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Review Article

Still Laughing Failures behind the Windows of Cancer Therapeutic Strategies

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Abstract

The multistep process, cancer is attributable from various geneses. Eventually, cancer is a complicated disease with unconstrained intercalation and impacts on the physiological system. Therefore, an ideal cancer therapy must be like a multi-edged sword. Broadly, currently, available cancer therapies are the cytoprotectives, inhibitors of oncogenes, correctors, and cell destructors. Doubtless, cancer therapists are most frequently handling apoptosis and autophagy inducers, targeting of tumor suppressor genes, epigenetic and immune therapies. However, each therapy has a number of challenges yet to be resolved. This revision is aimed to find out some important points, depicting till date, how successful we are and what are the failures behind those modes of therapeutic strategies.

Keywords: *Apoptosis; Autophagy; Cancer Therapy; Challenges; Tumor Suppressor Gene.*

Introduction

The most fearful disease, cancer is still ruling crudely throughout the world. The variations in cell types and adequate sources of occurrence are the key points of continuing challenges of cancer. The selection of therapy in cancers mainly depends on- origin (i.e. - source and tissue types) and stages, as well as patients pathophysiology. Up to date, a number of anticancer agents have been introduced with single and/or multiple activity pathways. Some of them can be used in combination and are followed by a step-wise treatment [1].

Surgery, chemo- and radiotherapy are more commonly attainable by the populations in comparison to other cancer treatment strategies. Each strategy has unique postulation on its mechanism(s). For an example, most of the chemotherapeutic agents and radiotherapy act through chronic induction of reactive oxygen species (ROS) on cancerous cells [1]. In recent years, some genetic materials synthesis inhibitors, anti-angiogenesis agents, apoptosis and autophagy inducers, immunotherapy, targeting epigenetic alteration correction and tumor suppressor genes have gained much attention. However, a controlled and effective action of each treatment and an overall managing power of cancer stages are great challenges along with the avoidance of a secondary cancer induction chance. Unfortunately, the success of each treatment strategy, after a moment has been raised questions for safety, efficacy and efficiency, resistance as well as applicability in other cancer types.

Cell death is essential for life, due to it plays critical roles in regulating embryonic development, maintaining tissue homoeostasis, controlling immune function, tumor suppression and infection resistance. Although, cell death eliminates unfit cells, but there must be a balance between cell death and cell proliferation [2]. Notably, cancer therapy constitutes growth inhibition and/or cell death. Thus, the reduction of cell mass is a reduction of physiological processes. It is doubtless that, a reduction in immune cells has been always dangerous. Moreover, every cancer treatment imparts a shunting effect on the immune system [1].

This revision focuses on an improved understanding of the negative sides (may be considered as challenges) of some commonly targeting anticancer pathways, these include apoptosis, autophagy, tumor suppressor genes, epigenetics and immunotherapy.

Autophagy

Macroautophagy (also known as autophagy) is a conserved eukaryotic cellular catabolic pathway that causes degradation of cellular organelles and other macromolecules via lysosomal activity as part of a recycling and protective process to maintain cellular fitness in a basal state as well as during stress [3]. Although, autophagy is important to maintain cellular homeostasis, disruption of autophagy can lead to disease including neurodegeneration, atherosclerosis and cancer [4]. Generally, the functions of autophagy are dynamic with both tumor-suppressive and pro-tumorigenic roles, which depend on multiple factors, including tumor stage, cellular context, and site of origin (tissue). It is evident that, tumor-suppressive selective autophagy pathways can mitigate oncogenic signals and conversely selective autophagic pathways may support tumor maintenance and progression [5].

Moreover, autophagy loss may cause tumor initiation, where it supports the transformation to invasive cancers [6]. In this case, loss of function of the autophagy machinery plays an important role. On the other hand, inhibition of autophagy leads to an accumulation of ROS, increases DNA damage, and mitochondrial defects, thus an implication of tumorigenesis [7]. In a recent study, in the mouse model, it has been reported that p62 accumulation upon autophagy loss can contribute to tumorigenesis [8]. It may be due to an over-expression of p62 promotes oxidative stress and tumor growth [9].

