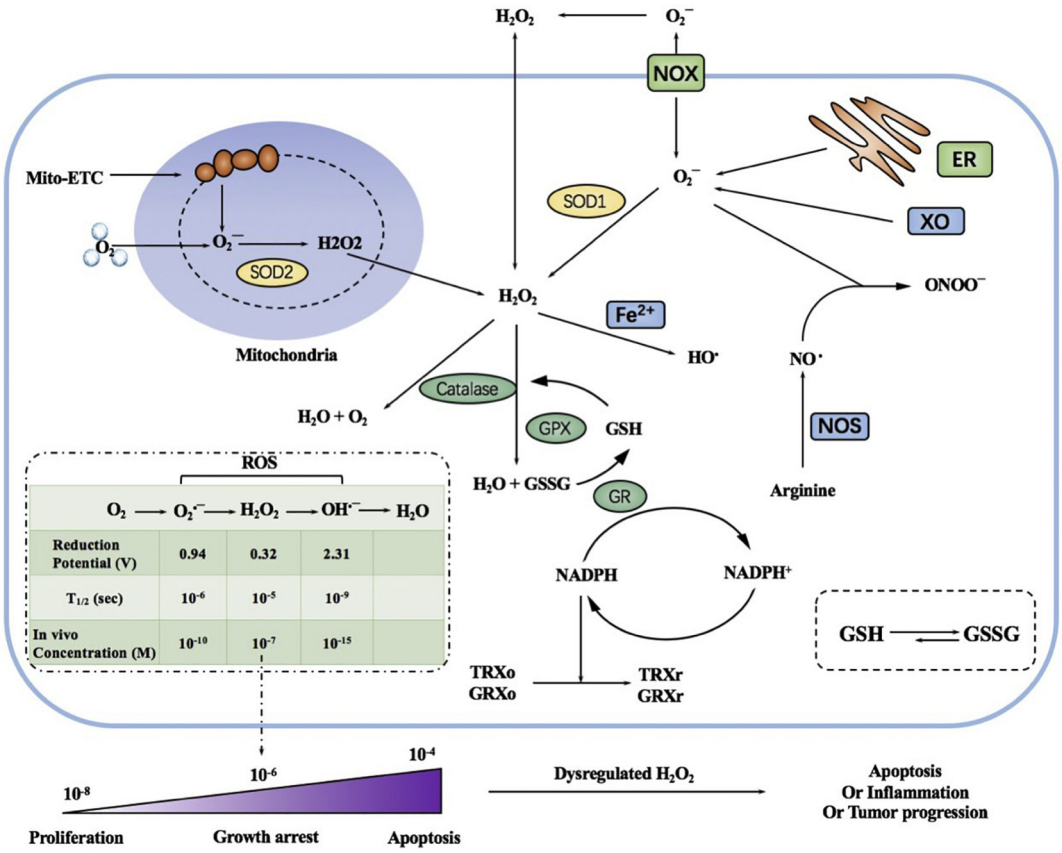


Fig. 13. The cellular redox homeostasis: production, reactions, and the concentration, $T_{1/2}$ and reduction potential of ROS.

6.2.1. GSH-responsive units

6.2.1.1. Disulfide bonds. By incorporation of dynamic linkages such as disulfide bonds into the copolymers, redox-sensitive polymeric nanocarriers can be fabricated for enhanced drug delivery and disease diagnosis [192,193]. The nanostructure with the disulfide bonds could formed the reduction-sensitive shell (or core) assembling micelles, or reversible shell cross-linked (or core cross-linked) micelles, for further drug delivery [194].

6.2.1.2. MnO_2 nanomaterials. MnO_2 has attracted enormous attentions and explored its biomedical applications as cell batteries, catalyst, and MRI contrast agents. In addition, MnO_2 nanomaterials not only have showed an intense and broad absorption for imaging utility but also have been reduced to Mn^{2+} by GSH, which lead to a new generation of nanoplantform for intracellular controlled drug delivery.

6.2.2. ROS-responsive nanomaterials

Because ROS can break various bonds, it provides sufficient candidates for the construction of ROS-responsive nanomaterials. Table 3 has listed some of the widely used ROS responsive units for nanoparticle construction. We are going to exemplify some of the ROS responsive nanosystems constructed by these units.

6.2.2.1. Thioketal groups-containing polymers. Thioketal groups in the polymer chain have been demonstrated in recent studies which they can be cleaved by ROS, leading to polymer chain scission and breakdown. Meanwhile, the thioketal bonding showed much higher sensitivity to ROS, facilitating the achievement of "on-demand" cargo releasing property as well as eliminating the excess ROS [195–199].

6.2.2.2. Thioether-based ROS responsive materials. Thioether-based oxidation-sensitive materials are another type of ROS-responsive materials. The hydrophobic thioether group is easily to form hydrophilic sulfoxide and sulfone under oxidative environment, such as the H_2O_2, and resulted in dissociation of the structure, thus, providing a potential platform for ROS-responsive cargo release. For another side, the ROS scavenging property of thioether-based materials also presented the alleviation of side effect to normal tissue during chemotherapy [211].

