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Review

Targets for improving tumor response to radiotherapy

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ABSTRACT

Radiotherapy is one of the most common treatment modalities for controlling a wide range of tumors. However, it has been shown that radiotherapy alone is unable to completely eradicate some tumors and could be associated with a high possibility of tumor recurrence. To date, various experimental and clinical studies have been conducted to explore some efficient targets within tumor microenvironment (TME) to enhance tumor response to radiotherapy; thus help eliminate or eradicate tumors. Although targeting DNA damage responses (DDRs) is associated with severe toxicities, studies in recent decade suggest that inhibition of some apoptosis/survival targets within TME is promising. This is also associated with changes in the numbers of T regulatory cells (Tregs) and cytotoxic T lymphocytes (CTLs). The inhibition of cyclooxygenase-2 (COX-2), phosphoinositide 3-kinase (PI3K), mammalian target of rapamycin (mTOR), mitogen-activated protein kinases (MAPKs) and vascular endothelial growth factor (VEGF) have also shown promising results. The combination of receptor tyrosine kinase (RTK) inhibitors with radiotherapy is interesting as well as the clinical use of some drugs and antibodies. Epidermal growth factor receptor (EGFR) inhibitors are the most common RTK inhibitors. Some clinical trials in recent years have shown very interesting results for immune checkpoint inhibitors (ICIs), especially programmed death-ligand 1 (PD-L1) and CTLs–associated antigen 4 (CTLA-4) inhibitors. It has been suggested that administration of ICIs during or after hypofractionated radiotherapy could lead to best results. In this review, we explain TME response to radiotherapy and potential targets for sensitization of cancer cells to radiotherapy.

1. Introduction

Radiotherapy is one of the main strategies for eradication of cancer cells and preventing tumor growth. Radiotherapy has less systemic effects compared to chemotherapy [1]. Some studies have estimated that 50% to 70% of cancer patients undergo treatment with radiation during their treatment course [2]. Although evidences show that radiotherapy is able to control some tumors and increases survival of patients remarkably; however, studies have also shown that treatment with radiotherapy alone has a high risk of tumor relapse [3]. Furthermore, experimental studies have suggested that radiotherapy may trigger adaptive responses in tumor, which lead to resistance to subsequent doses of radiation [4]. Thus, a large number of experimental studies have been conducted to investigate the molecular, biochemical and epigenetic modulations to improve the response of tumors to ionizing radiation [5]. Therefore, identifying the mechanisms of tumor resistance to radiotherapy and exploring effective targets for overcoming these resistance mechanisms are some of the interesting aims in radiobiology and radiation oncology. Despite the clinical applications of some targets, further research is required in this area. Radiotherapy

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in combination with targeted therapy and immunotherapy is growing and attracting interests in recent years. This review aimed to discuss the promising targets that can be proposed for tumor radiosensitization as well as having good chance for translation to clinical radiotherapy.

2. Tumor microenvironment (TME) and resistance to radiotherapy

Tumor contains various types of cells such as cancer cells, cancer stem cells (CSCs), cancer associated fibroblasts (CAFs), regulatory T cells (Tregs), macrophages, cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, neutrophils, myeloid-derived suppressor cells (MDSC) etc. [6]. Interactions between these cells and their secretions play a pivotal role in tumor response to therapy. Radiotherapy induces some changes that may increase or reduce resistance to subsequent doses of radiation [7]. It has been suggested that exposure to a dose of radiation causes resistance to subsequent doses; however, in recent years, some evidences show that radiation may help better management of tumor growth through induction of anti-tumor activity of the immune system [6].

2.1. Cancer cells

Cancer cells are among the most important targets within tumor. Killing cancer cells by radiation can attenuate tumor growth. However, cancer cells can release some factors in response to radiation to promote growth and invasion of tumor [6]. Cancer cells have positive feedback loop with other cells in favor of tumor growth. Cancer cell death following radiotherapy also triggers several signaling cascades to aid survival and tumor growth. Apoptosis can trigger the release of anti-inflammatory cytokines including TGF-β to help proliferation of cancer cells and also suppression of CTL activity [8]. Autophagy and necrosis can also trigger survival via supply of energy and suppression of death pathways [7]. Immunogenic cell death including necrosis or necroptosis can also cause the release of danger alarms which activate the immune system against cancer cells. In this condition, danger alarms activate dendritic cells to promote proliferation of anti-cancer natural killer (NK) cells and cytotoxic T cells [9]. Activation of NK cells and cytotoxic CD8+ T cells lead to the release of anti-tumor cytokines such as TNF-α, IFN-γ and IL-2, which are able to promote apoptosis in cancer cells as well as more proliferation of anti-tumor immune cells. These cytokines also attenuate the proliferation and activation of CAF, Tregs and CSCs, leading to the suppression of cancer growth factors such as TGF-β [10]. The balance between immunogenic and tolerogenic responses plays a key role in the fate of tumor therapy by radiation. The interaction of cancer cells with other cells within TME will be further discussed.

2.2. CAFs

It has been suggested that radiation augments survival of CAFs following upregulation of integrin [11]. Radiation also increases the release of TGF-β that promotes differentiation of fibroblasts into CAFs [12]. These CAFs further release more TGF-β to exacerbate tumor growing features. An increase in the survival of CAFs could lead to more survival of cancer cells through upregulation of the anti-apoptotic PI3K pathway [11]. CAFs are also able to promote autophagy in cancer cells, which stimulates recurrence and survival of cancer cells following exposure to radiation [13]. Results of irradiated lung tumors have shown that CAFs play a key role in tumor survival because of its immune suppressive ability [14].

2.3. Tregs

Tregs play a central role in tumor resistance to various types of cancer therapy, including radiotherapy. Tregs have a positive cross-talk with immunosuppressive cells within TME. On the other hand, Tregs inhibit the activities of CTL and NK cells. The expression of programmed death 1 (PD-1) plays a key role in this mechanism. The PD-L1 receptor PD-1 promotes proliferation of Treg; however, it prevents proliferation and activation of naive T-cells and facilitates apoptosis of CTLs [15,16]. Tregs are resistant cells to ionizing radiation. A study showed that Tregs are able to survive even after exposure to high doses of ionizing radiation [17]. This is because of lower incidence of apoptosis compared to their proliferation during radiotherapy [18]. Tregs are recruited into tumor following the release of some chemokines such as CCL5 and CCL22 [19]. Furthermore, the release of TGF-β by other cells like CAFs within TME facilitates the conversion of CD4+ T helper cells to Tregs [19].

Tregs release immunosuppressive cytokines including IL-10 and TGF-β into TME, thereby suppressing the activities of CTLs, and further promotes proliferation of Tregs [19]. A study showed that irradiation of different xenograft tumors with a high dose of radiation led to an increase in the numbers of Tregs. Analyses showed that Tregs, after irradiation, were active and able to suppress CTLs within TME. Interestingly, neither TGF-β nor IL-33 which were increased following irradiation have a role in activation of Tregs after irradiation [20]. It is well-known that immune system responses are highly dependent on radiation dose. In contrast to conventional radiotherapy, in hypofractionated stereotactic radiation therapy (HSRT), patients receive high doses of radiation in some lower fraction numbers. It has been suggested that in contrast to lower doses of conventional radiotherapy, a high dose of radiation in HSRT can augment numbers of CD8+ T cells, attenuate release of TGF-β by CD4+ T cells, and also reduce the number of Tregs [21]. Hence, using HSRT technique can be a useful strategy for modification of immune system activity within TME.

2.4. Macrophages

Macrophages have different roles in tumor response to therapy. M1 macrophages are activated by inflammatory cytokines such as IFN-γ, thereby activating immune responses. However, M2 macrophages are activated by anti-inflammatory cytokines such as IL-4, IL-10 and IL-13, leading to suppression of immune system [22]. The effect of radiotherapy on polarization of macrophages in TME is complicated and may depend on radiation dose and tumor type. Radiotherapy causes potent anti-tumor effects, while it may trigger some mechanisms that stimulate angiogenesis and tumor regrowth. In mice bearing prostate cancer cells (TRAMP-C1), irradiation as both single dose and fractionated doses have been shown to activate both M1 and M2 macrophages, leading to tumor growth [23]. A study by Pinto et al. suggested that irradiation of macrophages with 10 Gy led to an increase in the number of M1, but a reduction in M2 cells. These changes led to upregulation of pro-survival genes such as NFκB and Bcl-2, as well as increasing invasion and metastasis phenotypes [24]. However, exposure to a low dose of radiation may cause reprograming macrophages to M1 cells, which triggers infiltration of CTL into TME [25]. Similar results have been observed by Prakash and colleagues. They showed that a low dose of radiation causes induction of inflammatory responses and shifting into M2 macrophages [26].

Monocytes and macrophages are radioresistant compared to other types of immune cells [27]. The radiosensitivity of M2 macrophages may be different from M1 macrophages. For example, in glioblastoma, M2 cells are more resistant to radiation compared to M1 cells; thus the ratio of M2 to M1 cells after radiotherapy may be increased [28]. Hypoxia also triggers macrophage polarization to M2; thus increases the radioresistance of cancer cells [29]. Although radiotherapy may kill some macrophages in TME, local irradiation causes infiltration of monocytes to TME and polarization into macrophage; thereby promoting macrophage enrichment [30]. Infiltration and macrophage polarization following radiotherapy may lead to a reduction in survival of cancer patients [31,32].