Nowadays, it is clear that tumor suppression via cellular senescence is another important mechanism in autophagy, a program of permanent arrest of the cell division cycle that can be induced by cells in response to oncogenes in order to prevent malignant transformation [10]. GATA4, a master regulator of the cellular senescence program has been found to turn over by p62-mediated selective autophagy [11]. Thus, a transient inhibition of autophagy may lead to an accumulation of GATA4 in cellular senescence program. It should be noted that, cellular senescence in autophagy, if needed or not is yet to be resolved [12].

In some studies, autophagy has been found to link with an elevation of RAS-driven cancers initiation and growth [13,14]. Moreover, autophagy inhibition has been evident to exert an anti-tumor effect in multiple cancer types through both cell autonomous and non-autonomous mechanisms [5,7,15].

Although, from a mechanistic standpoint, the role of autophagy in supporting tumor proliferation is complex, but it may be due to an increase in metabolism and biosynthetic need in rapidly dividing cells in a tumor microenvironment [16]. Genomic instability leads a high degree of protein misfolding [17]. Therefore, selective autophagy is needed for the cancer cells, especially those who are suffering from adequate angiogenesis and correct protein folding events.

However, role of selective autophagy in promoting or maintaining cancer cell survival may be due to the maintaining capacity of appropriate levels of signaling complexes or degrading pro-apoptotic proteins. In a study, it has been reported that the selective autophagy pathway is important for regulating active Src levels in tumor cells to promote survival following the loss of focal adhesion kinase (FAK) signaling [18], which is evident for signaling to promote cell adhesion, invasion, proliferation, and survival [19]. Generally, Src proteins are frequently over-expressed and activated in solid cancers [20], while FAK is a critical binding partner of Src at focal adhesions where its activity is regulated and directed [21]. However, FAK deletion lead to a transition of active Src from an oncogenic driver to an overactive kinase, a toxin and the cancer cells were adapted a selective autophagic pathway for degradation of overactive Src [22]. Moreover, dysregulation of ferritinophagy may lead to some diseases [23,24].

Apoptosis

Apoptotic cell death is widely considered as a positive process that both prevents and treats cancer. However, it can also cause unwanted effects and even promote cancer. In some literatures, it has been suggested that too much or too little apoptosis may implicate

various diseases, including neurodegen¬eration and autoimmunity [25,26]. On the other hand, inhibition of apoptosis is evident to promote cancer sand blunting therapeutic responses [27].

Apoptotic cells can actively promote the proliferation of surrounding cells and as a physiological event this may enable apoptotic cells within a tissue to control their replacement by normal turnover or as a healing response. The ultimate result is the extensive tissue damage through the activating mitogen signaling pathway [28-30]. Apoptotic cells can stimulate the proliferation of stem cells in a caspase-dependent manner [31].

Prostaglandin E2 (PGE2), a key mediator in apoptosis-induced proliferation in mammalian systems. During apoptosis, caspases cleave and activate calcium-independent phospholipase A2 (iPLA2, also known as PLA2G6) and increase in production of arachidonic acid, which is converted to PGE2 *via* cyclooxygenase 1 (COX1) and COX2 (also known as PTGS1 and PTGS2) [32]. Thus, apoptotic tumour cells have an important role in tumour regrowth and repopulation after certain therapy such as radiotherapy. This may be due to caspase 3- and iPLA2-dependent manner, probably through the production of PGE2 [33]. Moreover, production of PGE2 by apoptotic tumour cells is reported to promote chemoresistance by stimulating cancer stem cell proliferation [34]. Generally, PGE2 has pleiotropic functions such as it may promote proliferation as well as skew immune responses towards a tumour promoting, anti-inflammatory phenotype [35]. Thus, via PGE2 pathway apoptotic tumour cells can exert an immunosuppressive effect.

Proliferating cells constantly compete with one another for nutrients. The losers may suffer contribute an apoptotic cell death. The p53, a key tumour suppressor protein might contribute to this effect [36]. Thus, the cells deficient with p53 proteins may proliferate and facilitate the accumulation of genetic lesions that lead to cancer [37,38]. Moreover, apoptosis is also evident to kill healthy cells [39-42].