6.2.2.3. Phenylboronic acid/phenylboronic ester-based ROS responsive polymers. Phenyl boronic acid and ester bonds are another kind of oxidative-responsible units which can be selectively broken by H_2O_2, generating the dissociated boronic acid. Herein, the Phenylboronic Acid/Phenylboronic Ester-based Polymers are utilized for vaccine or protein delivery based on a solubility switch strategy via H_2O_2 catalysis [206].

6.2.2.4. Selenium or tellurium-based ROS responsive polymers. Similar to the sulfur (S), selenium (Se) and tellurium (Te) are attracted enormous attention in the construction of responsive nanosystems, especially for their oxidation-sensitive ability. The hydrophobic-to-hydrophilic transition can also be observed in selenium- or tellurium-containing polymers after the oxidation. Hydrophobic selenides can be oxidized to selenoxides and selenones, while telluride possesses much higher sensitivity to ROS rather than selenide and sulfide, which enable the selenides or tellurides-containing block polymers as a new generation of ROS-responsive drug delivery platform [202].

6.2.2.5. Metal or metal oxide-based nanoparticles. The Pt-based nanomaterials with the SOD/catalase mimetic property are reported as high effective ROS-scavenger to reduce the oxidative stress during PPT treatment, and the ultrasmall Fe_3O_4 nanoparticles usually used as a catalysis by Fenton-like reaction to generate activated hydroxyl radicals for ROS-induced anti-tumor performance [210,212]. Moreover, MnO_2 nanopartices are of most interesting by the catalysis ability of catalyzing the H_2O_2 to O_2, which act as the H_2O_2-responsive T_1-MRI contrast agent, and also modulate the hypoxia environment of tumor region with cancer therapy [213].

6.3. Constructions and applications of redox responsive nanomedicines

6.3.1. GSH-responsive nanocarriers

Redox-sensitive nanosystems are of particular interest because of higher GSH levels in tumor tissues while compared with normal tissues [214]. A numerous of nanocarriers, including polymeric micelles, inorganic nanoparticles, and nanogels, have been designed as the GSH-responsive nanosystems for avoiding non-targeting drug release during circulation, and subsequently improving the efficacy of drug delivery by the microenvironment-responsive properties [215].

For example, GSH can be used as the stimulus to stepwise cleave the organosilica shell firstly which is coated onto the surface of a NO-prodrug NPQ-loaded micelles and then break the protective bond of the prodrug to trigger the release of NO [216]. Both the organosilica shell and the NO prodrug are GSH responsive. The hybrid nanosystem provides a vesicle for the passive tumor-targeting delivery of NPQ. Meanwhile, the accumulated GSH and GSTπ with high concentration inside the tumor cells form a suitable environment for the stepwise degradation of the hybrid nanosystem, thus, achieve controlled release of the cargos. More importantly, the NO prodrug is low-toxic and only exhibit toxicity to cells while they involve in the reaction with the GSH-GSTπ to release NO. It provides a promising strategy for the construction of redox-responsive nanosystems for drug delivery and the reduction of unavoidable adverse effects caused by the drugs.

Beside the disulfide bonds which is GSH-responsively cleaving, some metal oxides also have the potential of GSH-responsive. It has revealed that the manganese dioxide (MnO_2) is GSH-responsive. The MnO_2 can be fabricated into nano-MnO_2 with different shapes, e.g. nanospheres, nanosheets, etc. And the MnO_2 nanosphere can be doped into the porous structure of some other nanoparticles, and the nanosheet also can be coated onto the lanthanide-doped upconversion nanoparticles. In the case of MnO_2 nanosheet coated lanthanide-doped upconvesion nanoparticles, the MnO_2 can be used as the switch to turn the luminescence emitting from the lanthanide-doped upconversion nanoparticles due to the highly sensitive of MnO_2 to GSH. With this mechanism, this hybrid nanosystem can be used to visualize the GSH level in living cells. Because of the rapid and selective responsive inherent, GSH-responsive nanoparticles exhibit great potentials in targeted drug delivery or gene delivery or act as sensors to enhance the degree of accuracy in analysis [217].