2.5. Lymphocytes

CTLs are the most important anti-cancer cells within TME. These immune cells are able to induce apoptosis in cancer cells. Impairment of CTLs in TME leads to tumor immune escape during radiotherapy [33].

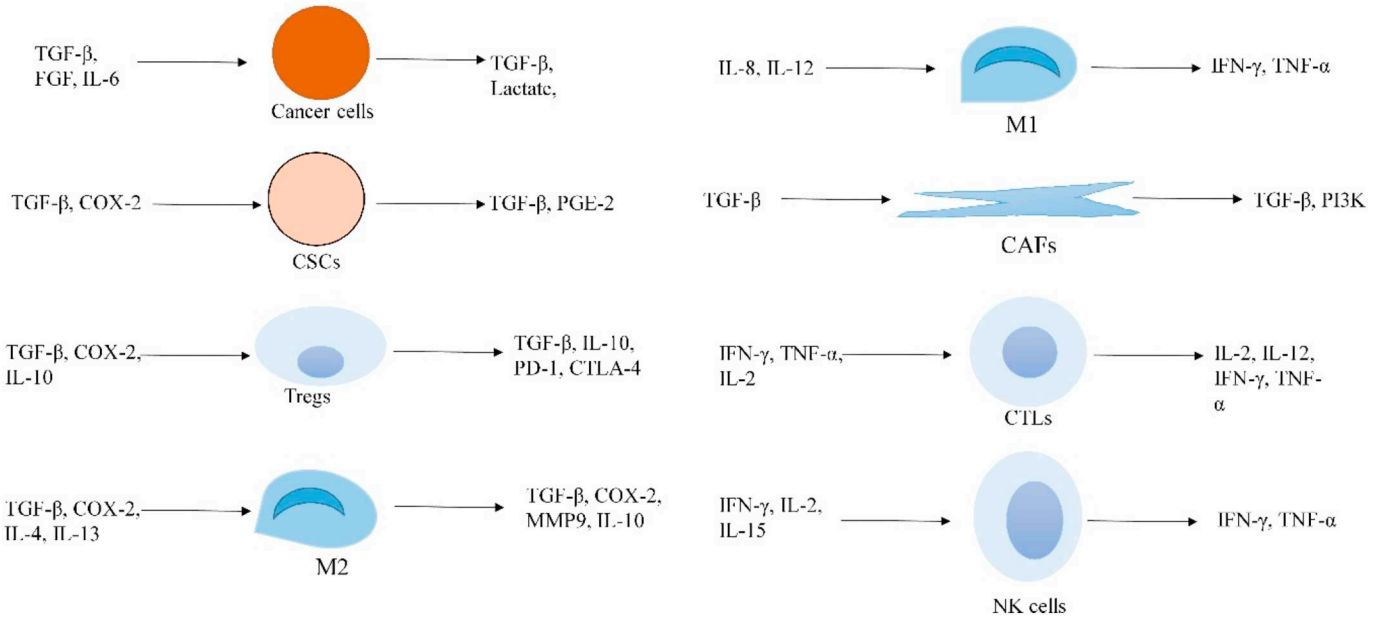

Fig. 1. TME including different cancerous and non-cancerous cells. CTLs, M1 macrophages and NK cells are the most important anti-cancer cells within TME. These cells have positive cross-talks with each other through the release of some cytokines such as IFN-γ, TNF-α, IL-2 and IL-12. Tregs, M2 macrophages, cancer cells, CSCs and CAFs also have positive cross-talks with each other to promote the proliferation and survival of cancer cells and CSCs.

CTLs are able to reprogram macrophages to M1 cells following the release of IFN-γ. These cells also have positive cross-talking with NK cells within TME. Irradiation of tumor, similar to normal tissues lead to infiltration of lymphocytes [34]. Exposure to radiation leads to the release of some chemokines that regulate recruitment of effector T cells to irradiated area [35]. Exposure of TME to radiation causes secretion of IFN-γ, which is associated with the expression of major histocompatibility complex (MHC) antigen class I and vascular cell adhesion molecule (VCAM)-1 [36]. This is linked to lymphocyte trafficking and increasing anti-tumor immunity [37]. These changes are associated with increased numbers of CTLs and induction of apoptosis in cancer cells [38]. Irradiation of twenty-three human carcinoma cell lines with 10 and 20 Gy radiation showed upregulation of CTL-mediated Fas expression [38]. Radiation has also been shown to activate lytic efficiency of CTLs [39].

Infiltration of lymphocytes to TME does not occur for all tumors and patients. It has been suggested that tumors with high radioresistance may prevent infiltration of lymphocytes to TME [40]. Furthermore, remarkable reduction of different subtypes of lymphocytes especially CD4+ CD8+ T cells is a concern for patients that undergo radiotherapy, which lead to attenuation of immune system [41]. An in vitro study suggested that T cells have a moderate radiosensitivity and dye mainly via necrosis following exposure to ionizing radiation [27].

2.6. NK cells

NK cells are one of the key cells of the immune system that act without deliberate immunization [42]. This property makes NK cells a direct killer of cancer cells that do not express MHC class 1 [42]. NK cells have positive cross-talking with other immune stimulator cells within TME, including CTLs and M1 macrophages. This interaction is activated via release of some pro-inflammatory cytokines such as IFN-γ and IL-2 [42]. Activation of NK cells also triggers differentiation of dendritic cells (DCs) [43]. It has been suggested that radiotherapy may increase infiltration and activities of NK cells [44].

2.7. Dendritic cells (DCs)

DCs are an important part of antigen presenting cells (APCs) that provide antigen presentation to CTLs [45]. The presentation of antigens in TME by DCs can facilitate cytotoxicity of CTLs against cancer cells [45]. Exposure of tumor to radiation may enhance anti-tumor activity of DCs following upregulation of toll-like receptors (TLRs) [46]. This is associated with higher presentation of damage-associated molecular patterns (DAMPs) to CTLs, leading to more release of anti-cancer cytokines [47]. Evidences have shown that exposure of DCs to a low dose of radiation (such as seen in hyperfractionated radiotherapy) enhances proliferation of CTLs, thus increasing the release of some anti-cancer cytokines such as IL-2, IL-12 and IFN-γ [48,49]. Interestingly, an in vivo study showed that although a low dose of radiation (0.1 or 0.25 Gy) induces DCs activity, exposure to a conventional dose (2 Gy) may not cause an increase in the presentation of DCs, and that CTL proliferation was independent on DCs activity [50]. Some studies also suggested reduced or no effect of irradiation on the activity of DCs, implying a cancer type and dose dependent response of DCs to radiotherapy [51,52]. Furthermore, it seems that high doses of radiation such as seen in HSRT (like 10 Gy in each fraction) may further amplify the release of immune stimulating antigens and more antigen presentation [53].

2.8. CSCs

As earlier mentioned, TME contains a range of cells with diverse activities. Among these, CSCs are the most important clonogenic cells that can generate new cells unlimitedly. The differentiated cancer cells can divide limitedly. Thus, it seems that killing CSCs can effectively aid tumor eradication. It has been suggested that exposure of differentiated cancer cells to radiation may cause them to reprogram in order to achieve CSCs function [54]. CSCs have some unique properties that make them radioresistant cells. PTEN, one of the most frequent tumor suppressor genes in cancer cells, may be mutated in CSCs. Suppression of PTEN is associated with aberrant upregulation of PI3K/AKT/β-catenin pathway, which stimulates resistance to radiotherapy via inhibition of apoptosis and maintaining stemness [55]. One of the important roles of CSCs in radiation resistance is triggering DNA damage responses (DDRs). The expression of DNA repair enzymes such as ATM, PARP1 and H2AX is higher in CSCs [56]. In total, it seems that CSCs have positive interactions with other cells within TME that increase resistance to radiotherapy in a positive feedback loop (Figs. 1 and 2).

