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# Molecular determinants as therapeutic targets in cancer chemotherapy: An update

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ABSTRACT

It is well known that cancer cells are heterogeneous in nature and very distinct from their normal counterparts. Commonly these cancer cells possess different and complementary metabolic profile, microenvironment and adopting behaviors to generate more ATPs to fulfill the requirement of high energy that is further utilized in the production of proteins and other essentials required for cell survival, growth, and proliferation. These differences create many challenges in cancer treatments. On the contrary, such situations of metabolic differences between cancer and normal cells may be expected a promising strategy for treatment purpose. In this article, we focus on the molecular determinants of oncogene-specific sub-organelles such as potential metabolites of mitochondria (reactive oxygen species, apoptotic proteins, cytochrome c, caspase 9, caspase 3, etc.), endoplasmic reticulum (unfolded protein response, PKR-like ER kinase, C/EBP homologous protein, etc.), nucleus (nucleolar phosphoprotein, nuclear pore complex, nuclear localization signal), lysosome (microenvironment, etc.) and plasma membrane phospholipids, etc. that might be exploited for the targeted delivery of anti-cancer drugs for therapeutic benefits. This review will help to understand the various targets of subcellular organelles at molecular levels. In the future, this molecular level understanding may be combined with the genomic profile of cancer for the development of the molecularly guided or personalized therapeutics for complete eradication of cancer.


**Contents**



*Abbreviations:* ROS, Reactive oxygen species; Cyt c, Cytochrome c; MT, Mitochondria; dox, Doxorubicin; WP, Warburg phenomenon; PFKFB's, 6-Phosphofructo-2-kinase/fructose-2,6-biphosphatases; PFK's, Phosphofructokinases; PK, Pyruvate kinases; VDAC, Voltage-dependent anion channel; OMM, Outer mitochondrial membrane; HK, Hexokinase; MLT, Melatonin; GTH, Glutathione; BSO, Buthionine sulfoximine; DDS, Drug delivery system; MAMs, Mitochondria-associated endoplasmic reticular membranes; ER, Endoplasmic reticulum; MCU, Mitochondrial $Ca^{2+}$ uniporter; TCR, T Cell receptor; UPR, Unfolded protein response; SRs, Sigma receptors; S1R, Sigma-1 receptor; S2R, Sigma-2 receptor; CEP1, Cephalostatin 1; CHOP, C/EBP Homologous protein; TX, Thioredoxins; TXR, Thioredoxin reductases; NCN, Nucleolin; CAR, Chimeric antigen receptor; NPC, Nuclear pore complex; NUPs, Nucleoporins; NLS, Nuclear localization signal; Imp, Importin; Exp, Exportin; SRSF, Serine/arginine-rich splicing factor; PRMT, Protein arginine methyltransferase; Txl, Taxol; CPs, Cathepsin; LMP, Lysosomal membrane permeabilization; LaMP, Lysosome-associated membrane protein; NPs, Nanoparticles; PS, Phosphatidylserine; PE, Phosphatidylethanolamine; ANX, Annexin; PRRs, Pattern recognition receptors; PPARγ, Peroxisome proliferator-activated receptor- γ; IGF, Insulin-like growth factor; HCC, Hepatocellular carcinoma; CEP1, Cephalostatin 1; NCs, Nanocarriers; LMP, Lysosomal membrane permeabilization.

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## 1. Introduction

Normal cells and tissue possess so well organized bio-functions through production and release of growth-promoting signals that affect normal cell growth as well as the cell cycle including apoptosis. On the contrary, cancer cells have different capabilities including proliferative signaling, escaping growth suppressors, resisting cell death, immortality, angiogenesis followed by invasion-metastasis (Gutschner & Diederichs, 2012). That is why, cancer remains as a leading cause of morbidity and mortality universally, and it is anticipated that approximately more than 20 million new cases will be registered by the year 2025 (Ferlay et al., 2015).

For the treatment of cancers, various chemotherapeutic regimes are available in use. However, they are associated with the problem of potential toxicities and damaging side effects due to the lack of their tumor specificity. Hence, the prime goal of the researcher of this field is to find a common marker/s or determinants of cancerous cells that can be selectively and easily targeted by anticancer drugs or drug carrier systems without affecting the healthy cells. Thus, there is an urgent and utmost need for improvements in conventional therapy to deliver the drug not simply into the target cell but also to its specific cell organelles.

The intracellular drug delivery is not an easy task because of the lipophilic and partially permeable nature of the cell membrane, and after crossing that cell membrane then they should reach to subcellular organelles. Concomitantly, it remains impermeable to molecules larger than 1kDa. For cellular access of large molecular complexes, a cell possesses some active internalization mechanisms such as endocytosis, pinocytosis etc. (Bareford & Swaan, 2007). There are various endocytosis pathways which are typically clathrin-independent and dependent endosomal transport systems (Le Roy & Wrana, 2005), cell adhesion molecule-mediated endocytosis (Christofori, 2003), fluid phase endocytosis (Duchini, Govindarajan, Santucci, Zampi, & Hofman, 1996), caveolin mediated receptor-mediated endocytosis (Schmid, 2017), etc. These pathways/mechanisms help in drug carrier internalization at the intracellular compartments. After crossing the plasma membrane barrier, the specifically designed and fabricated drug delivery system should reach to the cell organelles without loss of their integrity as well as drug payload to provide improved efficacy (Ge & Liu, 2013). Various pathological changes do occur in the case of cancer which has been exploited by the researchers to meet out the challenges regarding cancer treatment reorganization of subcellular organelles. The cancer cells possess various metabolic and complementary pathway(s) to fulfill the requirement of high energy etc. for cells survival, growth, and proliferation (Lunt & Vander Heiden, 2011). In the present scenario, scientists are more focused to exploit "the biochemically changed bio-environment" of cancer such as suppression or acceleration of metabolites or generation of reactive oxygen species (ROS), lactate, etc. as an adjunct clinical intervention along with targeted cancer therapy.

The drug targeting in a way will help to overcome the resistance that generally arises due to the metabolic plasticity of cancer cells. Also, the produced metabolites may serve as novel targets for improved treatment of cancer. In the present review, an effort has been made to explain various changes particularly in mitochondria (ROS, Voltage-dependent anion channel 1, suppression & expression of anti-apoptotic and pro-apoptoticproteins, release of cytochrome c (Cyt c), enhanced activity of caspase 9, caspase 3, aerobic glycolysis, etc.) (A. Agarwal et al., 2018; Ali, Mohamed, Abdelhamid, & Mohamed, 2017; Indran, Tufo, Pervaiz, & Brenner, 2011), endoplasmic reticulum (unfolded protein response, PKR-like endoreticulam kinase, activation of transcription factor 6, suppression of oncogenes, inositol-requiring enzyme 1 alpha enhancement for tumor suppressor activity, etc.) (Healy, Gorman, Mousavi-Shafaei, Gupta, & Samali, 2009; Vanacker et al., 2017), nucleus (nucleolar phosphoprotein, nuclear pore complex, nuclear localization signal and other genetic modification or inhibition) (He et al., 2016; Zimmermann, 2017), lysosomes (acidic environment, hydrolases, lysosomal membrane permeation enhancement etc.) (Anselmo Joanitti et al., 2017) and plasma membrane (targeting the changed asymmetry of membrane phospholipids) (Neves et al., 2013) with an intention to exploit these changes as an opportunity for therapeutic benefits. There are various molecular targets available for cancer treatments which are shown in Fig. 1.

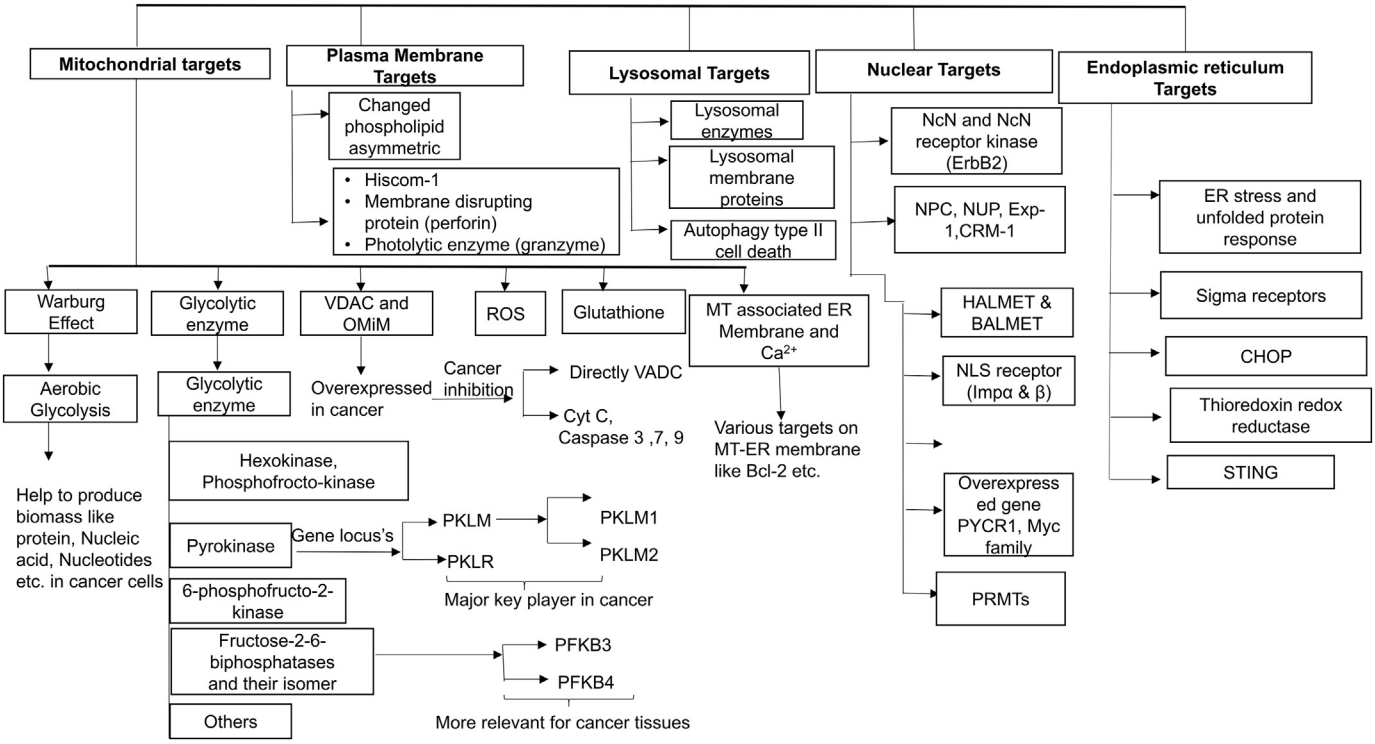


**Fig. 1.** Sub-cellular organelles molecular targets are available for cancer.

## 2. Targets for cancer

### 2.1. Mitochondrial targets

Mitochondria (MT) is one of the important cell organelles that provide the energy for all activities of the cells. Due to the rapid cell division, fast growth, and proliferation, the requirement of energy is very high in the case of cancer cells as compared to normal cells (Fadaka et al., 2017). Therefore, these cells alter their metabolic process for their survival, and these metabolic changes facilitate and try to fulfill the constant supply of nutrients and energy (DeBerardinis & Chandel, 2016). Since MT acts as the "powerhouse" of cells, they have proven to be successful targets for cancer treatment. Recently, Tan and co-worker have developed the cancer-cell-specific subcellular (mitochondrial) organelle-targeted photostable nanodiamonds (loaded with doxorubicin (dox)), and these nanodiamonds are attached with the two targeting ligands, i.e., folic acid and mitochondrial localizing sequential peptide. With such dual ligands attached carrier system, the drug doxorubicin is transported via plasma membrane and selectively delivered to MT of cancer cells to induce significant cytotoxicity followed by cell death (Tan et al., 2017).

Other than classical approaches for mitochondrial targeting, various biochemical pathways which affect cancer mitochondrial function can also be used for cancer treatment. Various research reports are available on cancer cells that they fulfill their requirement of energy in the form of ATP (adenosine triphosphate) by using the aerobic glycolysis that is referred to as the Warburg phenomenon (WP) (Cairns & Mak, 2016; Fadaka et al., 2017; Xian, Wei, & Lu, 2013). Moreover, glycolysis contributes to about 50% of the energy requirement of cancerous cells (Keibler et al., 2016). The normal differentiated cells fulfill their energy requirement for the cellular processes by oxidative phosphorylation within the MT in the presence of oxygen while under anaerobic condition and these cells produced a large amount of lactate (Vander Heiden, Cantley, & Thompson, 2009). But, in tumor cells, a large amount of lactate and two ATPs are produced through aerobic glycolysis from one mole of glucose (Fig. 2). The benefit of aerobic glycolysis for cancer cells is not yet clear. However, the probable reasons may be a high rate of carbon utilization for multiple branching pathways (that derived from glycolysis) and to produce a large amount of biomass such as protein, nucleic acid, nucleotides, etc. needed for rapid cell division and growth. Another benefit of WP in cancer cells may be the fulfillment of the high-energy requirement, alteration of the tumor microenvironment to escape the immunological detection and provide secondary signaling transduction via ROS or/and chromatin modulation (Liberti & Locasale, 2016).

The various intermediated and enzymes which are involved in aerobic glycolysis may provide an opportunity for the inhibition of cancer progression and ultimately cancerous cell death. The reduction in the production of ATP and biomass by suppression of glycolysis may be one of the explorable approaches to inhibit the cancerous cell growth. Targeting to various glycolytic enzymes such as 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 6 (PFKFB), phosphofructokinase (PFK), hexokinase (HK), etc. may help in the inhibition of cancer cell growth (Wang, Zhang, GuO, Xian, & Lu, 2016). Inorganic phosphate, 2-deoxyglucose and 3-bromopyruvic acid act as hexokinase inhibitors resulting in lower fructose 2,6-bisphosphate and the glucose uptake in cancer cells (Warmoes & Locasale, 2014).The isomers of PFKFB, i.e., PFKFB4 and especially the PFKFB3 seem to be the most relevant for cancer tissues (Bando et al., 2005; Ros et al., 2012) which are induced by hypoxia (Bobarykina et al., 2006). In one study (in Jurkat T-cell

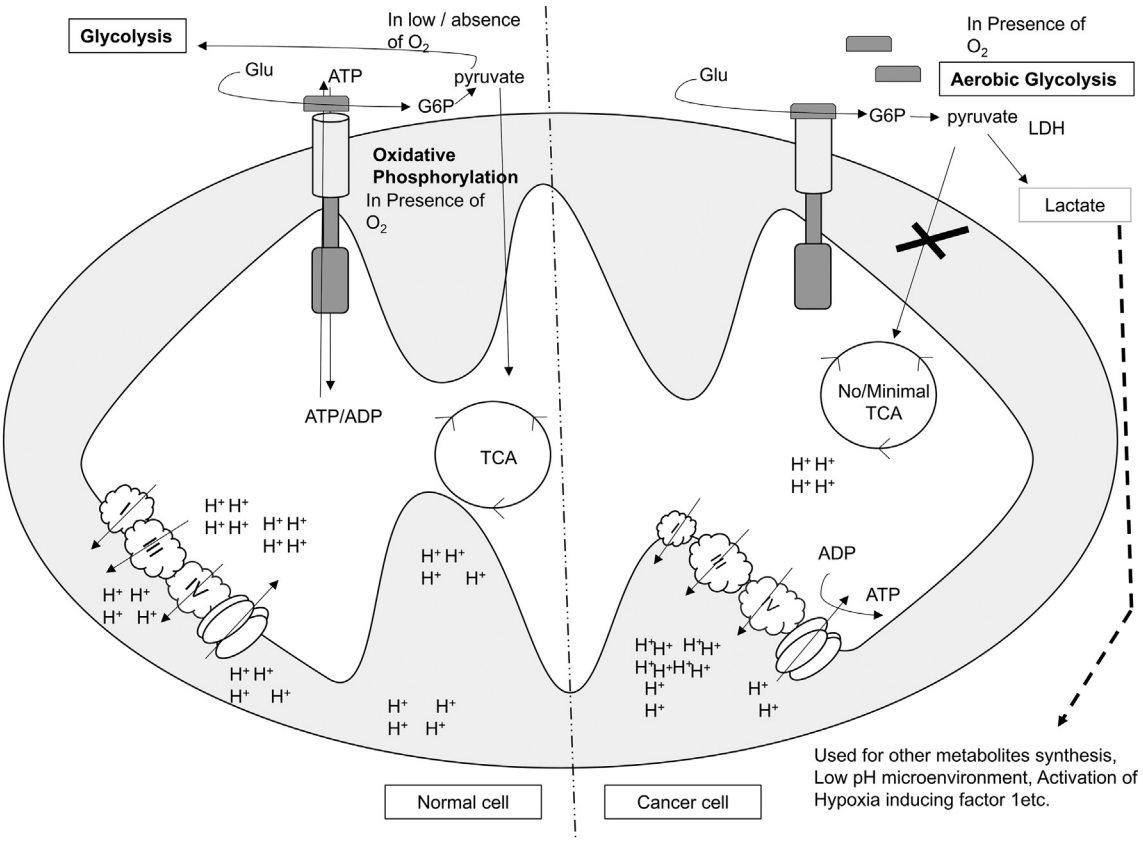


**Fig. 2.** In the normal cellular metabolic condition, pyruvate converted in acetyl CoA in the presence of Coenzyme A inside the mitochondria and further go for tricarboxylic acid (TCA) cycle, and in the absence of oxygen, pyruvate converted into lactate in the lactate dehydrogenase (LDH). But in a cancer cell, in the presence of oxygen, most of the pyruvate converted into the lactate and 2 ATP (aerobic glycolysis). Lactic acid decreases the pH of the tumor microenvironment and also helps to activate the hypoxia inducing factor 1(HIF1) which induces vascular endothelial growth factor (VERF) which leads to angiogenesis and also induces c-MYC oncogenes and tumor suppression factor p53. It also induces the glucose uptake by overexpression of GLUT- receptors. Lactate also used by cancer in the synthesis of various metabolites for rapid cellular functions.

leukemia cells), the 3-PO (3- (3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one) was used as PFKFB3 inhibitors which suppress the glucose uptake as well as lactate secretion. As a result, ATP and NADH steady-state concentration was reduced and an arrest in cell-cycle progression has occurred (Clem et al., 2008; Clem et al., 2013).