It has been thought that about one million cells in our bodies undergo apoptosis every second1. To be mentioned that, the apoptotic cells are efficiently engulfed and destroyed by phagocytic cells. In this regard, caspase-dependent events help to recruit the phagocytes at the apoptosis point by releasing 'find me' signals, and promote the engulfment of them by exposing 'eat me' signals [43]. Find me signals such as lipid lysophos¬phatidylcholine (LPC), nucleotides such as ATP, the proteins fractalkine (FKN; also known as C-X3 C motif chemokine ligand 1 (CX3CL1)) and lactotransferrin (LTF) may exert oncogenic functions through pleiotropic effects. FKN can stimulate angiogenesis and hypoxia-induced proliferation of prostate cancer cells and can enhance oncogenic ERBB2 receptor signaling [44,45]. Interestingly, adenosine (a degradation product of extracellular ATP), can be oncogenic, supporting tumour growth, angiogenesis and immune escape [46].

Apoptosis can promote tumorigenesis through the recruitment and activation of phagocytic macrophages at the tumour site [47]. Additionally, tumour-associated macrophages (TAMs) may come along with them [48]. It is also evident that, apoptotic cells can promote tumorigenesis in a non-cell-autonomous manner [49]. Besides promoting tumour growth, apoptotic cells may also facilitate metastatic tumour progression. Furthermore, through massive cell death, leading to extensive efferocytosis (clearance of dead cells), promoted TAM infiltration, stimulation of a wound-healing cytokine response and increase in metastasis, implicate the clearance of apoptotic cells in cancer progression [50].

Controlling of caspase activity is another important fact, as the level of caspase activity required to kill a cell is not so high [51]. Therefore, the caspase-dependent apoptotic cell death is under critically controlled environment. In a study, sub-lethal doses of tumar necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) (and FAS/CD95/APO1 ligand) were found to lead caspase-dependent mutations and genomic instability in surviving cells [52]. Moreover, caspase-activated DNase (CAD, also known as DFFB), under an apoptosis failure condition caused a limited CAD activity, thus the DNA damage [53]. Generally, stresses at sub-lethal doses can engage mitochondrial outer membrane permeability (MOMP) in limited numbers of mitochondria without killing the cell called minority MOMP, triggers a sub-lethal caspase activity (similar to TRAIL) and causes DNA damage and genome instability in a CAD-dependent manner. A repeated engagement of sub-lethal stress was proven to promote transformation and tumorigenesis in this way [54]. However, mitotic arrest has been found to

link in this pathway [55]. On the other hand, transgenic expression of pro-apoptotic BAX has been found to promote lymphomagenesis - characterized by genomic instability by suppressing the co expression of BCL 2 [56]. Moreover, not only CAD, but also caspase 3 dependent release of endonuclease G (ENDOG) from the mitochondria was also found to promote radiation-induced DNA damage and transformation [57].

The mixed lineage leukaemia gene *MLL* (also known as *KMT2A*) encodes a histone-methylating enzyme that functions as an epigenetic regulator. The *MLL* locus is highly susceptible to breakage and rearrangement, which can generate oncogenic MLL fusion proteins, lacking methyltransferase activity [58]. Rearrangements in *MLL* are recurrent oncogenic drivers in various leukaemias, including acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS) and acute lymphoblastic leukaemia (ALL) [59]. Otherwise, failed apoptosis causes caspase- and CAD-dependent break points in the *MLL* gene, thereby promoting Oncogenic rearrangements are also evident in surviving cells [60,61]. The latter situation may induce DNA damage under inflammatory conditions and promotes acquired resistance to apoptosis-inducing anticancer therapies [62].

Till date, various non-apoptotic roles have been ascribed to almost all proteins classically viewed as apoptotic [63-65]. Some of them function as oncogenic. For an example, BCL-2 is thought to regulate calcium homeostasis, metastasis and autophagy [66-68].