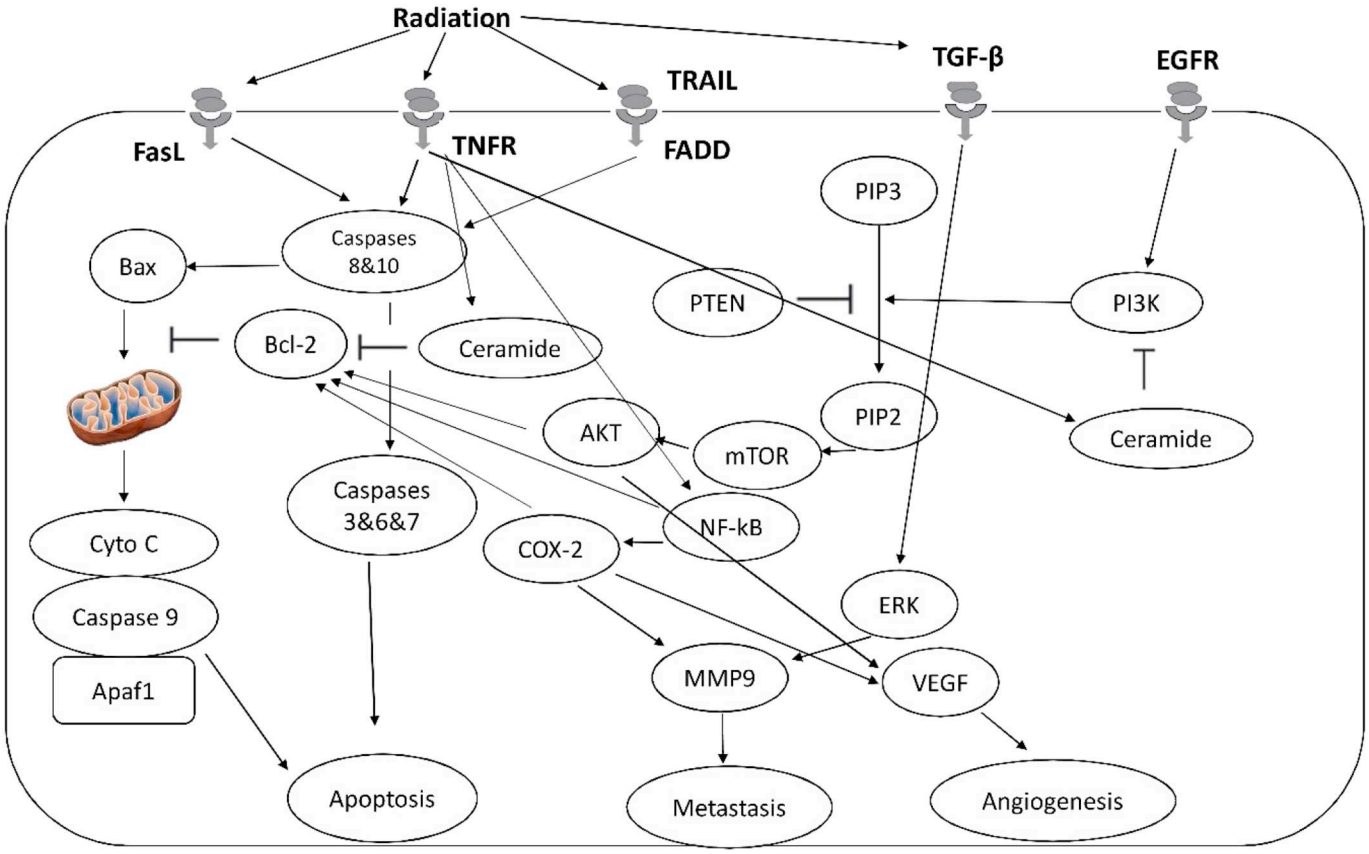

Fig. 2. Radiotherapy can affect the differentiation and proliferation of pro-tumor and anti-tumor cells via triggering release of pro-tumor or anti-tumor mediators. Exposure to radiation upregulates the expression of pro-apoptosis receptors such as FasL, TRAIL and TNFR. These receptors trigger the expression of Bax and pro-apoptotic caspase enzymes, which facilitate progression of apoptosis. On the other hand, upregulation of some factors such as EGFR and TGF-β stimulates anti-apoptotic mediators such as NFκB, COX-2, and PI3K. Furthermore, they can stimulate angiogenesis and metastasis via triggering the expression of VEGF and MMP-9. Targeting pro-tumor mediators such as VEGF, NFκB, COX-2, PI3K, EGFR and TGF-β are interesting for overcoming tumor resistance to radiotherapy.

3. Dying cells following radiotherapy modulates responses in TME

Radiation-induced cell death plays a key role in immune system shifting within TME. Although mitotic catastrophe is not immunogenic, apoptosis, necrosis, senescence and autophagy are able to stimulate immune cells within TME to release a wide range of chemokines and cytokines [57]. Apoptosis occurs following damage to DNA, mitochondria, and also oxidation of the membrane that leads to upregulation of apoptosis receptors on the cell membrane or release of cytochrome *c* from the mitochondria [58]. The most critical mediators for apoptosis are caspase proteins. Caspases 2, 8, 9 and 10 are initiators, while caspases 3 and 7 are activated later [58]. When caspase 3 is activated, apoptotic induction is unavoidable. Development of apoptosome complex leads to degradation of the genomic contents of cells, and generation of apoptotic bodies [58]. These bodies including cell cytoplasm do not trigger inflammatory responses [57]. Macrophages digest apoptotic bodies. Following this process, macrophages release tolerogenic cytokines such as TGF-β and IL-10, which lead to immune suppression within TME [57]. Apoptosis also has a direct relation with triggering DNA repair. Caspase 3 is a potent stimulator for repopulation of cancer cells [59]. Caspase 3 triggers the release of prostaglandin E_2 (PGE_2), which increases survival of cancer cells [59]. Caspases 2 and 3 can also cleavage with Ku80, leading to stimulation of non-homologous end-joining (NHEJ)-mediated repair of DNA [60]. Therefore, apoptosis is a double-edged sword, which can cause reduction of viability, as well as triggers repopulation in TME. Evidences have shown that senescence has a similar effect to apoptosis. The incidence of senescence can trigger the release of TGF-β, leading to upregulation of TGF-β–NOXs [61]. Upregulation of NOX genes such as NOX2 and NOX4 is associated with resistance of cancer cells to radiotherapy [62].

Necrosis and necroptosis are other types of cell death associated with the release of cell contents, including danger alarms from dying cells. Necrosis is seen following exposure to a high dose of radiation, which causes severe damage to membrane and other organelles such as mitochondria. Necroptosis can also be seen when the apoptosis process is overwhelming; thus cells are unable to complete apoptosis. Both necrosis and necroptosis release danger alarms such as HMGB1, uric acid, oxidized DNA etc. Some macrophages and DCs recognize these danger alarms and present them to T cells. Toll like receptors (TLRs) are able to recognize danger alarms. Overexpression of TLRs including TLR2, TLR4, TLR5 and TLR9 leads to upregulation of inflammatory mediators including STAT-3 and NFκB [63]. These transcription factors mediate the release of several inflammatory cytokines, PGs, nitric oxide synthase (NOS) enzymes etc.

Autophagy is another type of cell death after exposure to radiation. Although the incidence of autophagy is lesser compared to necrosis and apoptosis, evidences have shown that it plays a key role in resistance of cancer cells [64]. Autophagy recycles dying cell contents as fuel for other viable cancer cells. This helps proliferation of cancer cells, especially during hypoxia and nutrient deprivation [64].

Immunogenic and tolerogenic responses are highly dependent on radiation dose and type, as well as fractionation. It has been reported that proton particles are able to induce more necrosis and apoptosis in cancer cells, which is associated with more release of danger alarms from dying cells [65]. The presentation of danger alarms to T cells cause the release of anti-tumor cytokines such as IFN-γ and TNF-α [66]. Using hypofractionated radiotherapy with a high dose per fraction has also shown more potent immunogenic effect against cancer cells. It has been suggested that a radiation dose ranging between 5 and 12 Gy per

fraction is more effective for inducing immune system against cancer cells. It seems that following exposure of tumor to these doses of ionizing radiation, an increase in the number of infiltrated CD8+ cytotoxic T cells and NK cells occur, while the number of Tregs reduces. This is associated with more release of anti-cancer cytokines such as IFN-γ and TNF-α, while the level of immune suppressor cytokines such as TGF-β and IL-10 reduces. Lower doses of radiation do not cause enough presentation of antigens to effectively infiltrate CD8+ cytotoxic T cells. Also, higher doses of ionizing radiation may cause an increase in the infiltration of Tregs, which cause suppression of immune system via release of TGF-β and IL-10. This issue has been reviewed by Liu et al. and Siva et al. [67,68].

4. Potential targets for tumor radiosensitization

To date, several experimental studies have been conducted to explore effective targets for sensitization of cancer cells to chemo- and/or radiotherapy. An effective strategy is to use agents which sensitizes cancer cells. Thus, deep knowledge about TME and response of different cells within TME to radiotherapy is important. It seems that targeting some DNA repair pathways and modulation of immune system within TME are interesting approaches for overcoming tumor resistance.

4.1. Targeting DNA repair pathways

Radiotherapy and chemotherapy are two cancer therapy modalities that cause cancer cell death through induction of DNA damage. This is because of direct radiation interaction with DNA or generation of highly reactive free radicals. DDR includes the different pathways for base damage, single strand breaks (SSBs) and double strand breaks (DSBs). In response to base damage, base-excision repair (BER), poly (ADP-ribose) polymerase-1 (PARP-1) and apurinic/apyrimidinic endonuclease (APE1) play a key role in excision and replacement of damaged bases [69]. However, DSBs are repaired by either NHEJ or homologous recombination (HR). The main DNA repair genes involved in repair of DSBs include ataxia telangiectasia mutated (ATM), PARP-1, the complex of MRE11–RAD50–NBS1 (MRN), DNA-PK catalytic subunit (DNA-PKcs), the complex of Ku70/Ku80, BRCA1, and RAD51 [69]. In some cancers, the response to DNA damage may be more active because of aberrant upregulation of some DDR genes [70]. The high expression of ATM in breast cancer has a direct relation with resistance to therapy, and also metastasis [71]. Nowadays, some DNA repair inhibitors such as olaparib and veliparib as inhibitors of PARP-1, and MSC2490484A as inhibitor of DNA-PKcs have been proposed for sensitization of tumors to radiotherapy [72]. However, it seems that inhibiting the pathway of DDRs may lead to severe side effects in normal tissues and also increase the risk of secondary cancers [72].