Pyruvate kinases (PK) is involved in the last major step of glycolysis where phospho-pyruvate is converted into pyruvate with simultaneous generation of an ATP from ADP. PK is transcribed from two different gene loci designated as PKLR and PKM. Out of which the PKM is transcribed from a single gene locus that is located on chromosome 15 with two isoforms PKM1 and PKM2 which plays a major role in cancer metabolic specific adaptations. PKM1 form active tetramers protein complexes while PKM2 expressed in cancer cell alongside PKM1, have a lower affinity for phosphoenolpyruvate as compare to PKM1. PKM2 possesses several other characters that could make it a fascinating target to hit cancer's cell metabolism. Tumors may grow even in the absence of its activity that is why in some cases deletion of PKM2 may accelerate tumor growth (Cortés-Cros et al., 2013; Israelsen et al., 2013). Hence, PKM2 activators can be used for the treatment of cancer. Anastasiou and co-worker used TEP-46 as an activator of PKM2 for tumor growth suppression (Anastasiou et al., 2012).

It is well known that the MT (bilayer membrane cell organelle), has a very important role in cell life & death by involving mitochondrial signaling, biosynthesis, and bioenergetics and these bio-functions are the key players in tumor-genesis (Shoshan-Barmatz, Krelin, Shteinfer-Kuzmine, & Arif, 2017). Voltage-dependent anion channel 1 (VDAC1), is voltage-gated ion channel situated at the outer mitochondrial membrane (OMM), provides a selective entry of metabolites, fatty acid ions, Ca2+, ROS and cholesterol across the OMM and plays an important role in MT-mediated cellular apoptosis (Fig. 2) (Rostovtseva & Bezrukov, 2012). VDAC1 is a junction protein that interacts with other proteins of MT, cytosol, ER together to regulate the metabolic and signaling pathways (Shoshan-Barmatz, Ben-Hail, Admoni, Krelin, & Tripathi, 2015).

The overexpressed VDAC1 at OMM in cancerous cells may play an important role in cancer cell survival because of their well-established functions in cell metabolism and energy production, and these both functions are essential for high energy-demanding cancer cells. VDAC1 also interact with anti-apoptotic proteins such as the Bcl-2 family of proteins and hexokinase to prevent the release of Cyt c from mitochondria (Siddiqui, Ahad, & Ahsan, 2015). Therefore, the drug delivery system (DDS) that interacts with VDAC1 may provide an emerging targeting strategy for anti-cancer drugs. Jiang and co-worker, prepared the paclitaxel-loaded liposomes appended with 2,3-dimethyl maleic anhydride modified peptide for cancer treatment relying on apoptosis process (L. Jiang et al., 2015). Based on results they concluded that apoptosis took place via a mitochondrial signaling pathway involving the release of Cyt c and consequentially increased activity of caspase-9 and caspase-3 (Fig. 3).

It is well understood that MT is an important organelle that produces cellular energy and plays an important role in metabolism, and cell apoptosis. Thus any functional defect in MT may lead to cancer progression involving some aberrant, however distinct (from normal cells) functional molecules. Targeting these functional molecules may help in developing effective anti-cancer therapies that can kill cancer cells without harming normal cells. So for the targeting purpose, the interaction of small drug molecule with the VDAC or VDAC based drug strategies could be a better approach. Drug molecule such as oblimersen

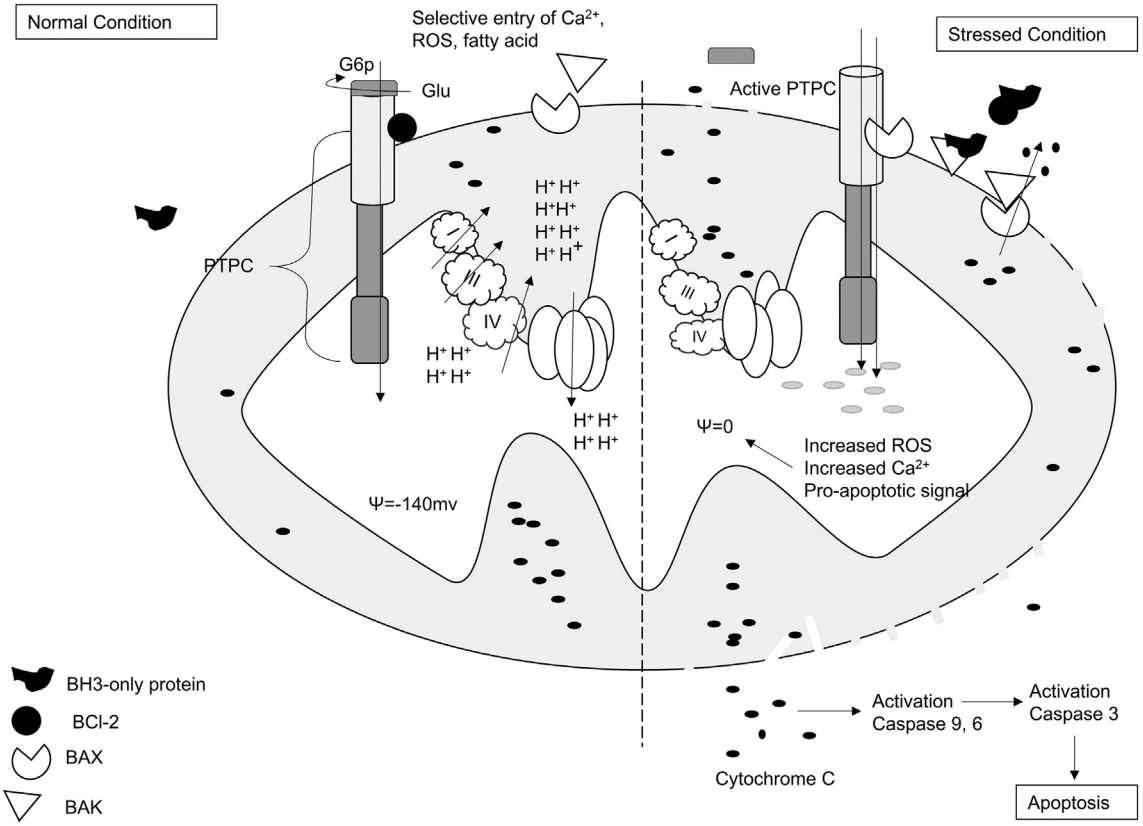


**Fig. 3.** In the normal cellular metabolic condition, the anti-apoptotic protein, i.e., Bcl-2 only protein attached to VADC and is in active form. The pro-apoptotic protein like Bax/Bak presents in the inactive form. Hexokinase attached to VDAC and convert glucose (Glu) to Glucose 6- phosphate (G6P). Permeability transition pore complex (PTPC) normally allows the selective entry and the mitochondrial transition potential is high, it is due to the respiratory chain and PTPC conductance is low. But, if any pro-apoptotic signal appears, the dissipation in mitochondrial potential takes place which activates the oligomerization of Bax/Bak, and Bax directly binds to PTPC and BH3-only protein bind to Bcl-2 and detached the from PTPC and finally enhancement in PTPC conductance. The OMM permeation increased by which Cyt-c release from intra-mitochondrial membrane space to cytosol which finally activates the caspase 3 and cell go for apoptosis.

directly interacts with VDAC and reduces its channel activity (Shoshan-Barmatz & Ben-Hail, 2012; Tan, 2012), drug avicin targets and closes VDAC (Haridas et al., 2007), thus decreases cell energy metabolism and pushed these cells towards the apoptotic pathway by changing the permeability of the OMM and release of Cyt c. While in the case of cisplatin it binds with the mitochondrial membrane proteins and preferentially to VDAC (Yang et al., 2006). Methyl jasmonate directly interacts with VDAC1, reducing channel conductance (Goldin et al., 2008) as well as it detaches HK from VDAC1 in a time- and dose-dependent fashion. This phenomenon leads in glycolytic and mitochondrial metabolic dysfunctions which are associated with inhibition of ATP synthesis, Cyt c release, and blockage of oxidative phosphorylation followed by irreversible bioenergetics loss which may be a leading cause for cell death.

It is well established fact that the use of gene-specific siRNA could selectively downregulate its expression and thus emerged as a useful approach in the treatment of cancer. In VDAC based treatment strategies, a single siRNA specific to the human VDAC1 sequence (hVDAC1-siRNA) is employed to inhibit the tumor growth (Arif, Vasilkovsky, Refaely, Konson, & Shoshan-Barmatz, 2014; Arif, Vasilkovsky, Refaely, Konson, & Shoshan-Barmatz, 2017). In another strategy engineered peptides which are based on the VDAC1 were studied, and it was found that they interfered with the activity of the prosurvival proteins, Bcl-2, Bcl-Xl and HK (Arbel, Ben-Hail, & Shoshan-Barmatz, 2012; Arbel & Shoshan-Barmatz, 2010; Arzoine, Zilberberg, Ben-Romano, & Shoshan-Barmatz, 2009; Ivanova, Kerkhofs, La Rovere, & Bultynck, 2017; Siddiqui et al., 2015). These engineered peptides act by the three mechanisms of action, i.e., energy and metabolism impairment, interference with the action of anti-apoptotic proteins, and triggering cell death (apoptosis induction). Thus, VDAC interaction and VDAC based strategies provide a promising opportunity for the development of new anticancer therapies with fewer side effects to adjacent normal cells and can improve the drug resistance of cancer cells (Shoshan-Barmatz et al., 2015).

ROS, a chemically reactive oxygen-containing species (superoxides, peroxides, hydroxyl radicals, etc.) involved in cell signaling and homeostasis are formed as byproducts of the normal oxygen metabolism and have important roles in cell signaling and homeostasis (Andreyev, Kushnareva, & Starkov, 2005; Devasagayam et al., 2004). Nevertheless, in oxidative stress condition, the ROS level is elevated dramatically, which damages and disfigure the cellular proteins, lipids, and eventually leads to oxidation of DNA thereby causing fatal lesions in cells that contribute to carcinogenesis (Tong, Chuang, Wu, & Zuo, 2015). ROS also activates different transcription factors such as activator protein-1 (AP-1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kLB), signal transducer and activator of transcription 3 (STAT3), etc. which leads to cellular transformation, tumor cell survival, tumor cell proliferation, angiogenesis, metastasis, etc. (Tabish, Zhang, & Winyard, 2018). ROS also controls the expression of various tumor suppressor genes and enhances the process of cancer development by modification of gene expression, causing genomic instability as well as changes in signaling pathways (Yang et al., 2016). Autophagy can also be regulated by ROS with the help of transcription factor activity for examples NF-kLB leads to the induction of autophagy gene expression (BECLIN1/ATG6 or Sequestosome-1/SQSTM1) in cancer cells (Boyer-Guittaut, Varambally, Darley-Usmar, & Zhang, 2017).

Now, it is evident that the cancer cells exhibit a higher ROS level compared to normal cells. In cancer cells, the elevated ROS level is counteracted by an increased activity of antioxidant enzymes. In such condition, either increased ROS generation or decreased antioxidant defense could be one of the therapeutic strategies that may limit the cancer cells progression. For ROS targeting, Wang et al. prepared the hyaluronic acid coated chitosan NPs and reported that the enhanced accumulation of the drug in tumor cell via overexpressed CD44 receptor and also concluded that the tumor cells apoptosis took place due to damage of MT which is caused by excessively produced ROS (Wang, Hou, Su, Zhao, & Shi, 2017). Similarly, Ren et al. studied the antitumor effect of alteronol on T47D breast cancer cells and found that the alteronol induced the cell cycle arrest and apoptosis by elevation of ROS production (Ren et al., 2018).

The Melatonin (MLT) is a tryptophan-derived molecule and chief secretory molecule from pineal gland; which has broad actions like a scavenger of a variety of free radicals, ROS, reactive nitrogen species, antioxidant, circadian rhythm regulator, immunoregulator, etc. (Tan, Manchester, Esteban-Zubero, Zhou, & Reiter, 2015). It is primarily synthesized in mitochondria and chloroplasts in all eukaryotic cells (Manchester et al., 2015). MTL is considered to detoxify up to 10 free radicals through the N-Acetyl-N-formyl-5-methoxykynurenamine pathway, directly scavenging toxic oxygen-based reactants and indirectly limiting the oxidative damage by enhancing/stimulating several antioxidant enzymes. The MLT acts as an antioxidant and pro-oxidant when used in human HepG2 liver cell lines (Yeh et al., 2017). MLT is also associated with membrane G protein-coupled receptors MT1 and MT2 which are very much abundant in numerous parts of the central nervous system and in peripheral tissues that regulate various biological activities (Su et al., 2017). MLT triggers some antioxidant enzymes, i.e., glutathione peroxidase, superoxide dismutase, G-6-P dehydrogenase, etc. that inhibit the ROS by catalytic activity. MLT inhibits the nitric oxide synthase as well as prooxidant enzymes, which catalyzes the production of nitric oxide, which results in nitrosate and oxidative stress (Akbulut, Gonül, & Akbulut, 2008). In the estrogen-dependent breast cancer, it plays an important role as oncostatic by two mechanisms, i.e., correcting the enzymatic activities which are responsible for local estrogen biosynthesis by suppressing its expression and transactivation. And by controlling the estrogen signaling pathways and limiting the level of estrogen receptor expression (Gurer-Orhan, Ince, Suzen, & Saso, 2017; Nooshinfar, Safaroghli-Azar, Bashash, & Akbari, 2017). MLT has anti-proliferative effects by regulating cell cycle arrest in the G1 phase as well as delaying its switching to the S phase (Gurer-Orhan, Ince, Konyar, Saso, & Suzen, 2018). Hevia et al. also reported that the concentration of melatonin reduces tumor uptake of glucose by competition between melatonin and glucose by the SLC2/GLUT family glucose transporters. The cellular concentration of melatonin increases and the glucose decreases which inhibit the progression of prostate cancer (Hevia et al., 2015).