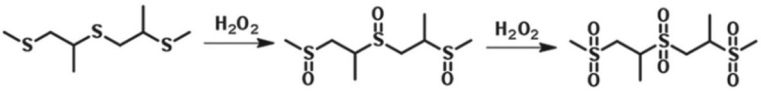
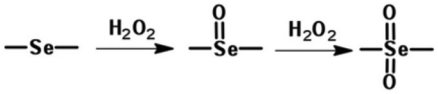
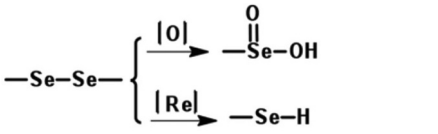
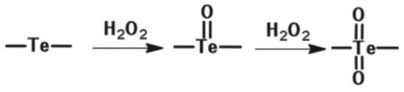
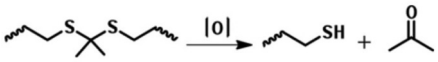
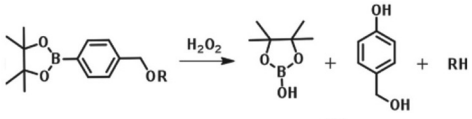
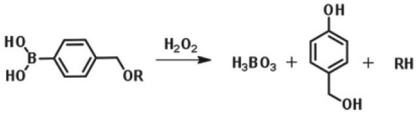
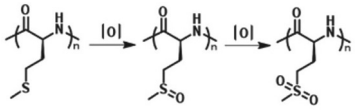
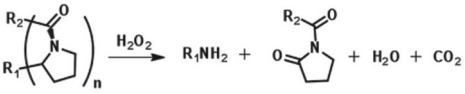
6.3.2. ROS-sensitive nanomaterials

Cao et al. reported an innovative ROS-responsive nanocarrier constructed by ROS-responsive poly(thioketal phosphoester) (TK-PPE) for the co-delivery of photosensitizer chlorin e6 (Ce6) and chemotherapeutic drug doxorubicin (DOX). Ce6-produced ROS can rapidly degrade TK-PPE core in situ under the irradiation of 660 nm laser, which led to size shrinkage of nanocarriers and promoted the burst release of DOX consequently. Meanwhile, the generated ROS also promotes the apoptosis of the tumor cell and enhances the chemotherapy and results in the desired antitumor performance [218].

Manganese dioxide (MnO_2) was also employed as another kind of ROS-Sensitive materials for further improving the anti-tumor therapeutic efficacy. In our recent reports, Prussian blue (PB)/manganese dioxide (MnO_2) hybrid nanoparticles (PBMn) with a small particle size was fabricated by a one pot controlled-synthesis process. The hybrid nanoparticles can produce oxygen by the catalysis efficacy of PB to H_2O_2 at tumor region. Meanwhile, PBMn also served as contrast agent as well as the property for enhancing the diamagnetic T_2-weighted imaging.

Furthermore, it also maintains its photothermal conversion efficacy for PTT, which favor the trimodal imaging-guided Photothermal Therapy for breast cancer. With a red blood cell (RBC) membrane coating

Table 3
The ROS responsive units for the construction of nanoparticles.

Polymers				
Poly(propylene sulfide)				[200]
Selenium-containing polymers				[201]
				[202]
Tellurium-containing polymers				[203,204]
Poly(thioketal)				
Phenylboronic acid/Ester containing polymer				[205]
				[206]
Poly(L-methionine)				[207]
Poly(L-proline)				[208]
Metals or metal oxides				
Fe_3O_4 or Ferumoxyltol	Fe_3O_4	Fenton reaction	ROS generation	[209]
Pt-based nanoparticles	Pt-based nanoparticles	Fenton reaction	$H_2O + O_2$	[210]
Manganese dioxide	MnO_2	ROS $+ H_2O_2$ or $+ H^+ + H_2O_2$ ROS	$H_2O + O_2$	[69]

and doxorubicin (DOX) loading, a stimulated nanocarrier of PBMn-DOX@RBC was constructed as H_2O_2-responsive oxygen generators for controlled drug release. Beyond the imaging-guided PTT of PBMn, the anti-tumor performance of the nanocarrier was further enhanced by the combination of chemotherapy/photothermal therapy [69,219]. It is worth noting that some small molecules are H_2O_2-responsive, for example, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) can be converted to oxidized form with strong near-infrared absorbance in the presence of H_2O_2 and HRP, resulting in the H_2O_2-responsive photoacoustic imaging of various diseases, such as inflammation and tumors, etc. [220].

Moreover, the ROS-responsive nanomaterials also provide the enhanced antitumor performance by relieved side effect during chemotherapy [221]. With the high catalysis property of metal such as platinum, the Pt as well as the Au@Pt nanoparticle were explored as the ROS scavenger [210]. The DOX/Au@Pt-cRGD nanosystem displayed near-infrared (NIR) controlled drug release behavior and photoacoustic imaging guided PTT. Moreover, the Au@Pt also can alleviate the oxidative stress damage caused by DOX. Combined with chemotherapy, the enhanced anticancer performances of the nanosystem and attenuated adverse effects of chemo-photothermal therapy were observed during the combinational therapy [70].