4.2. Targeting apoptosis/survival pathways

Increasing apoptosis incidence for cancer cells is an appropriate strategy for improving tumor response to radiotherapy and also increasing survival of cancer patients. Various mechanisms have been suggested for stimulating apoptosis via modulation of genes involved in this phenomenon. In most cancer cells, mutations in pro-apoptotic and tumor suppressor genes such as PTEN and p53 lead to aberrant upregulation of anti-apoptotic pathways. NFκB, COX-2, MAPKs and PI3K are the most common anti-apoptotic mediators whose targeting has been proposed for sensitization of tumors to radiotherapy.

4.2.1. NFκB

NFκB plays a central role in the survival of cancer cells. It has a positive cross-talk with PI3K/Akt pathway that is also involved in resistance to apoptosis [73]. NFκB also stimulates regulation of inhibitor of apoptosis (IAP), leading to downregulation of pro-apoptotic genes such as Bax and PUMA, as well as upregulation of anti-apoptotic Bcl-2 [74]. The expression of NFκB is upregulated in most types of cancer cells. Exposure to radiation also further amplifies overexpression of NFκB. It has been suggested that suppression of NFκB can reduce viability of cancer cells, while it may not cause significant toxicity in normal tissues [75]. Some studies have been conducted to sensitize cancer cells to radiation via targeting NFκB. Natural and herbal derived agents have potentials for this aim. Parthenolide is a herbal derived agent that inhibits NFκB via direct binding to IkappaB kinase beta (IKKbeta) [76]. In combination with radiation, parthenolide has been shown to sensitize cancer cells via NFκB inhibition, which is associated with upregulation of PTEN (suppressor of PI3K) [77,78]. Interestingly, NFκB inhibition by parthenolide has been shown to protect normal cells, while sensitizing prostate cancer cells to apoptosis [79].

Curcumin and resveratrol are other herbal NFκB inhibitors. Curcumin prevents activation of NFκB and its translocation into the nucleus. The direct effect of curcumin is mediated through IKK enzyme [80]. Furthermore, both curcumin and resveratrol are able to prevent the phosphorylation and degradation of inhibitor of NFκB (IκB) [81]. Curcumin has also been shown to suppress IL-1, leading to abrogation of cross-talk between PI3K and NFκB, which finally cause downregulation of NFκB [82]. In combination with radiation, curcumin has been shown to sensitize a wide range of cancer cells via increasing apoptotic induction. It has been suggested that suppression of NFκB via curcumin plays a key role in increasing apoptosis [83–85]. However, some other mechanisms such as activation of redox reactions within cancer cells may amplify apoptosis [86].

4.2.2. COX-2

COX-2 plays a pivotal role in inflammation and resistance to apoptosis. Its activity can be stimulated following upregulation of NFκB, extracellular signal–regulated kinase (ERK), p38, c-Jun N-terminal kinase (JNK), PI3K etc. COX-2 is mainly produced by cancer cells; however, other immune cells such as macrophages and fibroblasts amplify the release of COX-2 within TME [87]. It has been shown that COX-2 is produced in a higher level in TME compared to normal tissues, and plays a key role in the promotion of tumor growth and metastasis. Targeting of COX-2 has been proposed for sensitization of cancer cells to radiotherapy and chemotherapy [88]. It has been suggested that inhibition of COX-2 does not have a remarkable effect on tumor regression, while it can reduce tumor growth and proliferation of cancer cells. It seems that stimulation of apoptosis is responsible for reduction of tumor growth and proliferation [87].

Inhibition of COX-2 with celecoxib has been shown to increase apoptotic induction following irradiation for some types of cancer cells such as A549, murine mammary cancer cells (MCa-35), bladder carcinoma [89–93]. However, for some cancer cells such as PC-3 and DU145 cells, inhibition of COX-2 may not cause radiosensitization [94]. In vivo studies have also confirmed that COX-2 inhibition may lead to apoptosis and attenuation of tumor growth in some types of cancers. Inoue et al. examined the effect of diclofenac on COX-2 suppression as well as tumor growth in a xenograft LNCaP model. This study showed that diclofenac can reduce the level of COX-2, reduce tumor growth, and also induce apoptosis. Molecular analyses showed that COX-2 inhibition with diclofenac is associated with increased expression of TRAIL, an important receptor of apoptosis on cell surface [95]. In some clinical studies, the role of COX-2 in tumor resistance and regression have been confirmed. Furthermore, suppression of COX-2 has shown promising results for increasing survival and reducing tumor regression probability in patients with breast and lung cancers [96–99]. However, targeting of COX-2 has not shown suitable results in all clinical trials [100].

4.2.3. PI3K

The phosphatidylinositol 3–kinase (PI3K) is known as one of the most important players in cancer cell survival and proliferation. Overexpression of PI3K is associated with tumor growth and resistance to chemo/radiation therapy. PI3K is mainly regulated oppositely via

PTEN, a tumor suppressor gene. After p53, PTEN is the most frequently mutated tumor suppressor genes. The mutation in PTEN and upregulation of PI3K modulates regulation of some pro-apoptotic and anti-apoptotic genes. Furthermore, some microRNAs such as miR-20, miR-21, miR-106b miR-221 can suppress the expression of PTEN, leading to upregulation of PI3K and induction of radioresistance [101–105]. Inhibition of PI3K in combination with irradiation has also been shown to attenuate DDR in cancer cells, leading to a remarkable increase in apoptosis and reduced survival [106]. It seems that PI3K/Akt pathway plays a key role in DDR, and resistance to radiation [107]. It has been suggested that targeting this pathway leads to downregulation of ATM and DNA-PKcs; thus reduces DNA repair activity [108–110].

4.3. mTOR

The mammalian target of rapamycin (mTOR) is a signaling downstream to PI3K/Akt pathway and is a more favourable target for cancer therapy compared to PI3K or Akt. MTOR is involved in a wide range of cell functions such as proliferation, cell growth, metabolism and death [111]. MTOR is one of the important players in ribosomal biogenesis and protein synthesis. It works via activation of S6K and inactivation of 4EBP1 [112]. Inhibition of mTOR has been suggested for suppression of cancer cell proliferation in a wide range of cancer types [111]. Rapamycin is the most common inhibitor of mTOR. The combination of rapamycin and radiation can potentiate apoptosis in cancer cells [113]. Experimental studies performed so far have shown positive relationship between mTOR activity with radiation resistance, and the effectiveness of rapamycin application as an adjuvant for radiotherapy in multiplying cancer cell death [114–119]. Suppression of mTOR has also been shown to potentiate damage to tumor vascular [120]. Presently, rapamycin is undergoing a clinical trial study for safety in patients with rectal cancer (NCT00409994).

4.4. MAPKs

MAPKs include some subfamilies including JNK, ERK and p38 that translocate signals from the membrane to nucleus. Among these subfamilies, JNK and p38 are mainly induced by cell death signals such as tumor necrosis factor-α (TNF-α) and pro-apoptotic mediators, leading to a reduction in cancer cell survival [121]. However, it has been confirmed that p38 has a dual role and may trigger the survival of cancer cells [122]. Targeting p38 in some cancers may help suppress tumor growth [123]. NFκB is a potent suppressor of JNK, thus helps survival of cancer cells [124]. In contrast to JNK, the expression of ERK is stimulated following increased levels of cytokines and growth factors, leading to the promotion of survival and proliferation [124]. As the regulation of MAPKs is highly affected in cancer by ionizing radiation, it has been suggested that modulation of these genes can change tumor response to radiotherapy [124]. ERK is involved in resistance to apoptosis, leading to resistance to cancer therapy modalities [125]. ERK is activated secondary to application of MEK and BRAF inhibitors, leading to therapy resistance. This is due to the negative feedback interactions which exist between ERK with its upstream kinases (MEK and BRAF). Thus, targeting ERK in combination with anti-BRAF agents may be more useful for overcoming tumor resistance [125]. It has been suggested that activation of ERK following radiation exposure may be involved in DDR, activation of NFκB, inhibition of checkpoint kinase-1, and upregulation of Bcl-2 [121,126,127]. The radiosensitizing effect of ERK suppression has been observed for a large number of cell lines such as rhabdomyosarcoma, breast cancer, B-cell lymphoma, A549, Mia-PaCa2, and DU145 [126–131].