Normal cells are very well equipped with an enzymatic and non-enzymatic antioxidant system to maintain the redox homeostasis. Among them Glutathione (GTH) a highly reactive tripeptide plays an important role in various cellular processes, i.e., cell differentiation, proliferation, apoptosis, antioxidant activity, immune-defense systems and participation in antioxidant defense as well as other metabolic processes (Estrela, Ortega, & Obrador, 2006; Singh, Khan, & Gupta, 2012). The role of GTH and its mechanism in cancer is not so simple, and its metabolism is capable of both protective and pathogenic activities. It plays a lead role in the removal and detoxification of carcinogens. Its deficiency may lead to rises in the level of a carcinogen, free radical, ROS concentration, etc. that may cause initiation and progression of cancer. The decrease in concentration of GTH is also responsible for the stimulation of NF-klB (Balendiran, Dabur, & Fraser, 2004). On the other side, the elevated concentration of GTH and associated enzymes like γ-glutamylcysteine ligase (GCL), γ-glutamyl-transpeptidase (GGT) and their activities, a simultaneous higher expression of GTH-transporting export pumps which developed the resistance in cancerous tissues against the chemotherapy in the various types of tumors such as bone marrow, head and neck, colon, ovarian, breast, larynx and lung cancers, etc. (Gamcsik, Kasibhatla, Teeter, & Colvin, 2012; Traverso et al., 2013). Hence, for cancer treatment, the inhibition of GTH and GGT synthesis, as well as depletion of GTH, may become one of the important strategies. Beatty et al. studied the inhibition of glutathione biosynthesis in triple-negative breast cancer by using different biosynthesis inhibitor like CB-839 (glutaminase inhibitor), buthionine sulfoximine (BSO) (GCL inhibitor) and sulfasalazine (SSA) and erastin (cystine/glutamate

antiporterxCT inhibitor), and reports confirmed the suppression in the production of ROS and tumor cell survival by pharmacologic inhibition of glutathione biosynthesis (Beatty et al., 2018). Harris et al. used buthionine sulfoximine with sulfasalazine and auranofin to reduce tumorigenesis. The combination could inhibit of GHS and thioredoxin pathways (Harris et al., 2015).The approach used for the treatment of neuroblastoma by using BSO and melphalan (an alkylating agent) is under phase I study. In this study, BSO inhibits GTH synthesis and provides synergistic anti-neuroblastoma effect along with the melphalan (Villablanca et al., 2016). Xu et al. prepared silica Nano particulate-DDS containing anticancer drugs camptothecin and DOX, which were covalently bounded within the silica matrices via disulfide and hydrazone bonds in which disulfide is GTH responsive and a hydrogen bond is pH-responsive. They evaluated the system for its anticancer effects, release kinetics, etc. and concluded that both stimuli-responsive DDS with silica (as a prodrug) showed the controlled release of drug after exposure to GSH-rich or low pH environment of the tumor (Xu, Liu, Kang, & Wang, 2015).

MT and MT-associated endoplasmic reticular membranes (MAMs) both are the essential cellular components which are involved in the regulation of apoptosis and growth of the tumor (Danese et al., 2017). There are mainly three classes of MT-associated proteins, i.e., $Ca^{2+}$ channels, pumps, and exchangers that are directly involved in $Ca^{2+}$ homeostasis. $Ca^{2+}$ contributes to both proliferation and apoptosis by either activation or inhibition of these proteins thus enhance the efficacy of chemotherapeutics (Monteith, McAndrew, Faddy, & Roberts-Thomson, 2007).

$Ca^{2+}$ ions are the vital and one of the most abundant intracellular secondary messengers, stored in the endoplasmic reticulum (ER) by the Sarcoplasmic/ER $Ca^{2+}$-ATPase (SERA) and required for mitochondrial metabolism during uncontrolled proliferation of cancer cells. $Ca^{2+}$ ions present in MT are required for the productions of NADH and ATPs (Ivanova et al., 2017). The $Ca^{2+}$ ions released from the ER are involved in inositol phosphate 3 receptors (IP3Rs) and ryanodine receptors pathways. IP3Rs activation takes place by the IP3 (Foskett, White, Cheung, & Mak, 2007). The transportation of $Ca^{2+}$ ions from MT to ER takes place via MAMs. Several proteins are also associated with ER-MT $Ca^{2+}$ ions transportation like IP3Rs (ER sides) and VDAC1 (MT sides) via MT $Ca^{2+}$ ions uniporter (MTCU). The functions of MTCU are strictly regulated by modulator proteins that have an impact on cellular metabolism. Adequate transfer of $Ca^{2+}$ ions from ER to MT meets the sufficient availability of $Ca^{2+}$ ions in ER which is essential for the normal metabolism (Csordás, Weaver, & Hajnóczky, 2018).

In normal cells, the low $Ca^{2+}$ level in ER will reduce ER-MT $Ca^{2+}$ transfer where in case the level is high then ER-MT $Ca^{2+}$ transfer will tend to increase. Whereas, in the cancer cell, if the level of $Ca^{2+}$ in ER-store decrease, then it initiates several alternative survival mechanisms by using the several pro-survival proteins and oncogenes such as Ras, anti-apoptosis Bcl-2 and Bax inhibitor-1(BAX-1) (Ivanova et al., 2017). This not only renders cells to be more resistant against apoptosis but also triggers building facilities and provides protection for damaged or stressed cells resulting in oncogenesis and thus helps them to survive. The Bcl-2 has direct interaction with bilayer-reconstituted purified VDAC and decreases the channel conductance. The interference in the binding of Bcl2 to mitochondria by peptides of VDAC1 could be an effective strategy which would provide a suitable target for anticancer drugs to potentiate their efficacy (Arbel & Shoshan-Barmatz, 2010; Arzoine et al., 2009).

Molecular cloned Bcl-2 (Korsmeyer, Shutter, Veis, Merry, & Oltvai, 1993), is also identified as targets for a chemotherapeutic agent in drug development. The Bcl-2 antisense (oblimersen sodium) is the first agent that targets BCL-2 mRNA (Rai, Moore, Wu, Novick, & O'Brien, 2008). HA-14 Bcl-2, antimycinA, gossypol (AT-101), GX15-070, etc. are some of the examples of small molecules, which interfere with Bcl-2 family proteins. They may bind with the hydrophobic grooves of anti-apoptotic Bcl-2 proteins or oligomerized Bax or Bak, followed by depolarization of mitochondrial membrane potential to release Cyt c, etc. For Bcl-2 targeting, histone deacetylase inhibitor, depsipeptide, and a synthetic cytotoxic retinoid fenretinide have been reported to down-regulate the expression of Bcl-2 and other proteins in multiple myeloma cells (Kang & Reynolds, 2009; Khan, Maududi, Barton, Ayers, & Alkan, 2004)

If the $Ca^{2+}$ ions level is elevated then IP3Rs regulate the level of the $Ca^{2+}$ signal in the MT and help in the biosynthesis of macromolecules (like nucleosides), also in the production of ATP and NADH which support the cancer cell to survive and grow (Kania, Roest, Vervliet, Parys, & Bultynck, 2017). The low activity of the AMP-activated kinase decreases auto phasic phase. As a result, the mitochondrial $Ca^{2+}$ signals triggers and leads to the production of mitochondrial ROS (Zorov, Juhaszova, & Sollott, 2014). The produced ROS drives the transcription of the mitochondrial $Ca^{2+}$ uniporter (MCU), regulates breast cancer progression via hypoxia-inducible factor 1α (HIF1α)-target genes which function in metabolic reprogramming and start the metastatic attack (Rankin, Nam, & Giaccia, 2016; Zorov et al., 2014).

The regulation of Ca2+ ion is a critical step in T-cells activation and signaling through the T-cell receptor (TCR). The activation of adapter proteins is allowed by the activation of phospholipase Cy1 (PLCy1) involving hydrolysis of Phosphatidylinositol 4,5-bisphosphate. (Nagaleekar et al., 2008). Short-term TCR activation has been proposed to lead small and synchronized $Ca^{2+}$ waves which, in turn activate the nuclear factor of T cells. The activated T cells thus synthesize Interleukin-2 and other cytokines. TCR activation leads to a high and persistent elevation of the cytosolic free calcium concentration, which causes cell apoptosis (Danese et al., 2017; Missiroli et al., 2016).

Specifically, in this section, we have tried to highlight recent results related to the MT as a target for the anticancer drug delivery. Warburg Effect/phenomenon, heterogeneous glycolytic enzymes, ROS effect, Glutathione metabolism, roll of $Ca^{2+}$ ion, modulation of VDAC1 activities by associated proteins, etc. are suggested as a novel targets for cancer cell apoptosis and these targets may be utilized in the development of better strategies for the treatment of cancer without any side effect on the normal cells) (Fig. 4).

### 2.2. Endoplasmic reticulum target

The ER is one of the essential cell's organelles which regulate adaptive capacity by synchronizing a wide array of important processes at cellular level, i.e., lipid biosynthesis, transmembrane and secretory protein folding, signaling, calcium storage and drug detoxification (Cubillos-Ruiz, Bettigole, & Glimcher, 2017). In the cancerous condition, some changes occur in the ER viz. ER stress, $Ca^{2+}$ion associated with ER-MT transport, changes in molecular sensors on ER membrane, proteins folding, altered ER homeostasis, etc. which are associated with the tumor cells survival, and prevent the cells entering into apoptosis. These changes either by inhibition or acceleration of ER components or due to their associated signaling pathways and biosynthesis pathways may serve as a target for a chemotherapeutic agent in favor of tumor inhibition.

In a normal condition, ER-Protein-folding machinery makes it easy to organize the requirements of secretion pathways. The proteins on the cell surface are folded in and secreted by the ER and converted into multi-subunit complexes (Díaz-Villanueva, Díaz-Molina, & García-González, 2015). The "ER stress" has developed when the efficiency of secretory protein folding is disturbed. If unfolded proteins are deposited beyond the tolerant limits, these unfolded proteins bind and sequester immunoglobulin heavy-chain binding protein thereby activating the open protein reaction or unfolded protein response (UPR) which operates to clear unfolded proteins and restore ER homeostasis (Bravo et al., 2013).

However, activation of ER-stress beyond the tolerance level induces apoptosis. Although the role of prolonged activation of the UPR under

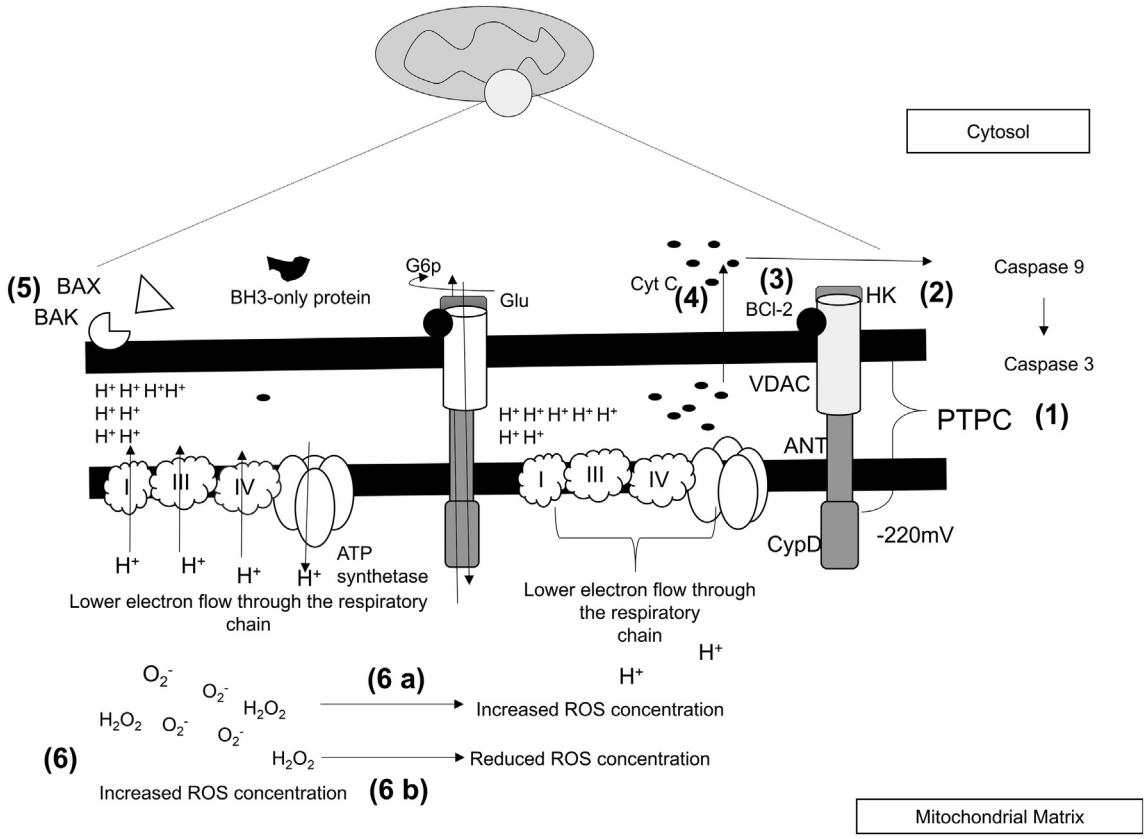


**Fig. 4.** Different probable and suitable MT targets for tumor cells apoptosis (1) Inhibition/reduction in the PTPC activity leads to apoptosis via membrane potential alteration and/or by preventing the binding of anti-apoptotic proteins. The inhibition of the activity of VDAC and ANT induce mitochondrial apoptosis and cell death (2) inhibition of oxidative glycolysis reduces/inhibits the supply of ATP and lactate (3) Inhibition anti-apoptotic Bcl2 leads to apoptosis (4) Increase in release of Cyt c from the MT to cytosol by OMM permeability enhancement (5) Increase in level of BAK/BAX initiates the apoptosis, because oligomerization of BAX and BAK protein and direct binding to the VDAC (6 a) Induced overproduction of ROS may lead to apoptosis via mRNA mutation and defective biosynthesis initiates and stimulates caspase activity (6 b) decreased ROS level may be corrective action toward the various transcription factors deactivation when preventing early events in tumor development, where ROS are important.

sustained ER stress in the regulation of cell apoptosis mechanisms is not known yet. So, such conditions may constitute a suitable target for the induction of apoptosis in cancer cells. Tunicamycin is an antibiotic, which prompts ER stress in cells by inhibiting the initial step of biosynthesis of proteins N-linked glycans that incorporates many misfolding in the proteins, inducing ER-stress and simultaneously stimulates apoptosis in prostate cancer cells (Guha, Kaptan, Gade, Kalvakolanu, & Ahmed, 2017). Calreticulin, a chaperone, and protein of ER-localized in the lumen play an important role in protein folding and also in $Ca^{2+}$ ions buffering. Therefore, any type of changes in calreticulin may cause caspase-dependent apoptosis followed by activation of ER-stress (Obakan-Yerlikaya et al., 2017). On the basis of the studies, we can say that the ER-stress beyond the tolerance limit induces apoptosis which could be used as a target for chemotherapeutics.

The sigma receptors (SRs) i.e. sigma-1 receptor (S1R) and sigma-2 receptor (S2R); are predominantly expressed and localized in plasmatic and subcellular membranes (mainly in ER) with the leading site of their activity at the ER where it acts as a gatekeeper in ER-stress (Tesei et al., 2018). S1R increases tumor cell aggression by potentiating aggression and angiogenesis, while S2R is closely involved in regulating cell proliferation, survival, and aggression (van Waarde et al., 2015). A recent paper has pointed out that the S1R is a key mediator of interleukin-24 (IL24; IL-24 generated from an adenovirus expressing this cytokine)-induced cancer-specific apoptosis. Thus the ER stress response, ROS production, and calcium mobilization appeared to be triggered by IL-24 via a sigma-1 receptor-dependent pathway and leads apoptosis (Do et al., 2013). Since SRs are commonly over-expressed in various types of tumors. Hence, it may be used as an attractive target for cancer diagnosis as well as for the drug delivery of anticancer drug for treatment purpose via inducing caspase-independent apoptosis (Korpis, Weber, Brune, Wuensch, & Bednarski, 2014). SW43, aligand of sigma-2 subtype demonstrated apoptosis in Bxpc3 and Aspc1 pancreatic cancer cell lines by changing the permeability of lysosomal membranes and increasing cellular oxidative stress, but independent of caspase-3 activation (Hornick et al., 2010). Fitzgerald et al. studied the anticancer effect of dilysin-cyclodextrin nanocomplexes bearing siRNA for S1R targeting for the treatment of prostate cancer cells. The prepared NCs protected the siRNA from serum-induced nuclease degradation, and high levels of siRNA cellular uptake were attended in prostate cancer cells, *in vitro* (Fitzgerald et al., 2016). In another investigation, Amata et al. synthesized and evaluated some novel hybrid compounds as the conjugate of SRs moiety, and Nitric Oxide photo-donor and found S1R and S2R effective selectively in MCF-7 and A2058 cells and a considerable loss of cell viability was detected (Amata et al., 2017).