6.3.3. Nanomaterials for improving ROS-generation in antitumor therapy

Huo et al. reported a biodegradable dendritic silica-based nanocatalyst co-loading with the natural glucose oxidase and ultrasmall Fe_3O_4 nanoparticles. Ultrasmall Fe_3O_4 nanoparticles are utilized as the catalyst for Fenton reaction, while the natural glucose oxidase (GOD) is an enzyme catalyst for glucose depletion to starve cancel cells and in situ generate abundant H_2O_2. Subsequently, these post-generated H_2O_2 molecules could be further catalyzed via a Fenton-like reaction to generate large amounts of highly toxic hydroxyl radicals, further inducing cell apoptosis and death. The novel designed double-functional

nanocatalyst represented selective and effective tumor therapy outcome based on their excellent catalytic properties [222].

Meanwhile, kinds of nanomaterials presented the improved anticancer effect of ROS-Mediated PDT. The upconversion nanoparticles (UCNPs) was designed for co-delivering of photosensitizer (PS) molecules and a bioreductive pro-drug (tirapazamine, TPZ), with a synergetic tumor therapeutic effect by NIR laser introduced UC-based PDT and the followed cytotoxicity of activated TPZ which was induced by oxygen depletion. The therapeautic effect of combination of UC-PDT and TPZ demonstrated the enhancement of the cytotoxicity of TPZ under hypoxia [223].

7. Tumor-associated macrophages (TAMs)

7.1. Formation of TAMs

Macrophages are mainly recruited in the inflammatory site to excrete various cytokines, such as TNF, IL-4, IL-10, IL-13, IL-12, IL-23, etc. to maintain the homoeostasis of the microenvironment of inflammation. Evidence has been provided to support the linkage between cancer and inflammation. During the development and progression of cancer, inflammation plays a critical role. Inflammation happens along with the progression of cancer. Leukocytes have been observed to recruit into the tumor. Macrophages are the most frequent inflammatory cells. The tumor associated macrophages (TAMs) are of the macrophages localized in the tumor stroma. Both the monocyte recruitment and the local macrophage proliferation determine the pool size of TAMs. Several tumor microenvironment factors favor the recruitment of monocytes in tumor stroma. These factors include hypoxia, acidosis, cytokines, and chemokines (CCL2), etc.

There two kinds of TAMs (activated macrophages (M1) and alternatively activated macrophages (M2)). It has revealed that the chemokine-CCL2 can polarize the monocytes to M2 subtype [224]. Other chemokines, e.g. several types of CXCL or CCL, etc. are also observed in tumor microenvironment which are playing various roles in initiating inflammation and promoting tumor progression as well as recruiting and polarizing TAMs [225–227]. Besides, hypoxia-inducible factor (HIF-1) can promote the expression of CXCR4 and CXCL12 to induce the recruitment of circulatory monocytes and induce the polarization of TAMs to M2 subtype by signaling pathway of ERK [228–231]. Moreover, the hypoxic cancer cell derived Oncostatin M and Eotaxin-1 have the similar potential with CXCR4 and CXCL12 in monocytes recruitment and switching them to M2 subtype by polarization. Furthermore, the activation of cyclooxygenase-2 (COX-2) pathway can consequently increase the generation of prostaglandin E2 (PGE_2) to induce the polarization of TAMs to M2 subtype [232].

7.2. Functions of TAMs

Macrophages are supposed to inhibit the tumor progression due to their functions as immune surveillance. The M1 subtype cells closely correlate with the antigen presenting and regulation of immunological response in cancer immunotherapy. They facilitate the excretion of proinflammatory cytokines such as TNF, IL-12, and IL-23 as well as reactive oxygen species (ROS) and nitric oxide (NO) which can be used to kill the cancer cell directly. Besides, the M1 cells also express high levels of major histocompatibility complex (MHC), including MHC-I and MHC-II, which favors the recognizing of tumor specific antigens presenting by macrophages to activate the maturation of leukocytes (T cells). In the initial stage of tumor development, the recruited TAMs indeed inhibit the tumor progression. However, as the further progressing of tumor, after the recruited TAMs "self and/or cross" talks with the tumor microenvironment, the M1 subtype TAMs are switchedly polarized to M2 subtype. M2 subtype TAMs has anti-inflammatory activity. It promotes the release of IL-4, IL-10, as well as IL-13. Among these cytokines, IL-4 and IL-10 can reduce the generation of some regulatory cytokines, e.g. CXCL10, CXCL9, etc. resulting in stalling the immune response induced by Th1. They also have poor antigen presenting potential, which may suppress the activation of T cells. The differences between the M1 phenotypic TAMs and M2 phenotypic TAMs in cellular components and functions have been reviewed by Singh et al. [233]. The TAMs have potential in promoting angiogenesis, suppressing immune activities and promoting tumor invasion and metastasis. It makes them a promising target for tumor microenvironment regulation.