On the other hand, many human tumour types are selectively sensitive to TRAIL-induced apoptosis [69] and they can gain some advantage from expressing TRAIL receptors (TRAILRs). TRAILR signal can promote cancer independently of its role in canonical apoptosis signaling [70]. TRAIL receptor 2 (TRAILR2) signal can promote invasion, proliferation and migration, independent of its apoptotic function but dependent on PI3K signalling. In some studies, on failed apoptosis, TRAILR signalling was reported to lead caspase-dependent cleavage of RHO-associated protein kinase 1 (ROCK1), activating RHO GTPase and causing membrane blebbing and cell migration [71].

Moreover, various non-apoptotic, pro-oncogenic functions were described in FAS signalling, including stimulation of proliferation and migration [72]. However, not only pro-proliferative effects, FAS signalling can also exert pro-survival functions. Inflammatory process coming from various sources, including apoptosis, associated with non-regulated, necrotic cell death can have both tumour promoting and tumour inhibitory effects [73,74].

Tumor suppressor genes

In 1969, Knudson first predicted the existence of tumor suppressor genes (TSGs) [75]. In cancer, the inactivation of one copy of a TSG will generally need to be followed by the loss of the remaining copy of the gene. A precancerous cell would only enjoy an advantage once it loses both functional copies of a TSG that had been suppressing growth [76]. TSGs, heterozygous loss of function can be associated with reduced gene dosage and tumorigenesis via haploinsufficiency [77,78]. TSGs can be silenced, such as epigenetic mechanisms, or changes in mutation frequency, such as those that occur in hypermutator phenotypes, as TSGs undergo alteration more frequently than the oncogenes. In this sense, it is harder for a drug to target TSGs, other than oncogenes.

Till date a well-described TSGs include genes in pathways are Wnt/APC (adenomatous polyposis coli gene [APC], AXIN1, and CDH1); apoptosis/cell cycle (cyclin-dependent kinase inhibitor 2A [CDKN2A], tumor p53 [TP53], RB1, TRAF7,and CASP8); chromatin modification (ARID1A/B/2, ASXL1, ATRX, CREBBP, KDM5C, KDM6A, MEN1, MLL2/3, SETD2, ten-eleven translocation-2 [TET2], WT1, and BAP1); DNA damage repair (ataxia telangiectasia mutated [ATM], ataxia telangiectasia and Rad3 related [ATR], BRCA1/2, mutL homolog 1 [MLH1], and MSH2/6); hedgehog (PTCH1); Notch (FBXW7 and NOTCH1); phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) (PIK3R1, phosphatase and tensin homolog [PTEN], and TSC1); Ras (CEBPA, von Hippel-Lindau [VHL], and NF1); transforming growth factor-β (SMAD2/4); and transcriptional regulation (GATA3 and RUNX1).

Among them, mutations in p53 (encoded by *TP53* gene), are the most frequent genetic alterations in cancer [79], as it accounts in 30% to 50% of human cancers [80]. The p53 is evident to exert a dominant-negative effect when mutated. It should be noted that, this protein (p53) is not a cell surface protein or an enzyme, thus the difficulty to target with antibodies or enzyme inhibitors [81,82].

The anticancer drug, tenovin-1 and tenovin-6 are evident to affect p53 posttranslational modification by inhibiting the protein deacetylation activities of sirtuins, thereby stabilization of p53 [83]. However, the nuclear export inhibitors such as leptomycin B, an inhibitor of the nuclear export protein CRM1, are able to increase local p53 protein levels [84], while the nutlin, another type of anticancer drug is used to target protein-protein interactions between p53 and MDM2 [85]. All these cases can accumulate p53 and lead to drug resistance.

Another major fact is the efficacy of such type of treatment. For an example, treatments with viral vectors are not able to achieve the necessary efficiency of transduction by p53 within tumors to be curative [86,87]. Moreover, repeat administration may be hampered by host immune reactions to the virus vectors. A modified approach, tumor-specific replication-competent oncolytic viruses are evident to bind and inactivate p53. Although, the viruses can only replicate within (and kill) cells lacking functional p53, but low efficiency of delivery and non-specificity in expression limit their application [88,89].

Notably, mutations in p53 can up-regulate the expression of platelet-derived growth factor receptor-β (PDGFRβ), which in turn capable to cause invasion and metastasis [90]. On the other hand, vaccines containing multiple p53 peptides are able to generate a T-helper type I response, although the responses have not yet been potent enough to be clinically beneficial [91]. In another approach used dendritic cells loaded with human leukocyte antigen class I p53 peptides, reports to induce changes in immune regulatory mechanisms along with a strong immune suppressive effect [92].