The UPR is facilitated by three molecular sensors which are present on the membrane of endoplasmic reticulum, i.e., PKR-like ER kinase, activated inositol-requiring enzyme-1 alpha and transcription factor 6 (Clarke, Chambers, Liniker, & Marciniak, 2014; Wang & Kaufman, 2014). Increases protein folding, transport, ER-associated protein degradation and attenuating protein synthesis are also a result of UPR. If protein misfolding is not resolved or corrective efforts are insufficient then the cells undergo apoptosis (Sano & Reed, 2013). In case of cancer either the hyperactivation of oncogenes (Ras, Myc, etc.) or loss of tumor suppressor genes (BRCA1, tuberous sclerosis complex (TCS)-1, TCS-2, etc.) can activate the UPR, promoting cell survival, oncogenic transformation or cell senescence or apoptosis, depending on gene mutations (Wang & Kaufman, 2014). Since UPR has both protective and deleterious effects on cell survival upon ER stress; its activation may facilitate as well as

suppress, malignant transformation (Wang & Kaufman, 2014).The targets of these UPR could be an approach for the tumor cell apoptosis and survival of other normal cells. Pan et al. studied physcion (a pigment of medicinal plants) induced apoptosis by increasing the endoplasmic reticulum stress through AMP-activated protein kinase in hepatocellular carcinoma (HCC) (Pan, Wang, Li, & Huang, 2018). Tamaki et al. reported that MT membrane potential is lost by synthetic short hairpin RNA (shRNA) i.e., psi/shRNA in HTC 116 cells. As a result, level of ROS increases which triggers the up-regulation of an ER stress sensor protein ATF6 and activates caspase-3 expression eventually leading to apoptosis probably due to ER stress-mediated mitochondria-coordinated cell death (Tamaki et al., 2017). In another investigation Sawant et al. studied the anticancer effect of a triterpenoid, i.e., *Ailanthus excelsa* chloroform extract-1 (AECE1) obtained from the bark of *Ailanthus excels* and the results of this study indicate that apoptosis induced by AECE1 in breast cancer by aggravation of ER stress and disturbance of ER-mitochondrial interaction and also suggested that aggravation of ER stress as a novel target for the treatment of cancer (Sawant, Dasgupta, Lavhale, & Sitasawad, 2016). Similarly, Tahtamouni et al. studied two cephalostatin 1 (CEP1) analogs, which are the members of strongly-related bis-steroidal compounds that possess strong anti-cancer effects in different cancer cell lines (Tahtamouni et al., 2018). The CEP1 induces apoptosis in the cells via ER stress, the pathways involved in the apoptosis are the release of caspase 4 from ER membrane and activates caspase 9 without any participation of Cyt c release from MT and caspase 8 activations. The treatment of CEP1 induces the release of smac/DIABLO but not Cyt c from mitochondria and induced phosphorylation of eukaryotic initiation factor 2 (eIF-2) leading to activation of caspase 4 in cancer cells (Fig. 5).

C/EBP homologous protein (CHOP) belongs to the cytosine-cytosine-adenosine-adenosine-thymidine/enhancer-binding protein and well known as growth arrest and DNA damage-inducible protein. The CHOP expression is induced by ER stress, UPR and integrated stress response mediated apoptosis through the protein kinase-R like ER kinase pathway (Tanjore, Burman, Taylor, Lawson, & Blackwell, 2017; Wang et al., 1996). Overexpression of CHOP leads apoptosis in the several cell lines, but CHOP-deficient cells have resistance toward the ER stress-mediated apoptosis (Anania et al., 2017). The compound Arsenic trioxide ($As_2O_3$) has an anti-carcinogenic activity by triggering the apoptosis in human hepatocellular carcinoma cells via ER stress through the induction of CHOP (Zhang et al., 2015). $As_2O_3$ also induce apoptosis through cytochrome c release and by caspase activation (Jiang, Wang et al., 2015).

Some oxidative proteins provide the cytoprotective effect in a tumor cell by maintaining the metabolic equilibrium. The thioredoxins (TX) and thioredoxin reductases (TXR) are such proteins which are involved in the conservation of protein thiol homeostasis (Lin et al., 2016) and play a cytoprotective role in the tumor cell. Therefore, it seems that TX-TXR system may be a possible therapeutic target for the treatment of cancer. The activity of TX-TXR system incorporated the change in the construction of protein disulfide bond during protein folding and resulted in conformational modifications (Harbut et al., 2015). Enhanced levels of ROS and interferences in the intracellular redox homeostasis, increases the mass of unfolded proteins in the ER and induce UPR (Wang & Kaufman, 2014). Muchowicz et al. prepared and evaluated the antitumor effect of peptidomimetic SK053 (a β-acyloxyacrylamide compound) by targeting the TX-TXR system and evaluation was performed using cell-free insulin reduction assay as well as on the cell lysates and they found that the SK053 gives a positive and strong cytotoxic effect on tumor cells (Muchowicz et al., 2015). Other TXR cytosolic isoenzyme selenoproteins, TXR-1 may also be used as a promising targeting tool for the anti-tumor drug. TXR-1 is overexpressed in various types of tumors and regulating the intracellular redox balance (Dong et al., 2016). TXR1 has an important part in tumor growth, progression, metastasis and resistance to chemotherapy (Poet et al., 2017). The TXR-1 is chemically reactive toward small metal electrophiles, e.g. cisplatin, platinum compounds, arsenic trioxide, nitrous compounds, some flavonoids through its nucleophiles (cysteine)

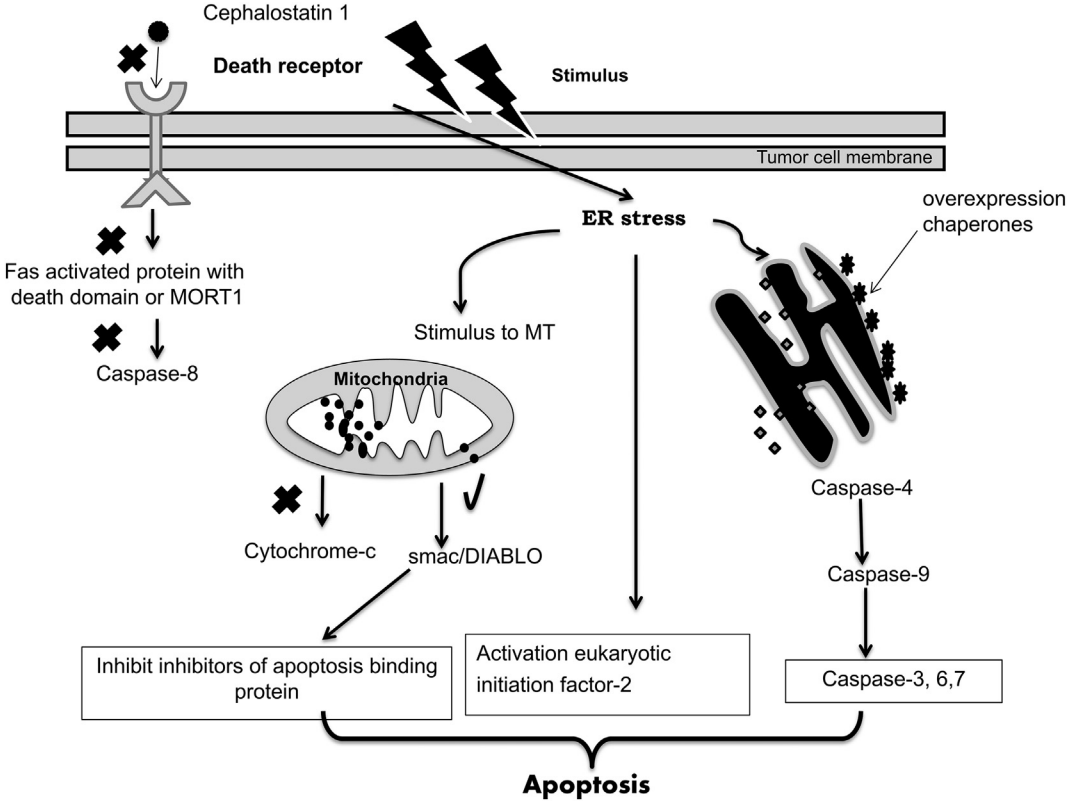


**Fig. 5.** ER stress pathway of apoptosis Via Caspase 4 activation.

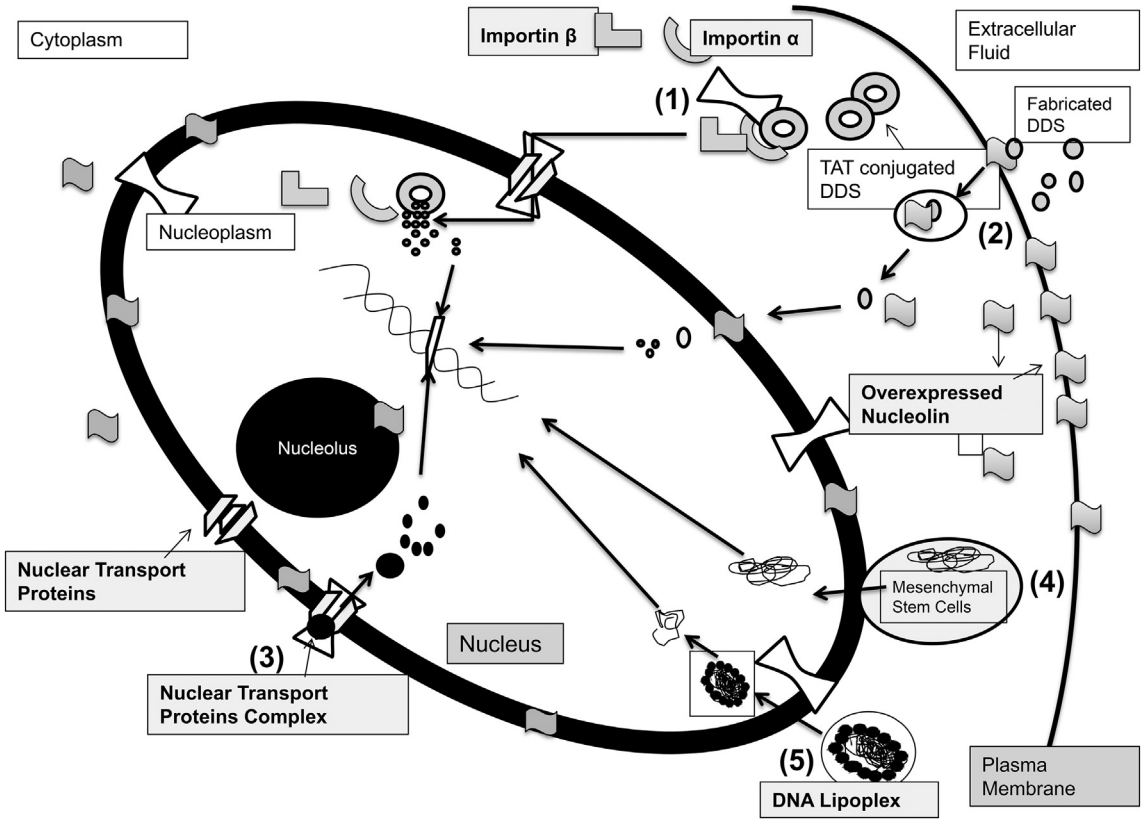


**Fig. 6.** Different approaches to target the nucleus of tumor and mechanism of cell demolition (1) Importin α and β exposed in cytosol inside the nucleus (2) Overexpressed nucleolin (3) Nuclear transport complex (4) mesenchymal stem cells as drug carriers (5) DNA lipoplex which transport drug delivery system in tumor nucleus.

residue and form their derivatives, which act as an antitumor drug (Peng et al., 2013; (Peng et al., 2013; Tonissen & Di Trapani, 2009). Zou et al. studied on a piperlongumine, a natural alkaloid isolated from the fruit of long pepper and established a piperlongumine alkaloids interaction with the TXR1 in gastric cancer whereby they inhibit to induced apoptosis via elevation of ROS (Zou et al., 2016).

The activation of interferon genes, i.e., STING is a protein that is associated with the ER and actsas a mediator of interferon production (Dobbs et al., 2015). Especially, interferon-β expression, STING agonists, such as cGMP and other cyclic dinucleotide are being developed as vaccine adjuvants to stimulate potent immune response and also to stimulate the strong anti-tumor responses by boosting host immune recognition of tumor antigen (Gonugunta et al., 2017). Corrales et al. studied the antitumor effect of STING agonist (5,6-Dimethylxanthenone-4-Acetic Acid) (Corrales et al., 2015) and Gonugunta et al. studied bafilomycin A1(a STING degradation blocker) for enhancing the immune response in mice (Gonugunta et al., 2017).

With the above discussion it is evident that the ER-associated changes/symptoms expressed in cancer cells such as ER stress, $Ca^{2+}$ ion associated with ER-MT transport, changes in molecular sensors on ER membrane, proteins folding, altered ER homeostasis, etc., could be utilized as specific target to treat (kill) cancer cells without adversely affecting the healthy cells.

### 2.3. Nuclear targets

The nucleus is a container of genetic material of cell organelle and contains RNA, DNA, and controls the activities of the cell and important to maintain the integrity of genes. A large number of proteins which bind to RNA & DNA and participate in cell processes such as replication of DNA, transcription, translation, etc. (Hudson & Ortlund, 2014). The nucleus targeted DDS is an approach developed to deliver the drug, genes or protein into the nucleus and interrupt/interact with the different event of cellular functions by damaging nucleus components or influencing with genetic processes involved in cancer (Fig. 6). Some proteins/peptide possess an intrinsic ability to bind to the nucleus and may help to target the anticancer drug to the nucleus (Belting, Sandgren, & Wittrup, 2005; Cai et al., 2017; Zhang, Hu, et al., 2013). However, access to the nucleus is one of the major difficulties posed and posted by both intra- and extra-cellular barriers including the plasma membrane, efflux proteins, endosomal escape, and finally the nuclear membrane (Cautain, Hill, de Pedro, & Link, 2015). Nuclear delivery may either follow a route through cytosolic delivery or direct targeted delivery to the nucleus. In the cytosolic delivery, drug carriers are diffused into the cytosol, and reach to the nucleus by their own styles. This type of targeting is also referred to as indirect nuclear delivery. On the other way, direct or nuclei-targeted delivery of drug carriers should cross various barriers and then deliver the drug into the nucleus (Jhaveri & Torchilin, 2016).

The protein Nucleolin (NCN), a nucleolar phosphoprotein in the nucleus of normal cells and is distributed in the nucleolus, cytoplasm and on the cell membrane. NCN involved in many activities such as rDNA transcription, RNA metabolism, and ribosome assembly/ribosomal biogenesis. NCN pools also contribute in tumorigenicity of cancer cells by participating in the generationof stress-conditioned activity via interactions with components of the stress-response machinery and in some cases were even NCN had been found to act as a cell surface receptor (Z. Chen & Xu, 2016). Its presence on the membrane of cancer cells is often elevated and found to interact with tumor-promoting proteins, such as “vascular endothelial growth factor (VEGF)” and “hepatocyte growth factor (HGF)” (Berger, Gaume, & Bouvet, 2015). The excessive expression of VEGF stimulates the proliferation of large neovessels, vascular malformations, circuitous glomeruloid bodies proliferation, capillaries proliferation as well as arterio-venogenic blood vessels and these features are common in most of the tumor vessels (Dvorak, 2015).

NCN is having binding efficiency with the ErbB2 (family of receptor tyrosine kinases, which mediates basic cellular processes such as cell survival, proliferation, and migration) and their complexes, i.e., ErbB2-NCN complexes are found endogenously in normal as well as in cancer cells. Its effect on tumorigenicity is mediated through activation of ErbB2 signaling, and their overexpression has been recorded in various malignancies, especially in breast cancer. Hence it could be a common easy target for the delivery of anti-cancer drugs (Wolfson, Goldenberg, Solomon, Frishberg, & Pinkas-Kramarski, 2016). In another investigation, Munisvaradass et al. have used trastuzumab, a humanized monoclonal antibody to target ErbB2 antigen in breast cancer treatment (Munisvaradass, Kumar, Govindasamy, Alnumair, & Mok, 2017). This humanized monoclonal antibody inhibits mitogen-activated protein kinases and phosphatidylinositol-4, 5-bisphosphate 3-kinase/protein kinase B pathways suppresess cell growth & proliferation owing to ErbB2 degradation through tyrosine kinase ubiquitin ligase (Szymańska, 2016). CAR (chimeric antigen receptor) has been synthesized by rDNA technology to target and inhibit ErbB2 in the treatment of breast cancer (M. Sun et al., 2014). A CAR links with scFv (an antigen-specific single-chain antibody fragment) to intracellular signaling domains of the TCR (Hudecek et al., 2013). The binding of the tumor-associated antigens (TAA) -specific scFv with their specific TAA could lead to desired T-cell activation and effector functions (Porter, Levine, Kalos, Bagg, & June, 2011;Xingshi et al., 1994). Therefore, these modified T-cells with CAR are capable of triggering an immune response in a non-major histocompatibility complex (MHC)-restricted manner. Due to these unique properties, said technology is superior and advantageous over to other available therapies as tumor cells could evade the immune system by downregulation of the MHC recognition complex (Kohga et al., 2010). Presently, the CAR technology is well documented with the various generation of CARs such as carbonic anhydrase IX (Lamers et al., 2006), mesothelin (Beatty et al., 2014), EGFR variant III (EGFRvIII) (Johnson et al., 2015), etc. for cancer targeting and treatment.