7.3. In vivo fate of nanoparticles while facing with TAMs

Because of the foreign body reaction caused by the nanoparticles and the intrinsic immune clearance properties of macrophages, while the nanoparticles encounter with macrophages, most of the nanoparticles will be engulfed by macrophages. Although the clearance rate of the nanoparticle by macrophages can be reduced by surface modification with PEG etc., still a large portion of nanoparticles cannot avoid the fate of macrophage-clearance. In a recently study, the results revealed that macrophages were the main cell type which capturing the active and passive targeting nanoparticles. Besides, the TAMs are mainly distributed near the blood vessels. And the proportion of TAMs is negatively correlated with the distance from the blood vessel and decreases dramatically while the distance increase (37.7%, 10 μm away from the blood vessel; 14.3%, 50 μm away from the blood vessel). It indicates that the TAMs have higher probability than the other cells in interacting with the nanoparticles extravagated from the tumor blood vessels. Moreover, because the nanoparticles cannot diffuse much far in the ECM structure (the primary barrier that the nanoparticles encountering upon extravasation from the tumor blood vessels), it further enhances the uptake of nanoparticles by macrophages. The TAMs act as a cellular barrier to nanoparticles in entrancing into the tumor.

We can conclude that the intratumoral fate for most of the nanoparticles is ended up in TAMs clearance. It may be the main reason for the poor therapeutic outcome of nanomedicines, even they can accumulate in the tumor site. Although we still do not know whether there are differences existing between the M1 phenotypic TAMs and the M2 phenotypic TAMs in clearance of nanoparticles, the TAMs can be a cellular target for nanoparticle-based strategies to reverse the polarization of M2 subtype to M1 subtype. And this strategy is a viable and reliable for cancer enhanced immunotherapy. The reversed polarization may favor the strengthening of immune response to tumor cells, thus, enhance the therapeutic outcome of cancer immunotherapy. Various therapeutic agents can be delivered by nanosystems and accumulated in the tumor microenvironment to realize the remodeling of the TAMs polarity. For example, the remodeling of the TAMs polarity can be realized by targeting delivery of anti-IL-10 and anti-IL-10 receptor oligonucleotides by a galactosylated cationic dextran nanocomplex. The primary uptake of TAMs to nanoparticles favors the accumulation of the nanoparticles in TAMs, it promotes the phenotypic reversion of TAMs. It also reduces the expression of the genes associated with M2 (Arg1, Msr2, Ym1, FIZZ1, Mgl, etc.) [234]. Moreover, the directly delivery of IL-12 poly-β-amino ester nanoparticles can also reeducate the polarization of TAMs, which cause limited adverse cytotoxicity [235]. And the prednisolone phosphate can also be loaded by nanoparticles to accumulate in TME to polarize the TAMs by significantly reducing the expression of a series proangiogeneic factors [236]. Besides, as clinical drugs to deplete TAMs, bisphosphonates can be delivered to the tumor site by calcium bisphosphonate (CaBP-PEG) via a mineralization method. The obtained CaBP-PEG nanoparticles are biocompatible and biodegradable, and effective in vivo in depleting TAMs. After the depleting of TAM, the angiogenesis in tumor was suppressed, the tumor vasculatures were normalized, and the intratumoral perfusion was also enhanced as well as the tumor hypoxia was also relieved [237]. By utilizing the delivering potential of nanoparticles, the TAMs in tumor microenvironment can be effectively reeducated and remodeled.

Beyond conventional drug-based inhibitors for reswitching the polarization of TAMs to M1 phenotypic subtype, some metal- or metal-oxide-based nanoparticles exhibited potential in controlling the polarization of TAMs. For example, ferumoxytol, which can be used to treat iron deficiency, can induce the macrophages polarizing to M1 subtype. While the cancer cells co-incubated with ferumoxytol and macrophages, comparing with the cancer cells only co-cultured with ferumoxytol or macrophages, the caspase-3 activity was increased. An increased mRNA expression which related with Th1-type responses was observed in the macrophages treated with ferumoxytol. Besides, the administration of ferumoxyltol efficiently inhibited the growth of adenocarcinomas and exhibited alleviation of liver metastasis [209]. Similar results have also been found in the iron oxide nanoparticles. In addition, as a promotor to induce the polarization of TAMs to M2 subtype, the down-regulation of HIF-1α may favor the reverse polarization of M2 subtype to M1 subtype. The manganese dioxide nanoparticles can catalyze or react with the hydrogen peroxide (H_2O_2) which is highly produced in tumor microenvironment to generate oxygen, then alleviates the tumor hypoxia [68]. By coating with mannan-modified hyaluronic acid (HA), the obtained mannan-conjugated MnO_2 particles can significantly increase tumor oxygenation and down-regulated HIF-1α and VEGF in the tumor. HA can reprogram the anti-inflammatory M2 phenotypic TAMs to pro-inflammatory M1 phenotypic TAMs. Mannan can be used as the TAMs-targeting ligand for TAM targeted delivery of the nanoparticles (Fig. 14) [238,239].