To date, some limited experimental studies have tried to improve radiation response of some cancers via targeting MAPK subfamilies. Zhao et al. showed promising results for combination of radiotherapy and p38 inhibition. Their study showed a significant increase in the p38 regulation for resistant MCF-7 breast cancer cells compared to primary cancer cells. They treated resistant MCF-7 cells with SB203580 to reduce phosphorylation of p38. Results showed that although irradiation can attenuate proliferation of cells, the combined treatment with both SB203580 and radiation can inhibit proliferation up to 3-fold [132]. Inhibition of JNK has also been shown to sensitize MDA-MB-231 and MCF-7 breast cancer cells to radiation. It has been proposed that JNK suppression enhances apoptosis and suppresses autophagy. It is possible that suppression of autophagy following JNK targeting plays a role in increasing apoptotic induction and radiosensitization of breast cancer cells [133]. However, it has been reported that no conspicuous relation exists between JNK inhibition and cell cycle arrest [134].

In contrast to mentioned studies, there are some evidences which suggest the positive role of JNK activation in radiosensitization of cancer cells. For example, in human cervical cancer cells, the upregulation of JNK is involved in promotion of mitochondrial apoptosis by radiation. Inhibition of JNK showed a remarkable downregulation of FasL and Bak [135]. In addition to positive or negative roles of p38 and JNK, it has been reported that these enzymes do not show a change following exposure to radiation and have no role in apoptosis and sensitization of non-small cell lung carcinoma (NSCLC) [136].

4.5. Targeting hypoxia

Tumor hypoxia is a common phenomenon in solid tumors. Hypoxia can occur in the inner layers of a solid tumor due to oxygen consumption by the outer layers of tumor cells. Furthermore, insufficient angiogenesis can disrupt oxygen supply within tumor. Tumor stiffness also increases pressure within tumor, which compresses vessels, leading to limited blood supply. Oxygen deprivation triggers several changes in metabolism and expression of genes involved in angiogenesis, cell cycle, and adaptation to low levels of oxygen and nutrition. Hypoxia-inducible factors (HIFs) are key regulators of adaptation of hypoxic cells to low oxygen levels. HIF-1 is the most common subfamily of these genes and regulates angiogenesis through upregulation of vascular endothelial growth factor (VEGF) [137]. HIF-1 can also trigger activation of rapamycin which inhibits mTOR; thus increases the incidence of autophagy [138]. Oxygen deprivation and HIF-1 upregulation can also cause a shift in oxidative phosphorylation (OXPHOS) to glycolysis, which is associated with generation of lactic acid [139]. Tumor acidity has a direct relation with poor survival of patients [139]. Hypoxia also plays a role in acquisition and maintenance of CSCs. The mentioned consequences of hypoxia show a potent relation with tumor resistance and make it an interesting target for radiosensitization.

It has been suggested that HIF-1 is involved in both radioprotection and radiosensitization. In irradiated cells, the expression of HIF-1 can activate p53, leading to more apoptosis. However, HIF-1 is a potent stimulator of VEGF; thus protects tumor via maintenance of endothelial cells and promotion of vacuolization [140]. HIF-1 upregulation also triggers mitotic activity following tumor irradiation. This results from its role in energy supply during hypoxia [141]. The dual role of HIF-1 following irradiation suggests that the radiosensitization effect of HIF-1 targeting is highly dependent on p53 activity and its role in apoptosis [142]. In some conditions like mutation and inactivation of p53, HIF-1 inhibition may be a promising strategy for sensitization of tumor to radiotherapy [143].

4.6. Targeting angiogenesis

Angiogenesis is one of the most critical issues in cancer therapy. Angiogenesis was known as a key player of tumor growth, when VEGF was identified in 1970 [144,145]. VEGF proteins include VEGF-A, VEGF-B, VEGF-C and VEGF-D [146]. VEGF applies its effect through its receptors, including VEGF receptor 1–3 [144]. It is well known that inhibition of angiogenesis via targeting angiogenesis stimulators such as VEGFR1–3 is associated with inhibition of tumor growth and increasing survival of cancer patients [146]. Upregulation of VEGF

receptors especially VEGFR-2 is associated with tumor growth and angiogenesis [144]. It has been suggested that the interaction of VEGF-A with VEGFR2 plays a main role in angiogenesis [147]. In addition to VEGF, some other factors such as fibroblast growth factors (FGFs), matrix metalloproteinase (MMP), angiopoietin-1 and 2, and platelet-derived growth factor (PDGF) are involved in generation of new vessels [148]. Nowadays, the most common anti-angiogenesis and anti-VEGF drug is bevacizumab, approved by FDA in 2004 [149]. It is a monoclonal antibody with ability to bind VEGF-A; thus reduces its binding to VEGFR2. Some other anti-VEGF antibodies such as aflibercept, ramucirumab and tanibirumab have also received FDA approval [150].

As the first FDA approved anti-VEGF, bevacizumab has been administered in some clinical trials. A clinical trial which began in 2006 tried to evaluate using bevacizumab as adjuvant in combination with hypofractionated stereotactic radiotherapy (HFSRT) for patients with malignant glioma. Patients received bevacizumab at a dose of 10 mg/kg. Radiotherapy was administered as 30 Gy in five fractions. This study reported well tolerated administration of bevacizumab without significant toxicity [151]. In another study which used bevacizumab in combination with temozolomide and radiotherapy, some side effects such as fatigue, thrombosis, and myelotoxicity were reported. However, authors claimed that the side effects were well tolerated [152]. These studies as well as another study by Chinot et al. did not report a significant effect for the combination of bevacizumab with radiotherapy except for an increase in progression-free survival times (PFS) [153]. However, Cuneo et al. reported a significant increase in overall survival [154]. The combination of bevacizumab with re-irradiation with HFSRT (3 × 11 Gy) has been shown to be useful for increasing survival in patients with recurrent glioblastoma [155].

To date, some studies have been conducted to determine the possible radiosensitization of some other anti-VEGF agents. As earlier mentioned, hypoxia can cause resistance of tumor to radiotherapy. Therefore, this issue may be a concern that inhibition of angiogenesis may lead to hypoxia; thereby attenuating tumor response to radiation. It has been confirmed that the combination of anti-VEGF and irradiation cause reducing vascular density [156]. Concomitant irradiation and treatment of colon and lung human tumor xenograft models with AZD2171 (a potent anti-VEGF) showed improvement in radiation response of tumor; however it was associated with increased hypoxia [157]. AZD2171 (also known as cediranib) is able to inhibit both VEGFR2 and VEGFR3 [158]. Concomitant irradiation of Calu-6 lung xenografts in combination with AZD2171 also showed a significant increase in apoptosis and necrosis in tumor. Although this was associated with increased hypoxia, it seems that VEGF suppression prevented repopulation of hypoxic cells [159]. Similar results were observed for renal cell carcinoma [160].

In a human tumor xenograft model of lung carcinoma 54A it has been shown that treatment of mice with 20 or 40 mg/kg anti-VEGFR2 (DC101) and radiation can cause remarkable increase in tumor delay compared to irradiation alone, while it was associated with developed ascites in some mice [161]. Also, DC101 can reduce proliferation and migration of endothelial cells following irradiation [162]. A study by Winkler et al. reported that DC101 administration 4–6 days before irradiation led to the most delay in tumor growth in mice-bearing human glioblastoma xenografts. At day 5, the fraction of hypoxic cells reduced dramatically. Also, increased apoptosis was observed 5 days after administration of DC101. The expression of angiopoietin was increased during some days after treatment with DC101, which caused oxygenation of tumor cells [163]. Another study showed that using a lower dose of DC101 (0.2 mg) can reduce tumor growth and angiogenesis. Irradiation of human-SSC-1 xenograft led to a 35% reduction in tumor volume after 75 days; however, the combination with DC101 increased it to 65% [164].

Although administering anti-angiogenesis drugs before irradiation has shown promising results for clinical application, it has been suggested that post-treatment injection may be more effective. This is as a result of upregulation of angiogenesis genes after irradiation. Administering ZD6474 (an inhibitor of VEGFR2 and EGFR) after irradiation showed more suppression of angiogenesis and tumor growth [165].

4.7. EGFR agonists and other receptor tyrosine kinase (RTK) inhibitors

RTKs are cell surface receptors that are involved in transferring several signals into cells [166]. Platelet-derived growth factor receptors (PDGFR), fibroblast growth factor receptors (FGFRs) and epidermal growth factor receptor (EGFR) are the most important subfamilies of RTKs. EGFR is an important receptor on the surface of epithelial cells that regulates proliferation and homeostasis [167]. Some mutations and dimerization may cause aberrant upregulation of EGFR [168]. The overexpression of EGFR in some malignancies such as breast as well as head and neck cancers have been reported to predict poor survival [169]. Targeting EGFR especially EGFR2 (HER2) has been studied in several experimental and clinical studies. Herceptin is the most famous anti-HER2 drug approved by FDA and is currently used for patients with HER2-positive breast cancers [170].