The overexpressed NCN in the cytoplasm of cancer cells where they are translocated onto the cell membrane can play an important role in the transfer of anticancer ligands from the cell surface to the nucleus. Hence, targeting the cell surface NCN are being developed as a potential anticancer therapeutics. The HB-19, N6L,and AS1411 are pseudopeptides which bind to the carboxy-terminal RGG domain of cell NCN, (structurally related to HB-19 pseudopeptide and a 26-nucleotide G-rich quadruplex-forming DNA sequence, respectively) are some examples of NCN targeting (Koutsioumpa & Papadimitriou, 2014). Thus, NCN may be a novel and promising target for the development of anticancer drugs, which inhibit the proliferation of cancer cells and can also be used as a marker for the diagnosis of cancer. Gilles et al. studied the effect of NCN-antagonist (N6L) which strongly suppresses the growth of primary tumors & liver metastasis in human specimens of pancreatic ductal adenocarcinoma (PDAC) and in orthotopic mouse model of PDAC, and result suggested that the significant inhibition in both human and mouse pancreatic cell proliferation as well as tumor invasion (Gilles et al., 2016). Another NCN-antagonist; HB-19 is a member of the multivalent pseudopeptides family has antitumor activity on human glioblastoma by targeting the NCN (Dhez et al., 2018). Zhang and co-worker prepared NCN-targeted F3 protein conjugated microbubble for the detection of the tumor by ultrasound molecular imaging and found that these NCN targeted microbubbles accumulation helped in the detection of murine-breast tumors (Zhang et al., 2017).

The active intra-nucleus transport through the nuclear pore complex (NPC) could be one of the strategies for nucleus targeting. The transportation of active molecules between the cytoplasm and nucleus taken placed with the help of NPCs. It consists of multiple proteins, which are known as nucleoporins (NUPs),and these proteins are constitutive building blocks of the Nuclear Perforation Complexes which control the bi-directional transport of diverse array of molecules from one end to the nucleus (Tran, King, & Corbett, 2014). The NUPs translocated promoter region is a prominent building of a nuclear group that sets the basket like structure on the nucleoplasmic site of the pore.

The passive diffusion via NPCs depends on the effective diameter (≤9 nm) of molecules and molecular weight (≤45 kDa) for a fast rate of diffusion whereas for molecules larger than 45 kDa are transported by active transport where transportation process triggered by specific transport signals (Görlich & Kutay, 1999; Rosenkranz, Ulasov, Slastnikova, Khramtsov, & Sobolev, 2014). The various reports confirm that some chemical generates caspase activation, DNA damage and consequently triggered cleavage of NPC family proteins, e.g., NUP 93, 153, and 214 proteins, and responsible for the disruption of lamins during apoptosis (Kwon, Lee, Shin, Kim, & Choi, 2015). Ding et al. prepared a "novel dox prodrug" for nucleus targeting which recognized the Glucose-regulated protein and transported it in the nucleus via NPS and these novel prodrugs have shown a strong growth inhibitory activity in colorectal cancer in-vivo and in-vitro and found to be safe and potent therapeutic agent (Ding et al., 2017).

HDACi histone deacetylase inhibitors (HDACi; example Trichostatin A) which are used to induce a hyperacetylated state of chromatin and NUPs. The HDACi treatment causes the translocation of NUP98, NUP153 and translocated promoter region from the nuclear pore to the interior of the nucleus and this accumulation forms intra-nuclear NUPs clusters. These transitory structural changes cause cell cycle arrest at G0/G1 phase and then inhibit the progression of cancer (Pérez-Garrastachu et al., 2017).

The nuclear localization signal (NLS)-dependent nuclear import pathway, namely, the NLS-receptor importin (Imp) α, Imp β,and two constituents, namely Ran and nuclear transport factor 2 (Ran-GTPase system) drive the translocation of active molecules into the nucleus, therefore they are considered as the actual transport receptor (Görlich & Kutay, 1999; Smith, Brownawell, & Macara, 1998). These NLSs contain peptide sequences that may be conjugated to cargoes to enable active transport of these conjugated cargo molecules to the nucleus.(Huo et al., 2014; Jhaveri & Torchilin, 2016). Some of the short cationic cell-penetrating peptides of proline-rich, arginine- or lysine- are identified by the members of the "Imp" proteins the superfamily of nuclear transport proteins, and these peptides bind nucleus directly through the NPC (Cerrato, Künnapuu, & Langel, 2017; Milletti, 2012). The Trans-Activator of Transcription (TAT) is a small peptide, which has the ability to translocate conjugated DDS in the nucleus via binding the import receptors i.e., Imp α and Imp β (Pan, Liu, He, & Shi, 2014). Other approaches by using NLS pathways have been studied using radiolabeled (177Lu, 90Y, 131I, etc.) proteins or peptides tagged with NLS. Therefore, the approach provides a potential target for tumor and tumor cell nuclei (Gedda & Edwards, 2012). The Auger-electron-emitting radionuclides (AEER) can be used to treat cancer by exposing and killing tumor cells to targeted radionuclide therapy to DNA in the nucleus of tumor cells (Olsen et al., 2013). The percept and rationale behind the use of AEER are to exploit the biological Auger effect that is caused by localized energy absorption of multiple low-energy electrons which may lead to the fragmentation of the deoxypentose moiety of complex double strands of DNA (Yokoya & Ito, 2017).

As the Imp, the inhibition of nuclear export is another most promising strategy. Nuclear export factor and CRM1 (chromosomal region maintenance 1) which are commonly known as exportin (Exp)-1, regulates the cellular localization and various functions of proteins which are crucial for the development of several cancers (Gravina et al., 2014; Zheng et al., 2014). The Exp-1/CRM is overexpressed in various types of cancers which transport nuclear export signal containing cargoes from the nucleus to the cytoplasm (Kırlı et al., 2015; Stade, Ford, Guthrie, & Weis, 1997). The upregulation of this transportation is quite common in cancers; thus inhibition of nuclear export kills cancer cells effectively. The upregulation is associated with drug resistance and responsible for poor prognosis factor in the case of many malignancies. The Exp-1 exports and mislocalized a large number of tumor

suppressors or oncogenes, such as BCR–ABL, eIF4E, surviving, etc. to the cytoplasm (Stade et al., 1997; Sun et al., 2016).

There are some peptides, proteins, and proteoglycans found abnormally distributed in cancerous cells. Either they provide a direct target, or form complexes with others to provide the antitumor effects. Decorin is a prototypical small leucine-rich proteoglycan that is capable of targeting the multiple receptor tyrosine kinases of the nucleus of tumor stroma as well as tumor parenchyma (Neill, Schaefer, & Iozzo, 2016).

The Other protein-complexes, i.e., HAMLET and BAMLET that are formed by partially folded human and bovine α-lactalbumin with oleic acid, respectively have selective apoptotic activity (Permyakov et al., 2012; Tolin et al., 2010). Basically, HAMLET is a compound of cytoplasm, and in normal cells, it is detected in very low and insignificant quantity in the cytoplasm but, in cancer, it is translocated into nuclei where it accumulates (Svanborg et al., 2003). HAMLET itself has various proapoptotic features such as potential changes in mitochondrial membranes, induces the release of mitochondrial Cyt c, disturbs the activity of proteasomes, and high binding efficiency with chromatin (Rosenkranz et al., 2014). Another cytotoxic protein "human gyrovirus-Apoptin (Hg-Apoptin)" has selective cytotoxicity toward cancer cells and affects cell cycle progression by arresting cell cycles in the G2/M phase (Chaabane, Ghavami, Małecki, & Łos, 2017). Similarly, "chicken anemia virus Apoptin (Cav Apoptin)" which is accumulated in nuclei of cancer cells selectively and arrest G2/M phase of cancer cells (Kucharski, Gamache, Gjoerup, & Teodoro, 2011; Rosenkranz et al., 2014) and triggers inhibition of downstream BCR-ABL1 signaling effects (Jangamreddy, 2015). Ho et al. studied on targeting affinity of nucleotide-binding proteins by HAMLET and found that it acts as a target for nucleotide binding proteins. The nucleotide-binding proteins-HAMLET alters the regulation of ATPase/kinase/GTPase machinery and initiate cell death due to the recognition of HAMLET in the tumor (Ho, Sielaff, Nadeem, Svanborg, & Grüber, 2015).

The serine/arginine-rich splicing factor (SRSF) 1 is another protein in which N terminal has one or two RNA recognition motifs and a serine/arginine enrich domain in the C terminal (Tan, Wang, & Ma, 2018). The family members of SRSF have various essential roles in the constitutive and alternative splicing as well as during several steps of RNA metabolism, i.e., elongation of RNA, polyadenylation of mRNA, transportation of mRNA, translation and nonsense-mediated mRNA decay (Haynes & Iakoucheva, 2006; Mavrou et al., 2015). Their normal roles are essential for proper cell cycle control. The overexpressed SRSFs, particularly SRSF1, SRSF2, and SRSF3 have oncogenic activities. The overexpressed SRSF1 promotes mammary epithelial cell transformation, prostate cancer, etc. whereas SRSF3 promotes human ovarian cancer. The inhibition of SRSFs thus induces cell cycle arrest and apoptosis; and provides a potential novel target for cancer therapeutics (Mavrou et al., 2015).

In another investigation, Lu and co-worker reported that caffeine induces tumor toxicity, it reduces the expression of p53αand induces the expression of p53β as a result expression levels of the SRSF-2, and SRSF 3 become altered (Lu et al., 2014). The SRSF 3 is a promising candidate for the SRSF responsible for the alternative splicing of p53 in response to caffeine treatment (Lu, Huang, et al., 2014). Apart from that, caffeine, as well as digoxin, can regulate epithelial-mesenchymal-transition and hypoxic conditions which inhibit the survival of tumor cells and could be a new pathway of caffeine-modulated tumor suppression via the alternative splicing of the target genes of SRSF-3 (Lu, Huang, et al., 2014; Lu, Liu, Huang, Chang, & Lin, 2014).

The post-translational arginine methylation which modifies protein-arginyl residues by protein arginine methyltransferases (PRMTs) is responsible for regulation of many biological processes, i.e., signal transduction, DNA repair, mRNA splicing, gene transcription, etc. (Blanc & Richard, 2017). The deregulation of these PRMTs enzymes is possible culprit which prevails in the pathogenesis of several diseases, including cancer. Yang and Bedfordreviewed exhaustively reported that an alteration in the PRMTs and their overexpression is frequently associated with various cancers (Yang & Bedford, 2013). Hence, the PRMTs (PRMT1, PRMT2, PRMT3, PRMT5, PRMT7, etc.) may provide viable targets for tumor targeting. It is known that some drug can target unusual isoform of PRMTs in cancer cells without affecting the other isoforms required for normal cellular function. This opportunity may further be synergized when a combination of PRMT inhibitors with chemotherapy drug like taxol (Txl) is used. PMRTs also affect the binding ability of the drug (Piller, Jwad, Hejazi, Gamsjaeger, & Sucher, 2015). The inhibition of methylation of protein arginine is used as a parallel treatment with Txl where an inhibitor inhibits the arginine methylation of tubulin-β, and as a result,Txl is fully utilized specifically for tubulin-β binding thus inhibiting of cell division in cancer-targeted therapy (Raposo & Piller, 2018). It is also reported that the cyanine-derivative preferentially bind to PRMT1 over other PRMTs and results in decreased leukemia cell proliferation (Hu et al., 2015).

The pattern recognition receptors are useful in cancer treatment, which is discussed in the following section, separately.

There are some genes that are overexpressed in cancer and involved in cellular metabolic processes. The PYCR1-genes are metabolic genes which are overexpressed in human tumors and encodes a mitochondrial enzyme, i.e., pyrroline-5-carboxylate reductase 1 (PYCR1) (Lukey, Katt, & Cerione, 2017; Phang, Liu, Hancock, & Fischer, 2015). The PYCR1 is involved in the synthesis of proline from glutamate. Its expression is upregulated by the oncogenic transcription factor c-Myc, which simultaneously downregulates enzymes that catalyzes proline catabolism (Lukey et al., 2017). The PYCR1 expression inhibition decline cell proliferation, resulting in cell cycle arrest at the G1 phase and apoptosis (Cai et al., 2018). PYCR1 and proline biosynthesis pathway can be exploited as one of the targets for cancer therapy.

The Myc gene family encodes three transcription factors (c-Myc, N-Myc, and L-Myc) that are involved in regulation of many essential cellular processes relating to cell growth, death, cell cycle, differentiation, and transcription. The overexpression of Myc is a special characteristic of most human cancer and responsible for an unexpected set of transformation such as DNA replication cell proliferation, cell growth and metabolism, cell cycle progression, adhesion, differentiation, and metastasis (Tansey, 2014). Small therapeutic peptides, i.e., H1-S6A and F8A (14-amino acid) which are derived from the helix 1 C-terminal region of c-Myc were used as a model drug for cancer treatment. These peptides inhibit the c-Myc DNA binding and effect the inhibition of cell proliferation and apoptosis in MCF-7 human breast cancer cells. Results of such studies suggested that the blocking of c-Myc activities provides a better therapeutic response in the nuclear region (Giorello et al., 1998; Marqus, Pirogova, & Piva, 2017; Tansey, 2014).

The use of genes for therapeutic purpose has great potential for the treatment of cancer (Zhong et al., 2015). A gene with therapeutic potential can be added into a plasmid vector and delivered to the nuclei of tumor cells. The gene therapy is commonly applied to achieve nuclear delivery of DNA or nucleic acids damaging agents (Fewell, Matar, Rice, Lewis, & Anwer, 2016). Mesenchymal stem cells are one of the auspicious tools for gene therapy in cancers and other various diseases due to their high proliferative capacity and ability to differentiate into many cell types. They have inherent tendency to migrate to malignant sites that make these cells predominantly capable for the effective cellular delivery of antitumor agents including cytokines, interferons as well as pro-drugs (Mohammadi, Jaafari, Mirzaei, & Mirzaei, 2016). Lipoplex, a drug carrier system which is used for DNA delivery to the nucleus, presently under clinical trial for the treatment of melanoma (Sakhrani & Padh, 2013).

### 2.4. Lysosomal targets

The lysosome is one of the important cell organelle considered as the regulator of cellular homeostasis and has an impact on the biological

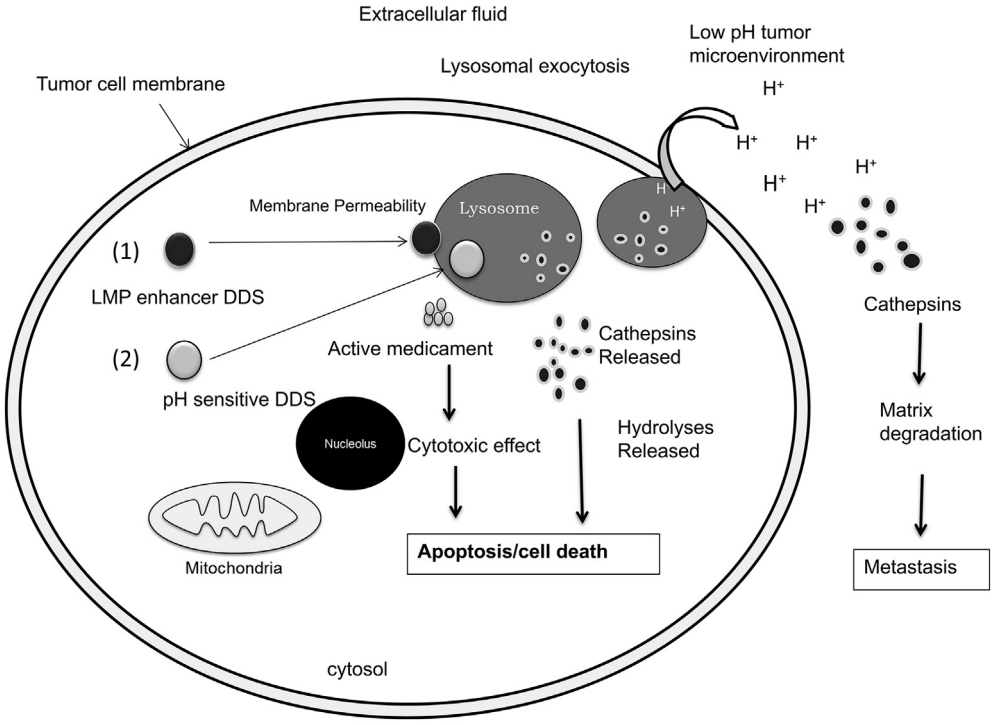


**Fig. 7.** The changes occurred in tumor cells and approaches to target lysosome. (1) LMP enhancer enhances the permeability of the lysosome membrane and promotes the release of cathepsins in the cytosol, which leads to apoptosis by the activity of hydrolyzes. (2) The pH-sensitive drug delivery system activates in low pH environment of lysosome and provides the cytotoxic effects.

processes. It regulates the renovation of the plasma membrane, degradation and waste removal, cholesterol homeostasis, cell death signaling (Appelqvist, Wäster, Kågedal, & Öllinger, 2013) and metabolic growth signaling (Davidson & Vander Heiden, 2017). In the case of a tumor, various dramatic changes occur in lysosomal activities, and these changes may be used in the effective treatment of tumor (Fig. 7).