The second messenger PIP3 activates target proteins, such as the kinases phosphoinositide-dependent kinase-1 (PDK1) and AKT1/2/3. AKT then phosphorylates as many as 20 progrowth targets relevant to cancer, including those activating the cell cycle, preventing apoptosis, and promoting cell growth via the kinase mTOR [93,94]. Hyperactivation of this (PI3K/AKT/mTOR) pathway resulting from inactivation of PTEN is, at least in part, similar to the sequelae of oncogenic alterations elsewhere in the pathway, such as epidermal growth factor receptor amplification or mutation, human epidermal growth factor receptor-2 (HER2) amplification, PIK3CA (the gene encoding the catalytic subunit of PI3K) mutation, or AKT1/2 mutation [95]. Targeting PTEN has a complexity of feedback networks. For an example, inhibition of mTOR with agents such as rapamycin is effective in attenuating signaling, but it relieves feedback inhibition of other upstream components such as insulin, insulin-like growth factor receptor, human epidermal growth factor receptor (HER)-3, and HER-4, which can then signal through other branches of the pathway such as forkhead box O (FOXO)-dependent transcription. Therefore, a combined inhibition of AKT, together with agents inhibiting HER kinases or with inhibitors of receptor tyrosine kinase stabilization by heat shock protein 90, is necessary to truly shut down signaling, as AKT inhibition alone is not able to achieve [96,97].

In cancer cells with an impaired DNA damage repair pathway, the cell becomes addicted to another DNA damage repair pathway. The gene poly(ADP-ribose) polymerase 1 (PARP1) is involved in non-homologous end joining (NHEJ), homologous recombination (HR), and base excision repair (BER). However, PARP1 inhibition is theoretically specific for BRCA-mutated cells [98,99], thus limiting the application of this kind of targeted therapy. In a study, mutations in *PTEN* have been reported to sensitize cells to PARP1 inhibition. It has been thought that, this may be due to a down-regulation of RAD51, a critical HR gene [100].

Radiotherapy, alone or followed by some other therapies such as surgery, is evident to cause double-strand DNA breaks [101]. Moreover, PARP inhibitors appear to have activity in combination with radiotherapy [102] and also chronic lymphocytic leukemias with ATM mutations that are sensitive to cytotoxic agents [103], this may also create a chance of secondary cancer.

In some instances, specificity is crucial, such as PARP inhibitors as well as several other synthetic lethal strategies targeting DNA repair proteins are evident to cause inhibition of DNA polymerases [104]. To be noted that, when TSGs undergo homozygous deletion, the region of deletion can be quite broad, and usually covers several neighboring genes. These passenger deletions may cause nearby gene deletion, including housekeeping genes, essential for cell survival [105].

Epigenetic therapy

The genetic pathways in cancer are straightforward, while reversibility and numerous unclear talks are plugged in epigenetic pathway.

In a recent revision, Islam [106] has pointed out a number of facts, including the challenges of epigenetic cancer therapy, found behind the spotlight. A summary of the revision has been plugged in here. Epigenetic events are believed to occur early in cancer development (first hit for tumorigenesis). In a study, it has been suggested that, an incomplete epigenetic resetting in an environment changing frequently can adaptively coevolve with plasticity or maternal effects, thus the trans-generational epigenetic inheritance spanning is possibility in biological systems. Otherwise, environmentally-occupied altered trans-generational epigenetic reprogramming has been signified in inherited diseases. Therefore, in the infrequent environmental changes relative to the generation are rescued for the incomplete epigenetic resetting. In the recent years, it has been demonstrated that the genetic and epigenetic mechanisms are not separate events in cancer. They intertwine and take advantage of each other. Being a short-term and reversible event, epigenetic change may be considered as a sub- or primary stage of genetic events. Therefore, identification of the 'first cancerous hit' and correct to the point will be a perfect epigenetic treatment strategy. It is because; the epigenetic change may turn to the normal, non-cancerous stage.