Cetuximab is an anti-EGFR that has been used in combination with radiotherapy and chemo-radiotherapy. Some clinical trials have shown promising results for its combination with radiotherapy (NCT00004227). Patients with grade 3–4 squamous-cell carcinoma of the head and neck received cetuximab weekly during conventional radiotherapy. Results showed no further toxicity with significant increase in the survival at 3 and 5 years follow-up [171,172]. Similar beneficial effects were observed for other EGFR monoclonal antibody, nimotuzumab [173]. In a phase 2 clinical trial for cetuximab combination with cisplatin and radiotherapy for head and neck carcinoma, an increase in survival was reported [174]. However, phase 3 clinical trial showed no increased survival. In addition, this trial found more toxicity for cetuximab compared to chemo-radiotherapy alone [175]. Similar results were also reported for patients who received 5-FU chemoradiation with cetuximab [176]. In addition to cetuximab, panitumumab as a monoclonal antibody have been used in combination with chemoradiation and showed no satisfactory results [177,178].

Clinical trials involving the combination of other tyrosine kinase inhibitors with radiotherapy are ongoing. Sunitinib, regorafenib, sorafenib, erlotinib and imatinib are the most common tyrosine kinase inhibitors that are used in combination with radiotherapy. These drugs were approved by FDA for treatment of some cancer types. Results of some clinical trial are presented in Table 2.

4.8. TGF-β

TGF-β is the most potent immunosuppressive cytokine. However, it has been reported that TGF-β has a dual role in the initiation and progression of cancer. It seems that TGF-β has a suppressive effect in the initiation of tumorigenesis via induction of apoptosis and cell cycle inhibition [8]. In contrast, TGF-β plays a key role in the progression and metastasis of tumor [8]. The main source of TGF-β is CAFs; however, it can be released by other tumor supportive cells such as cancer cells, CSCs and Tregs. On the other hand, TGF-β helps resistance of CSCs to anti-cancer drugs, stimulates differentiation of CD4+ helper lymphocytes to Tregs, and infiltration of CAFs into tumor. Suppression of TGF-β can reduce the numbers of Tregs and increase the number of CD8+ cytotoxic lymphocytes within TME. The combination of radiation therapy with TGF-β blockade has been proposed as a strategy for tumor vaccination. In an animal model, it has been shown that inhibition of TGF-β in combination with irradiation led to remarkable suppression of tumor growth compared to irradiation alone. Further analyses showed that TGF-β blockade increases the number of CD8+ T cells [179]. As earlier mentioned, upregulation of PD-1 following irradiation may lead to exhausting immune system activity via CD8+ T cells apoptosis. Thus, dual inhibition of TGF-β and PD-1 after tumor irradiation can cause more suppression of tumor and attenuates tumor regression

probability [179]. Opposite results have been shown for MIA PaCa-2, and p53 mutant pancreatic cancer cell. It has been shown that the loss of TGF-β receptor II (RII) leads to resistance of MIA PaCa-2 to radiation. However, activation of TGF-β and overexpression of RII leads to induction of apoptosis and cell cycle arrest [180] (Fig. 2).

4.9. Targeting immune checkpoints

4.9.1. PD-1 – PDL-1 pathway

As earlier mentioned, Tregs play a key role in radioresistance of tumors. The main effect of Tregs is suppression of immune responses against cancer via inhibition of CTLs and NK cells [18]. CTLs are more radiosensitive compared to Tregs in response to conventional radiotherapy. Thus, tumor response is affected because of increasing Tregs to CTLs ratio [19]. The main suppressive effect of Tregs on immune system responses within TME is mediated via PD-1-PD-L1 pathway. PD-1 is expressed on the surface of CD4+ and CD8+ cells, NK cells, B cells, and DCs [181]. Thus, targeting this pathway in combination with radiotherapy is an interesting strategy for boosting immune system and exhausting Tregs within TME [182,183]. Exposure of cancer cells to radiation may cause upregulation of PDL-1, leading to resistance to subsequent doses of radiotherapy [184]. Irradiation of cancer cells like Hela cancer cells showed an increased activity of Tregs and immunosuppression like decreased numbers of CD4+ and CD8+ cells. This was associated with increased expression of PD-1 and PDL-1 [185]. Suppression of this pathway in irradiated Hela cells has been shown to reverse immunosuppression and apoptosis in lymphocytes [185]. Inhibition of PDL-1 can abrogate depletion of CD4 and CTLs, thus sensitizes tumor to ionizing radiation [186]. In a murine model, it has been shown that using dual inhibition of PDL-1 and T cell immunoglobulin mucin-3 (TIM-3) in combination with radiation may be more efficient for tumor control. Inhibition of PDL-1 in combination with radiation showed an increase in TIM-3, leading to radioresistance of head and neck squamous cell carcinoma (HNSCC). Results showed that when both PDL-1 and TIM-3 were inhibited, the infiltration of CTLs increased, while the number of Tregs reduced. This was associated with elevated release of anti-tumor cytokines such as IFN-γ [187]. A clinical trial study for HNSCC patients using dual inhibitors of PD-L1 (Durvalumab) and CTLA-4 (Tremelimumab) is ongoing (NCT03426657).

Evidence from some radioresistant tumors show a high expression of PDL-1 and infiltration of Tregs [187]. Furthermore, high expression of PDL-1 in circulating cancer cells can predict poor survival of patients with cancer [188]. For clinical applications, to date, some PD-1–PDL-1 inhibitors have been examined. In a phase 1 clinical trial, using antibody of anti-PD-1 showed an increased response and tumor growth delay was reported for some cancers including NSCLC, melanoma, and renal-cell cancer [189]. Pembrolizumab (MK-3475) is a PDL-1 inhibitor approved by FDA for patients with advanced NSCLC [190], and is under study in a clinical trial for HNSCC patients (NCT03386357). In a clinical trial which used this antibody, promising results were obtained with minimal side effect [190]. Clinical trials for the combination of pembrolizumab with radiotherapy, chemotherapy and stereotactic body radiotherapy (SBRT) for patients with NSCLC and advanced Markel cell carcinoma are ongoing (NCT03924869, NCT03631784, and NCT03304639).

Nivolumab is another anti-PD-1 that has been approved by FDA for patients with lung squamous cell carcinoma (LSCC) [191]. A case report by Lazzari et al. reported the beneficial effect of adjuvant radiotherapy in combination with nivolumab for a patient with advanced squamous cell lung cancer. The existence of malignant nodules was confirmed in the both sides of the lung. However, a 3–year follow-up after treatment with radiotherapy and nivolumab showed no tumor regression [192]. A clinical trial study has also reported no further toxicity for radiotherapy and nivolumab combination [193]. Some clinical trials are ongoing for the combination of nivolumab and radiotherapy in patients with metastatic NSCLC, uveal melanoma, and brain metastasis (NCT02696993, NCT02434081, and NCT02831933).

PDL-1 and CTLA-4 are the most interesting targets for cancer radioimmunotherapy. It has been suggested that radiation plays a key role in the upregulation of these antigens. It has been shown that the production of IFN-γ by CD8+ cytotoxic T cells plays a central role for triggering PD-1 [194]. It has been suggested that upregulation of PDL-1 is an important biomarker for using immunotherapy in combination with radiotherapy. Increased expression of these immune checkpoints depend on mutations in tumor and also exposure to ionizing radiation [195]. An experimental study showed that irradiation of glioblastoma and melanoma cancer cells with fractionated irradiation (5×2 Gy) induces upregulation of PD-1, while a single dose of 10 Gy has a lower effect on the expression of PD-1 [195]. The evaluation of patients with HNSCC and rectal cancer also confirmed an upregulation of PD-1 following chemotherapy or chemoradiation [196,197]. It has been suggested that patients with overexpression of PD-1 are candidate for using immune checkpoint inhibitors in combination with radiotherapy or radio-chemotherapy [197].

4.9.2. CTLA-4

CTLA-4 is a glycoprotein which is expressed on the surface of lymphocytes. Ligation of this ligand causes reduced activity of naive T cells, thus it exhausts response of CTLs against cancer cells [181]. Targeting of CTLA-4 has been of interest in immunotherapy in recent years. CTLA-4 antibodies are one of the most common ICIs approved by FDA for suppression of Tregs and enhancement of immune system activity within TME [198]. In recent years, the combination of CTLA-4 targeting with radiotherapy has attracted interest as a radio-immunotherapy method [181]. The synergic effect of radiotherapy and CTLA-4 targeting has been reported in a case report in 2012, when a patient with melanoma received ipilimumab and radiotherapy. The patient's examinations showed a progression in disease following treatment with ipilimumab alone. However, after radiotherapy, an increase in tumor regression and increased number of CD4+ were reported [199]. There are other reports which suggest that radiotherapy in combination with ipilimumab triggers abscopal effect that aids cancer treatment via modulation of immune system in melanoma and lung cancer [200,201]. In a clinical trial conducted in 2014, ipilimumab was administered after radiotherapy for metastatic prostate cancer patients. The aim of this study was to evaluate the overall survival of patients who received ipilimumab compared to placebo. Results of this trial showed no significant difference; however, statistical analyses suggested a reduced hazard ratio for patients who received ipilimumab. This may indicate an increased survival at a longer time [202].

A study reported that the combination of radiotherapy with anti-CTLA4 may not overcome tumor resistance in patients with metastatic melanoma. Suppression of CTLA4 using anti-CTLA4 antibody in combination with radiation in a mouse model resulted in major tumor regression. Analyses showed that treatment with anti-CTLA4 antibody and radiation led to overexpression of PDL-1, leading to CTLs exhaustion. This study suggested that when an anti-PD-L1 antibody is added to treated cells, the activity of immune system is augmented and response of cancer cells increases remarkably [203] (Tables 1 and 2).