Overall, the TAMs is a double-edged sword in intratumorally delivering of nanoparticles. It can trap the nanoparticles in the ECM region then eliminate them, at the same time, to some nanoparticles or drug-loaded nanosystems, the functions of TAMs can be remodeled due to the existing of two reversible and total different phenotypic TAMs subtypes. The journey of the nanoparticles may come to an end while encountering with TAMs, but their effects on tumor development and progression or regression may be just at the beginning.

8. Local delivery and the intratumoral fate of nanoparticles

Beyond systemic administration of nanoparticle in vivo, local administration is also an alternative treatment for cancer therapy. In the case of cancer, local administration means intratumoral delivery in most cases, even though in some studies those have used drug-loaded micelles hybrid thermosensitive hydrogel to treat malignant pleural effusion and reduced pleural tumor foci as well as prolonged survival time have been obtained [240]. Although the intratumoral delivery can realize a highest drug accumulation in tumor site, a controversial issue still remains: if we could intratumorally deliver the therapeutics to tumor, why we just resect it by surgery? Recently, some studies have revealed that the intratumoral delivery of carbon nanotubes can stimulate the immune response of the host, and enhance cancer immunotherapy [241]. And by combining with photothermal therapy or radioisotope therapy, the check point blockage strategy-mediated immunotherapy could be further enhanced while comparing with direct surgery [242,243]. Moreover, by intratumoral delivery of DOX-loaded spiky gold nanoparticles, it demonstrated that the spiky gold nanoparticle-mediated PTT combined with chemotherapy could also stimulate enhanced anti-tumor immunity against metastasis [244]. It indicates that the local delivery of nanoparticles should focus on the immune modulation to further inhibit the tumor growth and metastasis. Beyond the applications of nanoparticles in directly destroy the primary tumors and then stimulating the immune response, after the resection of tumor by surgery, the local delivery of nanoparticle can also favor the inhibition of local tumor recurrence post-surgery and potential metastatic spread [245]. The calcium carbonate nanoparticles can be used to load anti-CD27 antibody, and the anti-CD47 antibody-loaded calcium carbonate nanoparticles can be further encapsulated in the fibrin gel. After surgery, the hybrid gel can be sprayed onto the tumor resection cavity, and the calcium carbonate nanoparticles can serve as H+ scavenger, while H+ is highly produced in the surgical would site. This process not only triggers the long-term release of anti-CD47 antibody, but also favors the polarization of tumor-associated macrophages to the M1-like phenotype (M2-like TAMs were reduced, and M1-like TAMs were increased, meanwhile, the level of IL-12 was increased while IL-10 was decreasEd.). It demonstrates that the intratumoral delivery of nanoparticles can remodel the tumor microenvironment by altering the physiological environment of tumor as well as controllably targeting to specific cell phenotypes. It also indicates that the fate of nanoparticles used for local delivery can be pre-designed due to the low-spreading of nanoparticles administrated intratumorally.