On the other hand, epigenetic dysregulation is reported to change in the pattern of gene expression, activating the tumor promoting, while silencing the TSGs. Till date, several agents have been approved by the food and drug administration (FDA) for the treatment of hematologic and malignancies, including DNA methyltransferases (DNMT) and histone deacetylase (HDAC) inhibitors, despite of their limited success.

Myelosuppression, including neutropenia and thrombocytopenia, as well as nausea and vomiting is the reported toxicities in nucleoside DNMT inhibitors. Moreover, these are cytotoxic thus the chance of a second cancer is higher with the treatment of DNMT. The nucleoside analogues cause inhibition of synthesis of DNA by forming covalent complexes with the DNMT, cause their depletation, thus the reversal of methylation patterns. The DNMT, 5-azacitidine and decitabine have low efficacy and non-specificity in their activity, while S110 is more stable and may allow prolong drug exposure time, and CP-4200 has potent cytotoxic activity.

On the other hand, the HDAC inhibitors activate both intrinsic and extrinsic apoptotic pathways and regulate the activity of TSGs (e.g. - p53 and p73). These kinds of HDAC inhibitors have proteasomal degradation, ROS generation and mitochondrial outer membrane potential losing capacity along with the inhibition of cell differentiation and growth. These are mainly anti-inflammatory drugs and the levels and targeted activity are quite complicated.

HDAC alone cannot express the hyper-acetylated gene. Moreover, combination therapy consisting of DNMT and HDAC used in hematological cancers has been found less efficacy for solid tumors. Otherwise, the tumor microenvironment (TME) in multiple aspects of cancer progression, particularly therapeutic resistance decreases drug penetration, confers proliferative and antiapoptotic advantages to surviving cells, facilitates resistance without causing genetic mutations and epigenetic changes.

Histone acetyltransferases (HATs) that install acetyl groups onto lysine residues of cellular proteins such as histones, transcription factors, nuclear receptors, and enzymes have been shown to play a role in a number of diseases, including cancers. Till date, several HAT inhibitors, like bi-substrate inhibitors, natural product derivatives, small molecules, and protein–protein interaction inhibitors, have been developed, despite of some undesired properties like anti-oxidant activity, reactivity, instability, low potency, or lack of selectivity between HAT subtypes and other enzymes. HATs have various cellular substrates ranging from histones and transcription factors for enzymes and nuclear receptors. The catalytic mechanisms of HAT activity in relation to enzyme kinetics of small molecule HAT inhibitors are still poorly understood.

In conclusion, the crucial challenges yet to be resolved in epigenetic cancer therapy are pointed under: clinical, laboratory development, cell biology, chemistry, target selection and toxicology.

Immunotherapy

Although, immunotherapy in cancer by these days experienced remarkable advances [107], but a number of crucial challenges are yet to be resolved such as – effects of pre-installation; efficiency and specificity; onset and duration of actions; host responsiveness (as suc-

cessive treatments reduce immune power; patient's pathophysiological conditions, therefore perception); impacts on secondary cancers; effects on resistant cancer cells to a particular or combination therapy and so on. In fact, cancer is believed to originate via multiple and complex pathways [1].

Conclusions

The dreadful effects in cancer may be due to: massive reduction of the number of cells (including immune cells) by killing effects of cancer treatments; mal and mass production of toxins by the rapidly proliferating abnormal cells; abnormal physiological function in place of its (cancerous cell) own duty; effects on neighboring normal cells (i.e. - hypoxia, ROS, nutrients, and other toxic metabolites); reduction of body immune power; and overall physiological outrageous networking.

Although, progress in recent years in cancer research is remarkable, but the translation of basic cancer research findings into successful therapies is a long journey. A steady progress in an effective treatment strategy is an aspiration of the cancer therapists. Understanding each fact clearly, following to a sturdy research on its pharmacology is able to bring novel strategies/compounds with anticancer potential to the clinic. Therefore, more research is needed to avoid controversial or unclear talks, prior to proceed on with a particular cancer therapeutic strategy.

Conflict of Interests

There is no conflict of interest at any point of view.

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Volume 5 Issue 2 January 2017