4.10. Dynamics of the immune responses in tumor after radiotherapy

Radiotherapy including hypofractionated techniques lead to serious changes in the immune system in favor of both tumor growth and suppression. The knowledge of changes in the expression of immune mediators such as immune checkpoints and angiogenesis stimulators can help control tumor growth. For example, it is known that angiogenesis may be triggered during some days after irradiation, thus administration of VEGF inhibitors starting after or during radiotherapy may be more efficient compared to before irradiation [165]. Similar results have also been suggested for immune checkpoint inhibitors. The dynamic changes in the infiltration of immune cells and secretion of cytokines may play a key role in the response of tumor to radiotherapy.

Table 1
Summary of results for radiosensitization of cancer cells via inhibition of different targets within tumor.

Route	Cell type/tumor	Drug	Target	Drug dosage	Radiation dose	Findings	References
In vitro	A549	Celecoxib	COX-2	100, 200 or 400 μM	6 Gy	Induction of apoptosis and reduction of proliferation following treatment with celecoxib	[89]
In vitro	PC-3, DU145, and LNCaP	Celecoxib	COX-2	5, 10 and 25 μM	2–15 Gy	Celecoxib does not cause sensitization of prostate cancer cells to radiation	[94]
In vivo	Xenograft LNCaP	Diclofenac	COX-2	10 to 1000 μM	2 or 4 Gy	COX-2 inhibition by diclofenac induces regulation of TRAIL, thus increases apoptosis	[95]
In vitro/in vivo	A549 mouse xenograft	PI-103	PI3K	1 μM	4 Gy	PI-103 can attenuate non-homologous end joining (NHEJ)	[108]
In vitro/in vivo	Bladder cancer xenograft	RAD001	mTOR	1.5 mg/kg daily	3 Gy daily for 3 days	Cell cycle arrest in G1 and G2 were observed.	[116]
In vitro/in vivo	H460 xenograft	Rapamycin	mTOR	2 mg/kg for 7 days	2 Gy daily for 5 days	Inhibition of mTOR can reduce survival via induction of both apoptosis and autophagy.	[118]
In vivo	Calu-6 and LoVo tumor xenograft	AZD2171	VEGF	3 or 6 mg/kg before irradiation	2 Gy daily for 3 or 5 consecutive days	Inhibition of VEGF led to hypoxia, it could reduce tumor growth.	[157]
In vivo	Calu-6 lung xenografts	AZD2171	VEGF	3 mg/kg	2 Gy daily for 5 consecutive days	Suppression of VEGF prevented hypoxic cell proliferation.	[159]
In vitro/in vivo	PC3 xenografts	Sunitinib	Multiple receptor tyrosine kinases (RTKs) inhibitor	1.3 mg for each mouse starting after the end of irradiation	2 Gy daily for 5 consecutive days	Sunitinib can reduce angiogenesis especially when administered after irradiation.	[211]
In vitro/in vivo	Glioblastoma or lung carcinoma xenografts	Sunitinib	RTKs inhibitor	40 mg/kg during irradiation	21 Gy (7 fractions)	Sunitinib increased apoptosis of endothelial cells, reduced angiogenesis and prolonged tumor regrowth delay.	[212]
In vivo	H226 or UM-SCC6 xenografts	Erlotinib	EGFR	0.8 mg daily	2 Gy twice per week for 3 weeks	An increase in apoptosis, cell cycle arrest and tumor growth delay were reported.	[213]
In vivo	Glioblastoma xenografts	Erlotinib	EGFR	100 or 150 mg/kg for 2 weeks	6 × 2 Gy (3 fractions per day)	An increase in glioblastoma response to radiation was reported.	[214]
In vitro	TP53 wild-type RT112 bladder transitional cell carcinoma	Imatinib	EGFR	3 or 6 μM	2–10 Gy	Imatinib may be useful for treatment of muscle-invasive bladder cancers.	[215]
In vivo	54A mouse Xenograft	DC101	VEGF2	20–40 mg/kg every 3 days × 6 injections	Up to 100 Gy in 5 fractions for 5 consecutive days	DC101 increased tumor delay, however it caused development of ascites in some mice following injection of higher doses of DC101.	[161]
In vivo	Human-SSC-1 xenograft	DC101	VEGF2	0.2 mg (twice per week for 3 weeks)	3 Gy twice per week for 3.5 weeks	DC101 reduced tumor volume and increased response of endothelial cells. No side effect was reported.	[164]
In vivo	Mice bearing U87 glioma	DC101	VEGF2	40 mg/kg	7 Gy × 3 fractions in 1 day	DC101 induced oxygenation via angiopoietin. The most effective time window for administering DC101 was 4–6 days before irradiation.	[163]
In vivo	Calu-6 lung xenografts	ZD6474	VEGFR2 and EGFR	50 mg/kg before each fraction or after last irradiation	2Gy for 3 days	Post-administration is more effective for suppression of angiogenesis and tumor growth.	[165]
In vivo	LY2 and MOC2 tumor xenografts	αPDL1 and αTIM3	PD-1 and TIM3	10 mg/kg for each antibody	10 Gy	Increased CTLs/Tregs ratio and survival following dual inhibition of PDL-1 and TIM-3.	[187]
In vivo	B16-OVA melanoma and 4 T1-HA breast carcinoma xenograft	Anti-PD-1 antibody	PD-1	200 μg for each mouse	10 Gy or 20 Gy	Higher dose of radiation caused more presentation of tumor antigens, inhibition of PD-1 increases infiltration of CTLs.	[53]
In vivo	Murine B4B8 and LY2 squamous cell carcinoma cells	Anti-PD-1 antibody	PD-1	10 mg/kg (twice per week for 3 weeks)	4, 8, or 25 Gy	Inhibition of PDL-1 led to increased infiltration of CD4 and CD8.	[186]
In vivo	4T1 xenograft	1D11	TGF-β	200 μg for each mouse from 1 day before to 11 days after irradiation	6 Gy in 5 consecutive days	Inhibition of TGF-β caused an increase in CD8+ T cells and release of IFN-γ.	[179]
In vitro	MIA PaCa-2	L744,832 (an inducer of RII)	TGF-β	5–10 μM	5 Gy	Activation of TGF-β can sensitize cancer cells to radiation via induction of apoptosis.	[216]
In vitro	MIA PaCa-2	Recombinant TGF-β	TGF-β	10 ng/ml	5 Gy	Suppression of TGF-β lead to resistance of cells to radiation.	[180]

Table 2
Results of clinical trials for improving tumor response using inhibition of different targets within tumor.

Tumor type	Drug	Target	Drug dosage	Radiation dose	Findings	References
Prostate cancers	Celecoxib	COX-2	400 mg twice daily	70 to 74 Gy	Administering celecoxib does not cause any side effect.	[217]
Squamous-cell carcinoma of the head and neck	Cetuximab	VEGF	250 mg/square meter/week	60 Gy as fractionation	9.5-month increase in locoregional tumor control and 20-month increase in overall survival at 3 and 5 years.	[171,172]
Squamous-cell carcinoma of the head and neck	Cetuximab	VEGF	250 mg/square meter/week	70 Gy (35 × 2 Gy) plus cisplatin	Cetuximab was well tolerated and results were promising for survival.	[218]
Head and neck carcinoma	Cetuximab	VEGF	250 mg/square meter/week	70 Gy (35 × 2 Gy) plus cisplatin	No increase in survival compared to chemoradiation alone was reported.	[175]
Glioblastoma	Bevacizumab	VEGF	10 mg/kg for 3 times during 28 days	30 Gy in 5 fractions	Administration of bevacizumab was reported as safe.	[151]
Glioblastoma	Bevacizumab	VEGF	10 mg/kg every 2 weeks as starting radiotherapy	30 × 2 Gy	Some toxicities such as fatigue, thrombosis, wound breaking and encephalopathy were reported.	[152]
Glioblastoma	Bevacizumab	VEGF	10 mg/kg at day of irradiation and two weeks later	5 × 5 Gy	An increase in overall survival was reported, bevacizumab did not cause any increase in toxicity.	[154]
Melanoma	Ipilimumab	CTLA-4	10 mg/kg	15.5 Gy	An increase in tumor regression and increased numbers of CD4+ were reported.	[199]
Resistant prostate cancer	Ipilimumab	CTLA-4	10 mg/kg	8 Gy (1–5 time)	Hazard ratio suggested an increased survival.	[202]
Extracranial oligometastases	Sunitinib	RTKs inhibitor	25–50 mg two times	40–50 Gy (10 fractions)	Sunitinib administration led to reduction of neutrophils, lymphocytes and platelets.	[219]
Metastasis renal cell carcinoma	Sunitinib or sorafenib	RTKs inhibitor	Sunitinib 50 mg daily, or sorafenib 400 mg twice daily	20 Gy	Administration of sunitinib or sorafenib was safe. No change in local tumor control was observed.	[220]
Non-resectable glioblastoma	Sunitinib	RTKs inhibitor	37.5 mg daily for 8 weeks	60 Gy as fractionation	No increase in survival was reported.	[221]
Recurrent high-grade glioma	Sunitinib	RTKs inhibitor	37.5 mg daily	30 to 42 Gy as fractionation	6-month increase in the free survival was reported.	[222]
Cecal cancer (a case report)	Regorafenib	RTKs inhibitor	Not reported	20 Gy	An unexpected myelopathy was reported following treatment with regorafenib.	[223]
Oligometastatic colorectal cancer (a case report)	Regorafenib	RTKs inhibitor	120–160 mg per day	54 Gy	3-year progression-free survival reported	[224]
Advanced HCC	Sorafenib	RTKs inhibitor	800 mg per day	30–58 Gy	Complete response of primary tumor	[225]
Advanced HCC	Sorafenib	RTKs inhibitor	400 mg/day	30–60 Gy	Using sorafenib in combination with radiotherapy is safe for patients with advanced HCC.	[226]
NSCLC with brain metastasis	Erlotinib	EGFR	150 mg per day for 6 days after radiotherapy	35 Gy (2.5 Gy per day)	Erlotinib was well tolerated and no neurotoxicity was reported.	[227]
NSCLC	Erlotinib	EGFR	150 mg/day per day	70.2 Gy as fractionation in combination with cisplatin	In spite of high toxicity, a high tumor response was reported.	[228]
Unresectable and symptomatic desmoid tumors	Imatinib	EGFR	300 or 400 mg daily	50–54 Gy (2 Gy per fraction)	Nausea and fatigue were reported as side effects but they were tolerable. The combination of imatinib and radiation therapy was effective for preventing tumor growth	[229]