The degradation and digestion of all major cellular macromolecules are carried out some acid hydrolases (AHs) like proteases, phosphatases, glycosidases, lipases, peptidases, sulfatases, nucleases, etc. (Gyparaki & Papavassiliou, 2014; Repnik, Cesen, & Turk, 2013). Lysosomal hydrolases (LHs) are also known as AHs because of their optimal activities in the acidic environment at pH 4–5 (Piao & Amaravadi, 2016).

The best studied LHs are cathepsins (CPs) proteases, which are further divided into three subcategories by the active site of amino acids, i.e., cysteine CPs, serine CPs, and aspartic CPs (Rodriguez-Muela et al., 2015). Cytosolic CPs can suppress tumor growth through activation of the intrinsic apoptotic pathway or by initiation of cell death by lysosomal membrane permeabilization (LMP) (Repnik, Stoka, Turk, & Turk, 2012). Deng et al. prepared an $H^+$-triggered bubble-generating nano-system which produced carbon dioxide gas bubbles in the lysosomal environment of tumor cells. As a result, the LMP increased, and simultaneously the level of CPs increased into the cytoplasm which led to apoptosis of cancer cells (Deng et al., 2017). Various studies confirmed that in most of the cases the presence of endosomal LHs and Low pH are essential for drug release from the carriers or for activation of some pH-sensitive materials. In another investigation, Liu et al. showed the activation of pH-sensitive hybrid micelles composed of the acid-sensitive copolymer and intracellular drug delivery for the tumor treatment (Liu, Li, et al., 2018). Dong et al. prepared a specific two-photon fluorescent probe attached with biotin (as tumor affinity module) at one end and morpholine at another end as a lysosomal specific group for the novel targeting to the tumor and monitoring the changes in lysosome pH. A strong one-photon and two-photon fluorescence responses were recorded in case of cancer while weak fluorescence response was observed in normal cells (Dong et al., 2017). Similarly, Qiu et al. prepared and characterized pH sensitive dox loaded, 2-(octadecyloxy)-1,3-dioxan-5-amine (ODA) ester conjugated hyaluronic acid micelles (HyAM). At low pH micro-environment of the tumor and organelle like lysosome, the HyAM are rapidly disassembled due to the pH-triggered hydrolysis of ODA releasing the drug in the cytosol till treatment of tumor (Qiu et al., 2017). The ester bond of modified DDS is hydrolyzed at low pH of the endosomal environment which facilitates the intracellular drug delivery for the effective treatment of the tumor. Chen et al. and Fan et al. prepared and characterized the dual, i.e., pH sensitive and redox reaction based nanoparticles (NPS) for tumor targeting in which cationic polymer was used for the delivery of siRNA-complexes (Chen, Wang, Xie, & Gong, 2017; Fan et al., 2017). The siRNA-complexed NPS are taken by the cells via endocytosis. Zhang et al. prepared and studied dual functionalized liposomal DDS which is modified with integrin αvβ3 and a pH-sensitive antimicrobial peptide i.e. [D]-H6L9 for solid tumors. The results of the study showed the ability of the targeted system in the identification of the tumor and also responding to low pH microenvironment of cancer (Zhang et al., 2016). Similarly, Wang et al. prepared hydroxychloroquine (HQ) loaded pH-sensitive liposomes decorated with a TH-RGD (Arginyl-glycyl-aspartic acid) peptide for the targeting to the integrin αvβ3 which is overexpressed on the surface of the tumor (Wang, Kaur, et al., 2016). The HQ was reportedly internalized in the tumor cells and accumulated in lysosomes at low pH environment.

The lysosomal membrane proteins have inevitable functions and may be used as potential tools for cancer targeting (Gyparaki & Papavassiliou, 2014). The lysosome-associated membrane protein (LaMP)-1 and LaMP-2 are the most abundant and represent 50% of lysosomal membrane proteins. Also responsible for lysosomal biogenesis, acidification, metabolism, transportation, and autophagy (Cárcel-Trullols, Kovács, & Pearce, 2017). LaMP1 is also known to inhibit cancer cell migration (Yao, Guo, & Gui, 2018). Huang et al. studied the overexpression of LaMP-1 in esophageal squamous cell carcinoma (ESCC) and evaluated its possibility as a cancer biomarker in ESCC through immunohistochemistry and analyzing the correlation between the levels of LaMP-1 expression and pathophysiological characteristics of such patients (Huang et al., 2017). Similarly, Agarwal et al. studied the role of

overexpressed LaMP-1 and its associated carbohydrates in lung cancer metastasis. They concluded that the downregulation of LaMPs results in its low-level surface expression and decreased metastasis. This is due to the interaction of poly-N-acetyllactosamine (carbohydrates) on surface LaMP-1 with galectin-3 on organ endothelium and become a critical rate-limiting step in the arrest and metastasis of melanoma cells to the lungs (Agarwal et al., 2015). Zhang et al. reported that peptide-conjugated ZnO nanoparticles (NPs), which selectivelyentered into the cancer cells by following the intracellular endocytic pathways and reached into the lysosomal compartment (Zhang, Xu, et al., 2013). Further, ZnO NPs also produce ROS which provides catalytic properties. Thus, these features offer a new strategy wherein ZnO NPs can be used for the targeted drug delivery of the anticancer drug involving inductionof LMP-dependent apoptosis in cancer cells (Zhang, Xu, et al., 2013).

Autophagy means "self to eat" is type II programmed cell death in which a cell degrades long-lived proteins and damaged organelles by multi-step lysosomal degradation process (Bottone et al., 2013). It may be of three types, i.e., macroautophagy, microautophagy, and chaperone-mediated autophagy (Cuervo, 2004). In cancer cells, autophagy may provide means of recycling macromolecules (to provide nutrients) or may lead to cell death via excessive cellular stresses (Liu, Bao, Yang, & Cheng, 2013; Wang, Yu, Zhang, & Liu, 2011). In cancer, the role of autophagy is slightly controversial because it acts as either a guardian or killer depending on the stage of cancer initiation and progression (Liu & Levine, 2015). Autophagy-related genes (ATG)-1 and ATG13, mTOR subnetwork, Beclin-1 interactome, p53 signaling, phosphatidylinositol 3-phosphate (PI3K) UNC51-like kinase, LaMP-2A, ROS, etc. may play major roles in autophagy (Morel et al., 2017; Sinkovics, 2016). Combination of all autophagic pathways could constitute promising new targets for cancer therapy. 3-methyladenine (3-MA) and wortmannin are the examples of PI3K inhibition that interferes with or blocks autolysosome formation and finally autophagy (Germic, Stojkov, Oberson, Yousefi, & Simon, 2017). Among others, Hydroxychloroquine is used as an inhibitor of autophagy and till now is only clinically-approved (Chude & Amaravadi, 2017).

Bafilomycin A1, vinblastine, and nuokaodazuo can inhibit the fusion step of autophagy ultimately interrupt autophagy (Fujiwara et al., 2007; Liu et al., 2013). Various studies suggest that type II programmed cell death may present opportunities for developing alternative anticancer therapies. Tamoxifen, an antagonist of estrogen receptor, has a high binding affinity for the microsomal antiestrogen binding site (a hetero-oligomeric complex involved in cholesterol metabolism) can be used as a ligand to induce breast cancer cell autophagy through inducing sterol accumulation (Ahmed et al., 2016). Apart from that rapamycin inhibits mTOR which is a major regulator of cell growth (Vella et al., 2017).

The Autophagy thus plays a dual role as a promoter as well as a suppressor of cancer with the help of several key autophagic mediators, including ATGs, PI3K, mTOR, p53, Beclin-1 interacome, and ROS. This mediator could be better targeted for the cancer treatment. However, much work is needed to study at the molecular level to find out the mechanism involved to especially relating to autophagic signaling pathways.

### 2.5. Plasma membrane targets

The plasma membrane of normal cells is possessed an asymmetric distribution of phospholipids on the membrane leaflets (Elvas, Stroobants, & Wyffels, 2017; Marconescu & Thorpe, 2008). In normal cells, the aminophospholipids, i.e., phosphatidylserine (PS) and phosphatidylethanolamine (PE) are asymmetrically distributed across the plasma membrane with essentially all the PS and the majority of the PE localized in the cell's inner membrane leaflet while, phosphatidylcholine and sphingomyelin in outer leaflets. Whereas tumor cells lose their capacity to maintain PS and PE asymmetry. As a result, these lipids appear on the outer leaflet of the cell membrane (Sugimura, Donato, Kakkar, & Scully, 1994;Winter et al., 2015).

In normal cells, the phospholipid membrane asymmetry is regulated by three enzymes, i.e., flippase, floppase and scramblase (Fig. 8). Flippases are ATP-dependent translocases that transport aminophospholipids (i.e., PS & PE) from the outer leaflet to the inner leaflet and floppases transport phospholipids from the inner leaflet to the outer leaflet. Scramblases are ATP-independent translocases that move aminophospholipids outer side to the inside and vice versa (Leventis & Grinstein, 2010). In the cancer cells, due to increase in the intracellular levels of $Ca^{2+}$ ions, the activation of a scramblase does take place which leads a non-specific movement of these aminophospholipids (Seigneuret & Devaux, 1984), decrease in the activity of flippase and increase the activity of floppase (Bern, 2017). Due to the oxidative stress, the asymmetry of the membrane is disturbed, and PS & PE are exposed on the outer leaflet of the cells. The expression of PS and PE at the cell surface may serve as a ligand (Emoto, Toyama-Sorimachi, Karasuyama, Inoue, & Umeda, 1997; Fadok et al.,

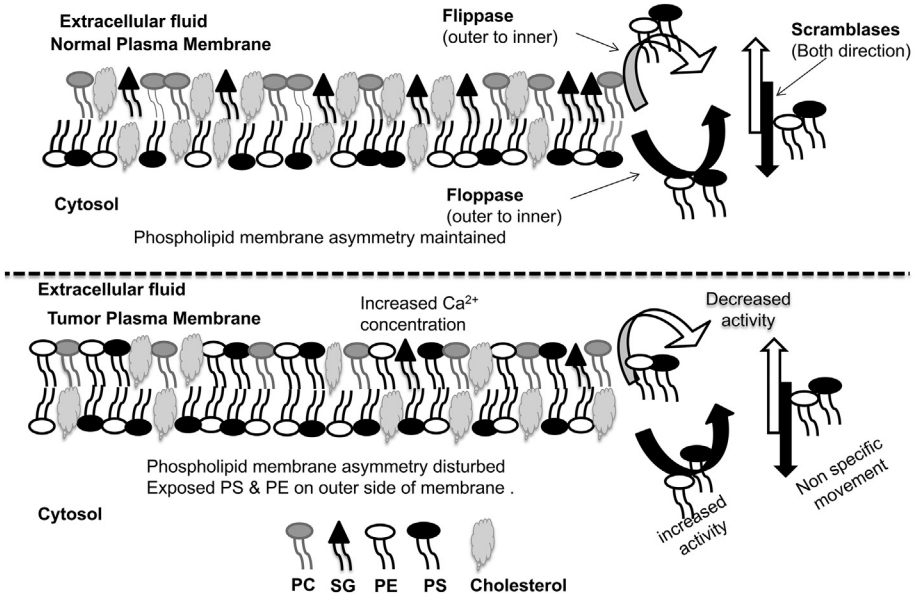


**Fig. 8.** Asymmetric tumor cell plasma membrane resulted due to alteration in the activity of ATP dependent scramblase, floppase, and flippase.

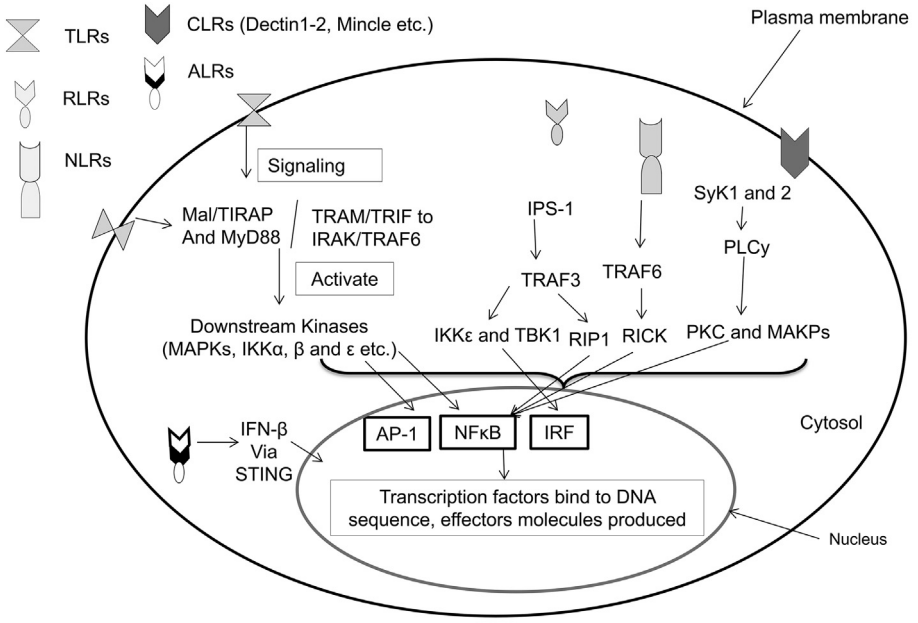


**Fig. 9.** Location, signaling and activation mechanism of different PRRS receptors (A schematic presentation).

1992) and targets to treat for cancer (Sharma & Kanwar, 2018). Annexin (ANX)-5 is a $Ca^{2+}$ dependent binding protein to phospholipid membrane, which is abundant and widely distributed in eukaryotes and known to have a high affinity specifically to PS (Neves et al., 2013; Pan et al., 2017; Sharma & Kanwar, 2018). The ANX-5 conjugated DDS (single-walled carbon nanotubes) has been established to target to PS of the plasma membrane of bladder cancer (Virani et al., 2017) and breast cancer (Neves et al., 2013). In anotherstudy, the ANX-A1/A5 was used to target PS for the delivery of human enzyme β-glucuronidase for treatment of solid tumors vasculature (Guillen, Ruben, Virani, & Harrison, 2017). Li et al. prepared calcium-dependent protein-drug conjugates for the treatment of cancer by targeting the PS, in which monomethyl Auristatin-E conjugated with synaptotagmin-1 (Li, Chiguru, et al., 2018). Garnier et al. prepared the ANX-A5 functionalized liposomes for targeting PS-rich membranes (Garnier, Bouter, Gounou, Petry, & Brisson, 2009) and Pan et al. prepared the ANX 5-conjugated mixed micelles as a potential drug delivery system for targeting to thrombolysis (Pan et al., 2017).

The protease ANX-1 and another endogenous protease inhibitor have a binding affinity for the PE (Hengst, Albrecht, Hess, & Monard, 2001).