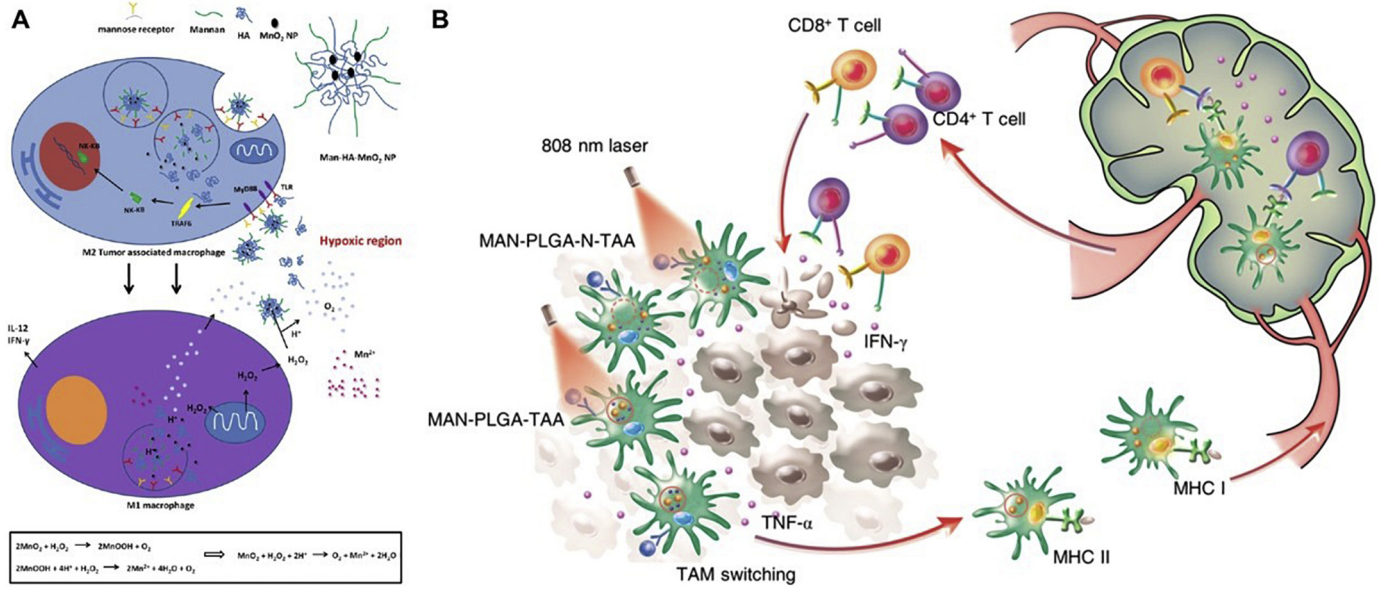


Fig. 14. TAM repolarization mediated by nanoparticles. A) Mannan-HA-modified MnO2 can target to the M2-subtype TAMs and reverse the M2-subtype TAMs to M1 subtype. B) TAA-loaded Mannan modified PLGA nanoparticles can also reverse the polarization of TAMs and enhance cancer immunotherapy. A was adapted from (ACS nano, 10 (2015) 633–647). Copyright (2015), with permission from American Chemical Society. B was also adapted from (Nano Lett., 2018). Copyright (2018), with permission from American Chemical Society.

9. Perspectives and challenges

We have briefly depicted the intratumoral microenvironment factors which the nanoparticles will encounter during the transportation upon extravasation from the blood vessels into the deep tissues of the tumor and briefly list some of the latest strategies in local delivery of nanoparticles. The main functions of these microenvironment factors are mainly including trapping the nanoparticles from further diffusion inside the tumor and dissociating the entity structures of the physical assembled or chemical crosslinked nanoparticles to realize drug activated release or activated targeting. Although the research about the interactions between the nanoparticles and these microenvironment factors are still at the initial stage, after the past decades, we have known more about them. And we have also developed corresponding strategies to remodel, utilize, or reverse these factors to enhance the accuracy of diagnosis and the therapeutic outcome. Beyond these factors, enhanced interstitial pressure, dysregulated vascular structure and lymphatic vessels, endocytosis of tumor cells, cell membrane receptor expression, etc. also play important role in the intratumoral fate of nanoparticles. The interstitial pressure can press the nanoparticles back to circulation, which make the nanoparticles have no chance to get though the tumor tissues. And dysregulated vascular structure and lymphatic vessels are the main biological foundations for enhanced permeation and retention (EPR) effect, which have been systematic and well-reviewed by other researchers. The other factors are mainly associated with the interaction between nanoparticles and tumor cells. Even they are important, but it is not some important if the nanoparticles cannot penetrate through the barriers, such as the ECM and TAMs. The ECM and TAMs act as biological barriers to impede the further diffusion of nanoparticles and attenuate the interaction between the inside tumor cells and nanoparticles. Collagenases or other antifibrous agent can remodeling the ECM structure, but the ECM is distributed all over the human body, non-targeting delivery of these agents main causes whole body adverse effects. Although the hyperthermia can rearrange the collagen fibers and enhance the transport of nanoparticle across the ECM, precisely controlling of hyperthermia (site, depth, intensity, etc.) is still impeding its further development. The TAMs also impede the further diffusion of nanoparticles to interact with tumor cells directly. But the phenotypic subtypes of TAMs can be remodeled. If we want to enhance the immune response of TAMs to cancer cells, we can realize it by reverse the M2 phenotypic TAMs to M1 phenotypic TAMs. Not only the delivery potential of nanoparticles can benefit the polarization of TAMs, but also the nanoparticles themselves can switch the polarization of TAMs by nanobiological effects. It provides an alternative strategy to enhance the cancer immunotherapy beyond immune checkpoint blockage or CAR-T strategies.

The other factors mentioned in this review are MMPs, acidosis, and redox environment. Their formation, secretion, distribution and functions are more uncovered than the other factors. They are prevailing in tumor tissues, and their functions can be activated intracellularly or intercellularly. Up to date, these factors mainly serve as stimuli to trigger the dissociation of the nanoparticles by disrupting entirely or breaking the agent-carrier bonds. They provide opportunities to realize the nanoparticle-based precise tumor diagnosis and therapeutic agent