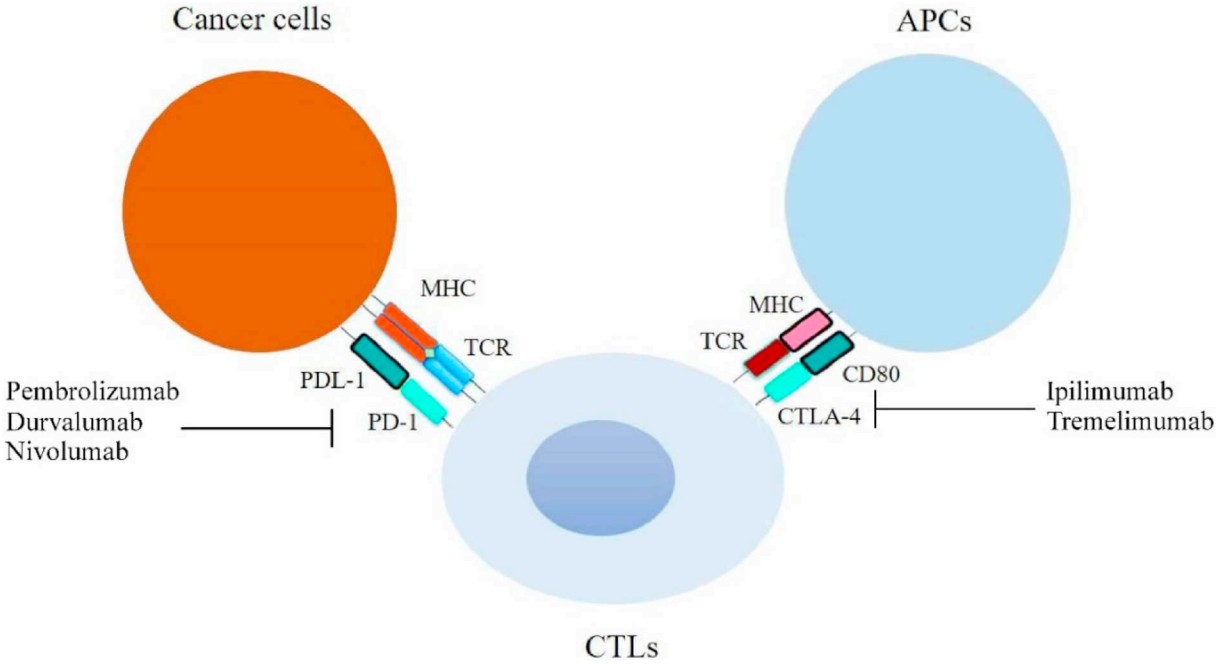

Fig. 3. Boosting the immune system against cancer cells using immune checkpoint inhibition. The expression of PD-1 and CTLA-4 cause apoptosis of CTLs, leading to exhaustion of the immune system. Inhibition of PD-1 and CTLA-4 can boost the activities of CTLs.

Irradiation of colon cancer cells showed an increase in the infiltration of macrophages between 5 and 10 days and infiltration of CD8+ T cells after 8 days. Tregs and myeloid-derived suppressor cells (MDSCs) also showed regular turnover [204]. Another study confirmed that the most obvious increase in the CD8+ cytotoxic T cells to Tregs ratio occurs 5–8 days after hypofractionated irradiation [205]. In vivo studies suggest that suppression of PD-1 and CTLA-4 starting some days after irradiation is the most effective strategy for the prevention of CD8+ cytotoxic T cells exhausting [206–209]. However, clinical studies with some months delay for starting immunotherapy after hypofractionated radiotherapy have shown interesting results (Fig. 3) [210].

4.11. Conclusion

Response of TME to radiotherapy is critical for exploring new strategies for improving tumor control. Radiotherapy is usually performed using a dose of 2 Gy per fraction for some weeks. However, in recent years, some studies suggested using new techniques such as SBRT, which uses few fractions with a higher dose in each fraction. This method is more suitable especially for brain tumors and has shown better results. It has been suggested that a high dose of ionizing radiation is more efficient to release immune antigen stimulators, leading to more antigen cross-presentation. It seems that HSRT causes an increase in the CTLs to Tregs ratio compared to conventional radiotherapy, leading to more activity of immune system within TME. Polarization of macrophages and their roles in tumor response to radiotherapy is very complicated. Although M1 cells have anti-tumor activity, in response to radiation, activation of both M1 and M2 macrophages may trigger tumor regrowth following upregulation of anti-apoptotic, angiogenesis and metastatic genes.

Inhibition of DNA repair may sensitize a wide range of tumors to radiotherapy; however, this may cause severe toxicity in normal tissues and also increase the risk of carcinogenesis. Stimulation of apoptosis is an interesting strategy for suppression of tumor proliferation and increasing survival of patients. NFκB and COX-2 is the most common mediators that increase survival of cancer cells via inhibition of apoptosis. Inhibition of these mediators have been shown to sensitize cancer cells, while it may not cause normal cells/tissues toxicity. In spite of promising results, some animal and clinical studies have suggested no remarkable improvement in tumor response following treatment with celecoxib. TGF-β is another player in apoptosis induction in cancer cells. In addition, it has a wide range of effects on the survival and invasion of tumor. Thus, selective inhibition of this pathway may be suitable for tumor control.

Results of MAPKs targeting show different roles for JNK and p38, although it seems that ERK is a potential target for radiosensitization of cancer cells. JNK and p38 may be involved in apoptotic induction via triggering the release of cytochrome *c* and depolarization of mitochondria. However, in other cancer cells, these genes may not cause a remarkable change in survival, or may trigger survival. This suggests that targeting JNK and p38 cannot be proposed for sensitization of different types of cancers. Also, for a specific type of cancer there is a need to detect the role of these genes in different cells lines. Similar effects have been shown for HIF-1. It stimulates p53 and apoptosis, as well as angiogenesis and protection of endothelium. Therefore, its targeting may attenuate both apoptosis and angiogenesis. It seems that direct targeting of angiogenesis in combination with radiotherapy is more favourable for tumor growth inhibition. VEGF inhibition can reduce the density of vessels within tumor. This is associated with hypoxia within tumor. However, xenograft studies as well as clinical trials have shown that inhibition of VEGF sensitizes tumor to radiotherapy. As irradiation alone triggers upregulation of angiogenesis genes, it has been proposed that administering anti-angiogenesis drugs post-irradiation may be more useful for the management of tumor vascularization and growth. In clinical trials, no remarkable increase in survival of patients with high grade glioblastoma was reported. However, it may cause an increase in overall survival and may also be useful for combination with re-irradiation for recurrent tumors.

The combination of SBRT with immune checkpoint inhibitors has also attracted a lot of interest in recent years and some clinical trials have been performed for some tumors, including glioblastoma and NSCLC. PDL-1 and CTLA-4 are the most common immune checkpoints for tumor targeting in combination with radiotherapy. Thus, inhibition of PDL-1 or CTLA-4 may cause upregulation of another. It seems that dual targeting of both PDL-1 and CTLA-4 is more effective for some cancers. Emerging evidences have shown no further toxicity compared

to SBRT alone and suggest phase 3 clinical trials. In conclusion, the combination of radiotherapy with immune targets is interesting for more sensitization of a wide range of tumors. It seems that the combination of ICIs with hypofractionated radiotherapy techniques is the most promising strategy for treatment of cancer.

Compliance with ethical standards.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not applicable.

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