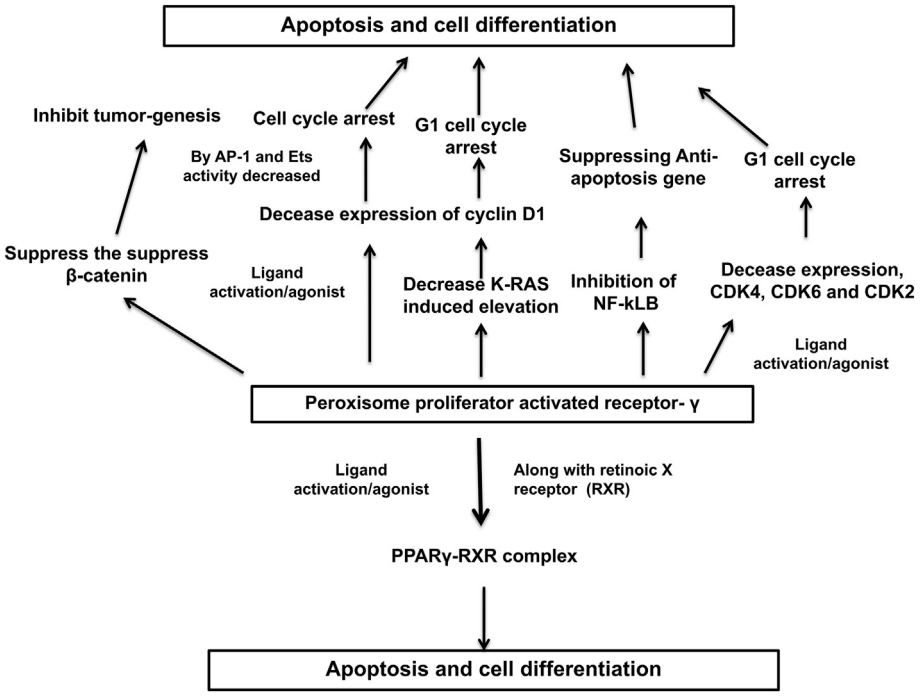


**Fig. 10.** The different mechanism associated with PPARγ in tumor targeting.

**Table 1**
Sub-cellular organelles targeted NCs and their mechanism of actions.

| Drug delivery systems | Types of cancer/tumor targeting | Mechanism(s) | References |
|---|---|---|---|
| Mitochondrial- Endoplasmic reticulum targeting | | | |
| Amphipathic tail anchoring peptides conjugated magnetic core cell NPS | Brain and breast cells cancer | Delivery of MT targeting pro-apoptotic amphipathic tail-anchoring peptide (ATAP) for the treatment of malignant brain and metastatic breast cancer cells via MT. | (Shah et al., 2014) |
| Curcumin and SH-aspirin loaded mPEG-PLGA NPS | Human ovarian carcinoma | Mitochondrial induced apoptosis via transcription factors, growth factors, kinases, inflammatory cytokines, apoptosis-related proteins, etc. | (Zhou et al., 2015) |
| Baicalein loaded nano-LPS | Human chronic myeloid leukemia | ROS generation | (Wang, Wen, Bell, & Appiah, 2018) |
| Peptide, 2,3-dimethyl maleic anhydride and 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine modified peptide liposome loaded with paclitaxel | Lung cancer A549/Taxol cells | Dual Mitochondria and pH-responsive, increase Cyt-c and caspase-9 and 3 | (Jiang, Li, et al., 2015) |
| Palmitoyl ascorbate hybrid micelles PEG-b-poly [2-((((4-(4,4,5,5,-tetrmethyl-13,2,-dioxaborolan-2yl)oxy) carbonyl)oxyl methacrylated NPS | Breast cancer cells | ROS elevation and anti-oxidative suppression | (Yin, Li, Ke, Zha, & Ge, 2017) |
| Glucose oxidase and catalase embedded cancer cell membrane-camouflaged porphyrin metal organic frameworks | 4T1 cell lines | Decomposition of intracellular glucose in presence of $H_2O_2$ | (Li et al., 2017) |
| Chitosan, ursolic acid, and folate-based NPS | Breast cancer | ROS overproduction induced apoptosis | (Jin et al., 2016) |
| DOX and photosensitizer rose bengal loaded apoferritin NPS | Breast cancer | ROS and low pH-responsive, exploiting L-apoferritin receptor SCARA 5 for specific targeting | (Du et al., 2018) |
| PEGylated poly(L-lactic acid)(-IR780)-b-hydrophobic poly (phenyl isocyanide)-b-hydrophilic poly(phenyl isocyanide) NPS | Hela cell lines | Oxidation and low pH dual responsive carriers, enhance the treatment. | (Chen et al., 2017) |
| Bioinert anodic alumina nanotubes loaded with thapsigargin retreated with 3-methyladenine | Human fibroblast cells, human monocyte cells, human breast cancer cells | Endoplasmic reticulum stress and autophagic signaling | (Wang et al., 2015) |
| Silver NPS | Breast cancer cells | Upregulation of transcription factors ATF-4 and GADD153/CHOP and initiate initiating caspase-9 and the effector caspase-7 | (Simard, Vallieres, De Liz, Lavastre, & Girard, 2015) |
| Cystine/citric acid-coated confeito-like gold NPS | Breast cancer cells | Accumulated in Lysosomes, MT and ER, chemotherapeutic by photothermal effect | (Saw et al., 2018) |
| Adamantine-Cyclodextrin inclusion complex NPS with siRNA | Prostate cancer cells | S1R (Sigma-1) receptor targeting on ER | (Fitzgerald et al., 2016) |
| Low pH environment/Lysosomal degradation | | | |
| DOX-Heparin engineered NPS | Primary and metastatic cancer treatment | Low pH sensitive and inhibit P-selectin interaction with tumor cells | (Mei et al., 2017) |
| Arginine-α, β-dehydrophenylalanine, and DOX-NPS | C6, HCT-116 and AGS cell line | pH-responsive release enhance cellular internalization and increased cancer efficacy | (Singh, Chibh, Dube, Chauhan, & Panda, 2018) |
| Stearate acid-degradable hydrazone bond coupled doxorubicin-loaded PEGylated LPS | Breast cancer cells | Cell-penetrating peptide and acid sensitive DDS which has exerted higher efficiency on internalization and anti-tumor efficacy | (Ding et al., 2015) |
| Anti-Her2-gold nano-constructs | Breast cancer | Lysosomal degradation, G0/G1cell arrest | (Lee, Dam, Ha, Yue, & Odom, 2015) |
| Nucleus and nuclear components targeting | | | |
| α-galactosylceramide incorporated octaarginine-modified LPS | Murine dendritic cell line (JAWSII) | Activates NKC-T | (Nakamura, Yamazaki, Yamauchi, & Harashima, 2013) |
| Ruthenium polypyridine complex containing theranostic nanoparticles (NPS) | Breast cancer | DNAbreaks | (Shen et al., 2017) |
| Erlotinib-loaded core-shell type lipid albumin hybrid NPS | Lung Cancer | Inhibition of EGFR tyrosine kinase | (Mandal, 2015) |
| Virus-based NPS conjugated with an amino acid (GE-11) | Epidermoid, colorectal and triple negative breast cancer | EGFR targeting | (Chariou et al., 2015) |
| MicroRNA-34a loaded PEG-coated NPS | Melanoma cells | Downregulation of CD44 | (Fan et al., 2017) |
| Ca-chloroquine diphosphate and pDNA loaded polylactic-co-glycolic acid (PLGA) NPS | Human embryonic kidney cells | Gene transfection/therapy | (Yang, Hu, et al., 2015) |
| All-trans retinoic acid (Pin1 inhibitor) loaded poly L-lactic acid NPS | Hepatocellular carcinoma | RAS, Myc and other oncogenes suppression | (Yang et al., 2018) |
| PEG-PLGA nanoparticles loaded with docetaxel | Her2/neu Overexpressed Human Breast Cancer Cells | ErbB2 targeted | (Yang, Tang, et al., 2015) |
| Dox-loaded nanoparticle | Osteosarcoma, breast, prostate and colorectal cancer | ER, NPC and nucleus | (Friedhuber et al., 2015) |
| 1,7-bis (3,4-dimethyoxyphenyl)-5-hydroxyhepta-1,4,6-trien-3-one loaded PLGA NPS | Breast cancer | G2/M cell cycle arrest | (Verderio et al., 2014) |
| Gemcitabine loaded AS1411 aptamer-decorated biodegradable PLGA nano-polymersomes | Lung cancer | NCN targeted | (Alibolandi, Ramezani, Abnous, & Hadizadeh, 2016) |

(continued on next page)

**Table 1** (*continued*)

| Drug delivery systems | Types of cancer/tumor targeting | Mechanism(s) | References |
|---|---|---|---|
| Chitosan and PEGylated chitosan nanoparticles containing siRNA | Colon cancer | β-catenin protein decreased | (Rudzinski, Palacios, Ahmed, Lane, & Aminabhavi, 2016) |
| Heptapeptide (A7R) modified LPS | Subcutaneous tumor | EGFR-2 and NUP-1 | (Ying et al., 2016) |
| An endogenous vaccine based NPS and fluorophore-loaded LPS coated with a multivalent immunoadjuvant (HA-CpG) | Colon cancer cell lines | TLRs 9 (PRR) recognition | (Li, Yang, et al., 2018) |

Spectrin is the major protein of the red blood cell membrane cytoskeleton which has an affinity toward the PS and PE (Bitbol, Dempsey, Watts, & Devaux, 1989). Lea et al. studied and established the PS-positive exosomes as a diagnostic marker for the detection of ovarian cancer (Lea et al., 2017). Pitchaimani et al. prepared a membrane concealed fusogenic liposomal deliverysystem named as "NKsome" loaded with doxorubicin for targeted tumor therapy using natural killer cells. Natural killer cells, which go through natural immunosurveillance of tumor stressed cell. "Major Histocompatibility Complex Class I (Hiscom-I)" molecules and "cell stress marker" abnormally expressed on tumor surface provide the affinity to NKsome (Pitchaimani, Nguyen, & Aryal, 2018). NKsome can also act by inhibition or activation of the receptors on its cell surface. The mechanism involves the release of "perforin" a membrane disrupting protein and "granzyme" (proteolytic enzyme) which leads to the lysis of tumor cells or by enhancing the expression of death receptor ligands such as Fas and TNF-related apoptosis-inducing ligand (Dahlberg, Sarhan, Chrobok, Duru, & Alici, 2015).

So, the plasma membrane phospholipids asymmetric distribution and Hiscom-I exposure may be suitable targets for tumor targeting without harming the normal cells.

### 2.6. Other targets

#### 2.6.1. Pattern recognition receptors

The pattern recognition receptors (PRRs) are the group of receptors play important role in human immunity, which is directly involved in the recognition of antigen determinants of approximately all groups of the pathogenic organism (Pandey et al., 2015). Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), C-type lectin receptors (CLRs), DNA sensors and NOD-like receptors (NLRs) are forming the PPRs receptor (Galluzzi, Buque, Kepp, Zitvogel, & Kroemer, 2017; Shekarian et al., 2017). These have various vital functions like regulation of apoptosis, DNA repair, autophagy, and angiogenesis (Shekarian et al., 2017). The PPRs activation may frequently protect the human host from pathogenic agents and prevent them from the carcinogenic occurrence. The deregulation in the function of PRRs triggers cancer by losingimmunity (Garlanda, Bottazzi, Magrini, Inforzato, & Mantovani, 2018). Simultaneously, PRRs activation may also trigger cancer by generating a suitable pro-inflammatory microenvironment, which supports tumor progression and resistschemotherapy (Galluzzi et al., 2017; Kutikhin & Yuzhalin, 2015). The chronic activation of PRRs (Fig. 9) is associated with the aggressiveness of various cancers. The minimization of PRRs may be one of the pioneer'stumor-targeting tools. The antagonists and agonists of PRRs both are useful for tumor targeting. The combination of therapies of PRR agonists along with immune checkpoint targeted antibodies, e.g., anti-CTLA-4, or anti-PD-1 provide endurance to immune checkpoint obstruct monotherapy (Shekarian et al., 2017).

For the cancer treatment, the minimization of PRR activity to reduce the effect of inflammation could be a promising targeting strategy (Kutikhin & Yuzhalin, 2015). To prove such strategies the PRR antagonists such as TLR4 antagonists, i.e., CRX-526 (a monoclonal antibody), which is mimic to synthetic lipid A and 1A6 have investigated for preventing multiple sclerosis (Podda, Nyirenda, Crooks, & Gran, 2013), inflammatory bowel disease (Fukata, 2012) and another autoimmune disease (Clanchy & Sacre, 2010). These agents such as interleukin (IL)-1neutralizing antibodies, anakinra which is a recombinant IL-1R antagonist, and IL-18 binding proteins which target TLR signaling have been already established as therapeutics for cancer suppression (Dinarello, 2014; M. Fukata & Arditi, 2013). A synthetic NOD2 agonist, muramyldipeptide (MDP)-Lys (L18) in combination with IFN-β has been investigated for the induction of antitumor immune response against malignant melanoma. This combination leads to the stimulation of the human monocyte-derived dendritic cells significantly, augmented the production of TNF-alpha, IL-1beta mRNA, and IL-6, etc. as well as expression of costimulatory molecules CD 86, CD80 and CD40. *In vivo* studies showed that the IFN-MDP-Lys18 suppressed the growth of B16F10 melanoma significantly, and it can be apromising tool for malignant melanoma therapy (Fujimura, Yamasaki, Hidaka, Ito, & Aiba, 2011). Similarly, Tashiro et al. have developed chronic lymphocytic leukemia (CLL)-1 specific CAR T cells and showed their specific activity against CLL-1 (Tashiro et al., 2017).

#### 2.6.2. Peroxisome proliferator-activated receptor- γ

Peroxisome proliferator-activated receptor- γ (PPARγ), is a ligand-activated nuclear type steroid hormone receptor of family PPAR (Fajas, Fruchart, & Auwerx, 1998). It is a promoter of immune tolerance via putting effects on dendritic cells, regulatory T cells and macrophages (Tyagi, Gupta, Saini, Kaushal, & Sharma, 2011). PPARγ is associated with various biological activities like metabolism of carbohydrate, cell adipogenesis, inflammatory response, differentiation and apoptosis of tumor cells. It possesses four functional domains; i) Non-ligand-dependent transcriptional activation domain which is a regulatory region with phosphorylation, ii) DNA binding domain (initiation and regulation for gene transcription), iii) regulatory domain with transcriptional activity and iv) ligand binding domain at the carboxy-terminus of PPAR (Xu & Xu, 2018). Other than the PPARγ, there are many subtypes also identified, i.e., PPAR-α, β, and δ (Fanale, Amodeo, & Caruso, 2017). The effects of PPAR-γ agonists may provide a promising tool in anti-cancer therapy. IGF-RAs result tumor cells undergo apoptosis (Polvani, Tarocchi, Tempesti, Bencini, & Galli, 2016; Xu & Xu, 2016). These roles of PPARγ activation create an attractive option for cancer targeting. Although there are many signaling pathways for PPARγ insulin-like growth factor (IGF) signaling pathway has been studied very vastly. In the cancerous cells, there is an inappropriate expression of IGF components like IGF-I & II, overexpression IGF-I receptor, IGF-insulin released receptor (IGF-R), and others related to IGF-R (Tachibana, Yamasaki, Ishimoto, & Doi, 2008). The isomer of IGF-R, i.e., isomer A (IGF-RA) is notably expressed in cancer cells which has a high binding affinity with insulin as well as IGF-II. The overexpressed IGF-R also play a role to amplify signaling of IGF-II and IGF-I by the hybrid receptors formation of IGF-R/IGF-IGF-R (Fanale et al., 2017). The PPAR-γ agonists drop down the concentration of circulating insulin by which various key pathways of Insulin/IGF axis are regulated like PI3K/mTOR, mitogen-activated protein kinase and β-catenin cascades. These pathways are responsible and used for survival by cancerous cell, cell reprogramming, and differentiation (Vella et al., 2017). Ji et al. studied on GW501516 PPARβ/δ agonist and found that the PPARβ/δ activation occurred that also inhibited the proliferation and induced apoptosis in nasopharyngeal carcinoma cell lines (Ji, Li, Wang, & Gu, 2018).