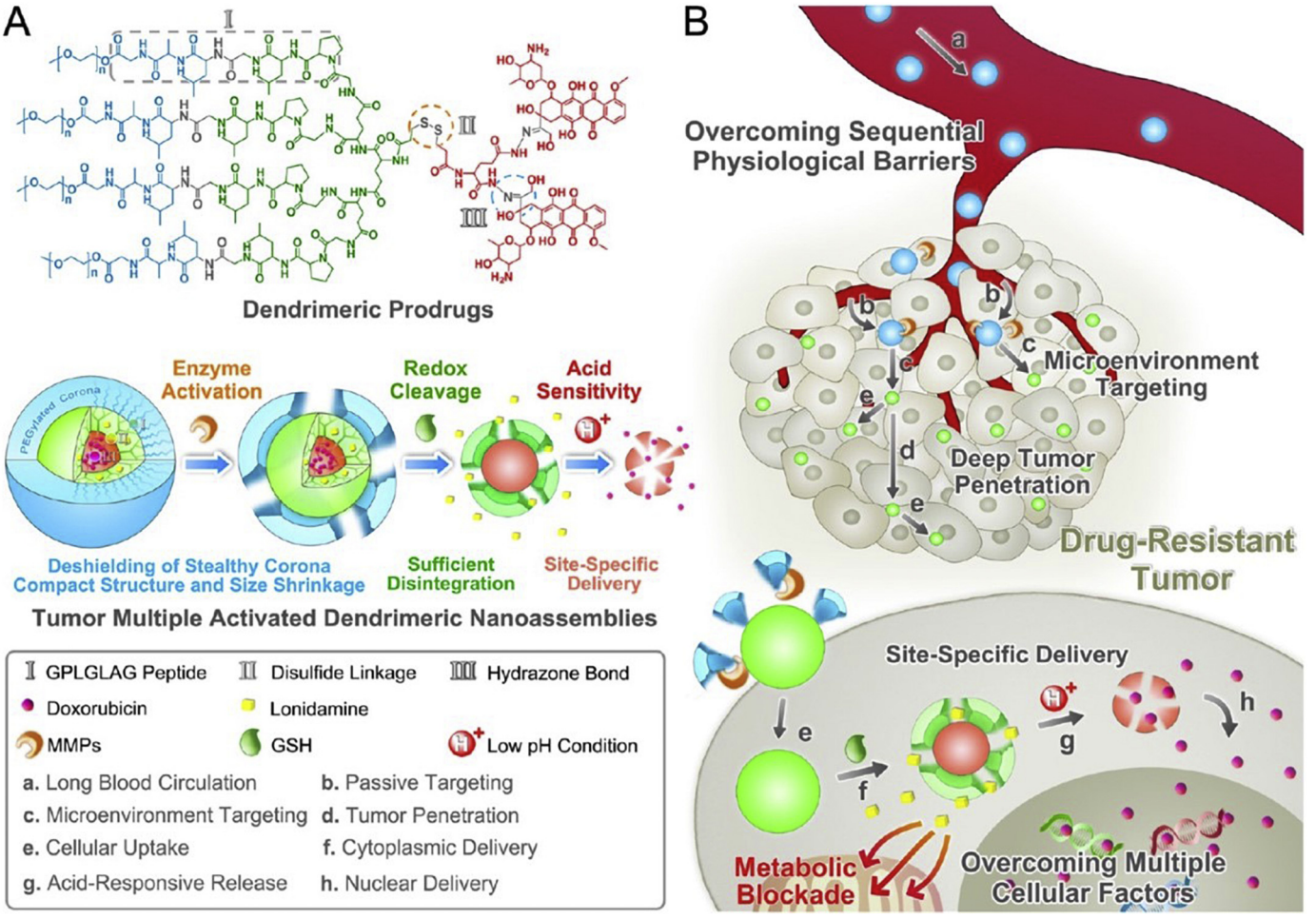


Fig. 15. Stepwise responsive nanoparticles. By fine designing, a dendrimeric prodrug assembled nanomedicines with stepwise activation can be obtained: first enzyme activation, second redox cleavage, finally acid sensitivity. It provides a alternative strategy to control the intratumoral fate of nanomedicine inside tumor tissue and to enhance the therapeutic outcome of nanomedicines. Adapted from (ACS nano, 11 (2016) 416–429). Copyright (2016), with permission from American Chemical Society.

delivery, which will enhance the therapeutic outcome. However, beyond the dissociation, what more can we do or utilize these factors? Is it possible to construct nanomedicines with stepwise responsiveness? If possible, what is the order? MMPs first, then acidosis then, and redox last? (Fig. 15) [246] Will it overdesigned? It needs for further studying.

Because of the heterogeneity of tumor, the strategy focuses on single microenvironment factor will obtain limited information about the tumor and poor therapeutic outcome. It has been well-documented about the advantages and therapeutic outcome of combinational therapy. And local delivery of functional nanoparticles may provide more opportunities in tumor microenvironment remodeling and obtain enhanced therapeutic outcome if the strategies used for immune response stimulation could have been reasonably designed. By suitable combination, each therapeutic manner can be strengthened. It may provide another opportunity for enhancing the therapeutic outcome.

Acknowledgements

This work was financially supported by the National Natural Science Fund for Distinguished Young Scholar (NSFC31525009), National Natural Science Funds (NSFC31771096 and NSFC31871008), and Sichuan Innovative Research Team Program for Young Scientists (2016TD0004), Distinguished Young Scholars of Sichuan University (2011SCU04B18).

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