**Table 2**
Some patents and their mechanism of cellular organelles targeting.

| Title | Patent/application no. (year) | Mechanism/description | References |
|---|---|---|---|
| Cancer treatment including glycolytic inhibitors. | US7338940B2 (2008) | Liposome formulation of 2-deoxyglucose and its analogs as an inhibitor of the glycolytic pathway to create ATP for energy anaerobically and cancer cells that aerobically generate ATP. | (Lampidis & Priebe, 2005) |
| Systems and methods for treating human inflammatory and proliferative diseases and wounds, with fatty acid metabolism inhibitors and/or glycolytic inhibitors | US8071645B2 (2011) | The invention combines an oxirane carboxylic acid, etomoxir, with a 2-deoxyglucose- compound. The systems are used for the treatment of inflammatory, proliferative diseases, and wounds, via the mechanism of fatty acid metabolism inhibitor, a glycolytic inhibitor, and/or an agent able to alter cellular production of reactive oxygen. | (Newell, Newell, & Villalobos-Menuey, 2011) |
| Inhibitors of glycolysis useful in the treatment of brain tumors | USOO9149489B2 (2015) | Inhibit glycolysis of the structural Formulas I and II are provided (Chemical compounds) for treatment of brain tumor. | (Priebe et al., 2015) |
| Iodo-hexose compounds useful to treat cancer | US8299033B2 (2012) | Iodo-hexose a 2-deoxy-2-iodo-D-hexose compound including 2-deoxy-2-iodo-D-mannose, 2-deoxy-2-iodo-D-talose, 2-deoxy-2-iodo-D-galactose, and/or 2-deoxy-2-iodo-D-glucose may act as new targets for treatment of pancreatic cancer by signal transduction pathways and molecules involved in angiogenesis, particularly, the Ras oncogene signaling pathway and inhibitors of the MMP family. | (Priebe, Szymanski, Fokt, Conrad, & Madden, 2012) |
| Mannose derivatives for killing tumor cells | US8242167B2 (2012) | The mannose analog such as 2-DG or 2-FM or 2-CM either interference with glycosylation to inhibit the cancer cell growth. | (Lampidis, Kurtoglu, & Maher, 2012) |
| Acetates of 2-deoxy monosaccharides with anticancer activity | US8927506B2 (2015) | Novel compounds acetate of 2-deoxy monosaccharides was used to inhibit glycolysis to treat cancer. | (Priebe et al., 2015) |
| Cancer treatment using FTS and 2-deoxyglucose | US8278349B2 (2012) | Farnesyl thiosalicylic acid (FTS) and analogs are Ras antagonist and 2-deoxyglucose (2DG) is an inhibitor of glycolysis. | (Kloog, Goldberg, & Brownstein, 2012) |
| Inhibitors of pyruvate kinase and methods of treating disease | US8877791B2 (2014) | PKM2 used to treat cancer via the conversion of phosphoenolpyruvate to pyruvate during glycolysis. | (Cantley, Vander Heiden, & Christofk, 2014) |
| Using cells reprogrammed with oncogenic factors for screening anti-neoplastic agents | US20120196311A1 (2012) | The establishment linkages between induced pluripotent stem (iPS) cells reprogramming and its potential roles in neoplastic transformation and thus establishes a foundation for using iPS cells as a class of cells reprogrammed with oncogenic factors for screening anti-neoplastic agents and the screening process involves examining the capability of a single agent or a combination of multiple agents in suppressing a neoplastic process including aerobic glycolysis and the related anabolism and thus inhibiting excessive reproduction of the neoplastic cell. | (Liu, 2012) |
| Compositions and methods for glucose transport inhibition | US20160137585A (2016) | Provide new insights into the role of glucose transport and metabolism in tumorigenesis, as well as in apoptosis. | (Chen & Bergmeier, 2016) |
| Compositions and methods for treating cancer | US9060993B2 (2015) | ATP citrate lyase inhibitor and/or tricarboxylate transporter inhibitor are used to treat cancer. | (Thompson, Bauer, & Hatzivassiliou, 2015) |
| Compositions and methods of treating cancer | US20180085350A1 (2018) | The present invention relates generally to cellular immunology as a more specific method to treat cancer by administering dendritic cell/tumor fusions in combination with an immunomodulatory agent (lenalidomide). | (Avigan, Rosenblatt, & Kufe, 2018) |
| VDAC1 compositions and methods of use thereof for regulating apoptosis | US8119601B2 (2012) | This invention is related to VDAC1 and amino acid & polynucleotide sequences to induce or regulating apoptosis such compositions are also useful for the treatment of diseases associated with aberrant apoptosis. | (Shoshan-Barmatz & Ben-Hail, 2012) |
| Method of modulating apoptosis and compositions thereof | US20050085420A1 (2005) | The invention provides methods of promoting or inducing apoptosis by disrupting or inhibiting the formation of a VDAC2/BAK complex. Also produces certain compounds that promote/disrupt the VDAC2/BAK complex. | (Korsmeyer & Cheng, 2005) |
| VDAC1 compositions and methods of use thereof for regulating apoptosis | US8648045B2 (2014) | The present invention related to the inducing or regulating apoptosis via VDAC1 & polynucleotide & amino acid sequences. | (Shoshan-Barmatz, Abu-Hamad, Arzoine, & Zaid, 2014) |
| Method for identifying apoptosis modulating compounds | US6165732A (2000) | Methods for identifying apoptosis-modulating compounds using lipid bilayers are provided. One method involves contacting a compound of interest with a lipid bilayer which contains an ion-channel formed by an anti-apoptotic or pro-apoptotic polypeptide of the BCL-2 family and assaying for changes in the ion conductance properties of the channel, including ion selectivity, single-channel conductance, and rectification. | (Korsmeyer & Schlesinger, 2000) |
| ROS-activated compounds as selective anti-Cancer therapeutics | US20130230542A1 (2016) | The compounds are activated in the presence of ROS and are therefore selective anti-cancer therapeutics for cancers associated with elevated ROS. | (Merino, Mulloy, Li, & Bell-Horwath, 2016) |

(continued on next page)

**Table 2** (*continued*)

| Title | Patent/application no. (year) | Mechanism/description | References |
|---|---|---|---|
| Coated nanoparticle therapy for skin cancer | US20130337070A1 (2013) | The polymer-coated cerium nanoparticles as a therapy against skin cancer by increasing ROS level and oxidative damage of tumor cells. | (Brenneisen & Seal, 2013) |
| Combination of opioids and anticancer drugs for cancer treatment | US20150265594A1 (2015) | The invention the opioid receptor agonists which act as an anticancer by cleavage of caspase-3 and poly(ADP-ribose) polymerase (PARP) as resultapoptosis initiated in the tumor cell, and/or cleavage of caspase-9 and down-regulation of X-linked inhibitor of apoptosis protein and/or down-regulation of the Bcl. | (Friesen & Miltner, 2015) |
| Compositions and methods for reducing C/EBP homologous protein activity in myeloid-derived suppressor cells | US9752145B2 (2017) | By inhibiting the level of CHOP activity, the immunosuppressive function of Myeloid-derived Suppressor Cells is disrupted. | (Rodriguez & Ochoa, 2017) |
| Increasing cancer patient survival time by administration of dithio-containing compounds | US20160287540A1 (2015) | Dithio-Containing Compounds decreased DX and/or glutaredoxin. | (Hausheer, 2015) |
| Use of STING agonist as a cancer treatment | US20160287623A1 (2016) | Methods and compositions for treating cancer by intratumorally administering a stimulator of interferon genes STING agonist for the treatment of cancer. | (Gajewski et al., 2016) |
| Use of multivalent synthetic ligands of surface nucleolin for treating cancer or inflammation | US20110065649A1 (2016) | Compound with three pseudopeptides grafted compound with multivalent synthetic ligands of nucleolin surface for cancer treatment. | (Courty, Briand, Guichard, Hamma, & Hovanessian, 2016) |
| Method of diagnosing cancer using a nucleolin specific aptamer | US9018185B2 (2015) | Invented G-rich oligonucleotide aptamers and use it for diagnosing and/or treating a nucleolin-associated disease. | (Lee, Kim, et al., 2015) |
| Anti-mucin1 antibodies for cancer diagnostics | US20130039974A1 (2013) | The overexpression transmembrane mucin-1 found in most human carcinomas and anti-mucin-1 antibodies used for diagnosis of cancer. | (Kufe & Kharbanda, 2013) |
| Encapsulation of plasmid DNA (lipogenes™) and therapeutic agents with nuclear localization signal/fusogenic peptide conjugates into targeted liposome complexes | US20030072794A1 (2016) | Method for complex formation of DNA with cationic lipid molecules and liposomes of fusogenic/NLS peptide conjugates encapsulating plasmids, oligonucleotides or negatively-charged drugs for the cancer treatment. | (Boulikas, 2016) |
| Nuclear transport modulators and uses thereof | WO2011109799A1 (2017) | Synthesis of use of these substituted-heterocyclic azole compounds in the treatment of cancer and other neoplastic disorders modulation and/or prevention of physiological conditions associated with CRM1/Exp-1. | (Shacham, Kauffman, Sandanayaka, & Shechter, 2017) |
| Therapeutic combination | US20090036368A1 (2009) | HAMLET and histone deacetylase inhibitor combination synergized anti-cancer efficacy. | (Brest & Svanborg, 2009) |
| Cancer treatment compositions comprising therapeutic conjugates that bind to amino-phospholipids | US6818213B1 (2004) | Prepared conjugates of Antibody-therapeutic agent for aminophospholipid targeted system for diagnostic and therapeutic constructs use in tumor intervention. | (Thorpe, Ran, & Brekken, 2004) |

Other than IGF/IGF-R, there are many other mechanisms of activation of apoptosis and cell differentiation in cancer cells have been reported by various scientists which are summarized with the help of Fig. 10. The ligand-activated PPARγ forms a heterodimer complex with retinoid X receptor/glucocorticoid receptors, who further form a complex of protein-DNA after linking with peroxisome proliferator response elements and consequently, activates the several target genes (Tachibana et al., 2008). PPARγ agonist can inhibit tumor cells differentiation and proliferation, stimulate apoptosis and inhibition of inflammation, all of which combine to inhibit tumor growth.

Researcher Goyal studied and concluded that Granulocyte-macrophage colony-stimulating factor - secreting tumor-cell vaccines could stimulate antitumor immunity. It was also suggested that PPARγ agonists could be a useful tool for cancer immunotherapy (Goyal, 2015). Ory et al. used PPARγ agonist (i.e. efatutazone) to activate the endogenous PPARγ ductal carcinoma in situ (DCIS) and studied the effect of its activated form in the progression of cancer in MCFDCIS xenograft

**Table 3**
Peptides used as the targeting key and their suitable targets.

| Cellular targeting peptides | Sequences | Targeting for organelles/sites | References |
|---|---|---|---|
| Amphipathic tail anchoring peptide (ATAP) | KFEPKSGWMTFLEVTGKICEMLSCPEAILLTRKQTPYC (ATAP sequence of gene Bfl1) KLEPKSGWMTFLEVTGKICEMLFCPEAILLTRKDTPYC (ATAP sequence of gene HCCS1) | Mitochondrial membrane permeability to induce apoptosis | (Ko et al., 2007; Ko et al., 2011) |
| Transactivator of transcription (TAT) | CYGRKKRRQRRR | Lysosomal and nucleus via binding the import receptors Imp α and Imp β | (Cerrato et al., 2017; Pan et al., 2014) |
| peptide D [KLAKLAK]2 (KLA) | KLAKLAKKLAKLAK | Mitochondrial signaling pathway and $Ca^{2+}$ MT-$O_2$ pathway | (Bouchet, Tang, Fava, Legrand, & Bauvois, 2016; Jiang, Li, et al., 2015; Qiao et al., 2016) |
| C/EBP homologous protein (CHOP) | TGCAGATTGCGCAATCTGCA | ER stress, ER kinase pathway | (Bruhat et al., 2000; Tanjore et al., 2017) |
| Protein F3 | HQLPVECKHYY | Nucleus, NCN targeting | (Dyall-Smith & Pfeiffer, 2018; Zhang et al., 2017) |
| RGD peptide | HHLGGAKQAGDV | Integrin αvβ3 and accumulated in the lysosome | (Siemion, Kluczyk, & Cebrat, 2013; Wang, shi, et al., 2016) |
| ANX-V (human) | MAQVLRGTVT DFPGFDERAD AETLRKAMKG LGSSG | PS, Plasma membrane | (Garnier et al., 2009) (https://www.uniprot.org/uniprot/D6RCN3) |

and C3(1)/Tag transgenic mice. The results of such studies suggested that the PPARγ activation downregulated Akt phosphorylation, with no effect on ERK pathway (Ory et al., 2018). Liu et al. studied the microRNAs (i.e., miR-1468) which are abnormally expressed HCC development and contributes its progression. They used Glu/Asp-rich carboxy-terminal domain 2 (CITED2) and Up-frameshift protein 1 (UPF1) as direct downstream targets of miR-1468 in HCC cells, via activation of (PPAR-γ)/AKT signaling (Liu, Wang, et al., 2018). Hence, the activation of the PPARγ/AKT pathway by targeting CITED2 and UPF1 could be a suitable and efficient tool for the development of a therapeutic strategy for HCC patients.

*2.6.3. Argininosuccinate synthetase (enzyme)*

The arginine auxotrophic (inability to synthesize arginine) is quite common in the tumor cells. Arginine is synthesized using the urea cycle as a de novo pathway. The argininosuccinate is biochemically formed in the presence of ATP from citrulline and aspartate by the catalytic action of enzyme argininosuccinate synthetase (ASS) and further conversion of argininosuccinate into arginine is resulted by the enzymatic action of argininosuccinate lyase enzyme (Allen et al., 2014). The loss of ASS1 expression occurs in certain cancers, which causes arginine auxotrophic in the tumor cells and this ASS1-deficiency promotes proliferation by enhancing aspartate supply for pyrimidine synthesis (Lukey et al., 2017). The tumor cells fulfill the arginine requirement from extracellular arginine whereby it is uptaken through the members of the SLC7 family of transporters. This is an approach to treat cancer by the depletion of the plasma pool of arginine to effectively deprive these tumor cells of arginine. Beddowes et al. studied and reported the results of phase 1 dose-escalation study of PEGylated arginine deiminase (enzyme convert arginine to citrulline) along with Cisplatin and Pemetrexed in Patients of thoracic cancer with ASS1–Deficiency. They have also suggested the dose, safety, and tolerability of cisplatin & pemetrexed combined regimens (Beddowes et al., 2017).

## 3. Nanocarriers for intracellular targeting

Some invasive and non-invasive approaches have been investigated to allow efficient drug delivery to the cancer cells including pH buffering, endosomal membrane destabilization, photochemical destabilization, osmotic or photochemical disruption, use of cell penetrating peptide coupled nanocarriers (NCs), receptor-mediated delivery of drug-bearing nanocarriers, etc. Some of the NCs used for subcellular organelle targeting are mentioned in Table 1 with their mechanism of action and uses for the treatment of specific cancer/their cell lines. Although, the details are out of the scope of this review.

Table 2 shows some patent with their title and mechanism/description of the strategy on which they based. Table 3 shows some peptides sequences and their suitable targets.

## 4. Conclusions

The features of cancer mainly comprise of six biological changes which are acquired for the progression of human cancer, i.e., proliferative signaling, escaping growth suppressors, resisting cell death/apoptosis, replicative immortality, profuse angiogenesis, and activating invasion and metastasis (Hanahan & Weinberg, 2011). These changes have promisingly been exploited therapeutically for designing chemotherapeutics against cancer. Mitochondria is a site of aerobic respiration and possesses metabolic and signaling pathways for cell cycle. Thus, any alteration related to mitochondrial function and/or their pathways as that prevails with cancer would be used as a target in cancer therapy. Therefore some group of researchers has successfully used mitochondrial ROS, VDAC1, glutathione, melatonin, $Ca^{2+}$ ion and TOL receptor, etc. as a target for cancer treatment.

Similar concept, i.e., changed the environmental/condition of endoplasmic reticulum also studied by the various scientist for the development of specific drug delivery system for cancer targeting without affecting normal cells. For that, purpose "ER stress" is used to initiate cell apoptosis and physcion, CEP1 are some of the well-studied molecules for the same. TX-TXR system and STING are the ER-associated proteins could also be the suitable targets for cancer therapy.

The CAR to act on the overexpressed ErbB2, HB-19, N6L,and AS1411 for overexpressed NCN and trichostatin A via NUPs transportation, etc. are some of the examples, which studied extensively and successfully used for the nuclear targeting. The lysosome canalsouse as targets, as it is capable of digesting all major cellular macromolecules with the help of acid lysosomal hydrolases. Most studied LH is cathepsin proteases, and their activation leads apoptosis and can initiate cell death by lysosomal membrane permeabilization. Various pH-dependent drug release and peptides based drug delivery systems for enhanced lysosomal membrane permeabilization and hydroxychloroquine as an autophagy inhibitor, etc. used for lysosomal targeting. Changed asymmetry of Plasma membrane of the cancer cell has also been recognized as a characteristic feature of cancer and be a subject for cancer targeting. Monomethyl auristatin-E conjugated with synaptotagmin-1, ANX-A1/A5 & Spectrin coated drug bearing formulations, NKsomeis successfully used to target PS and PE that are exposed on the outer side of the cancer cell. This is a distinct feature of cancer cell from the normal cell. Apart from organelle targeting, drug delivery through Pattern recognition receptors, Peroxisome proliferator-activated receptor- γ and argininosuccinate synthase (enzyme) is another subject of research to enhancing the target potential and efficacy of chemotherapeutics or drug delivery systems for the war against cancer.

Hence, targeting tumor-associated metabolism pathways and other alterations at cell organelles yet remains as an attractive strategy because of the metabolic and other variations within and between tumors are unique as compared to normal cells.

## 5. Future prospective

"Explore the possibilities to treat cancer more effectively" is the dream of every scientist who is involved in cancer treatment research. Traditionally the treatment of cancer is organ-specific. Presently, we focus to treat cancer at molecular levels by using distinct features of the cancer cell (with the normal cell) for drug targeting purposes. However, targeting at the molecular level is still in its infancy. Nowadays, the genomic profile of cancer can be developed with the development of advanced analytical techniques. On the basis of molecular tumor genomic profile should try to develop a treatment strategy to match the right drug to the right patient, to pave the way towards molecularly precise therapies/personalized therapy.

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## Author contributions

TH and VS prepared the preliminary draft for the manuscript. TH, VS, and RT contributed to the writing of the manuscript. SPV, TH, and VS jointly developed the structure and arguments for the paper. SPV and VS made critical revisions and approved the final version of the paper. All authors reviewed and approved the final manuscript.

## Declaration of interests

The authors declare that there are no conflicts of interest.

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