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Targeting DNA Damage Response Kinases in Cancer Therapy

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SUMMARY

Cancer cells die when their decimated DNA damage response (DDR) unsuccessfully handles DNA damage. This notion has been successfully exploited when targeting PARP (poly ADP-ribose polymerase) in homologous recombination-deficient cells. With the greater understanding of DDR achieved in the last decade, new cancer therapy targets within the DDR network have been identified. Intriguingly, many of the molecules that have advanced into clinical trials are inhibitors of DDR kinases. This special issue is devoted to discussing the mechanism of cell killing and the level of success that such inhibitors reached in pre-clinical and clinical settings.

INTRODUCTION

The DNA Damage response is a signaling network that senses DNA damage and promotes both the adaptation of DNA replication and mitosis to changes in the quality of DNA templates and the activation of DNA repair mechanisms [1]. Because classic chemotherapeutic agents increase the load of DNA damage, it has been suggested that targeting the DDR of cancer cells may enhance their killing. Over the last decades, numerous screenings were performed to identify the effect of eliminating single DDR components on cancer cell killing. Breast cancer gene 1 (BRCA1) and 2 (BRCA2)- deficient tumors models were particularly suitable for this type of study as only the tumors cells, but not the healthy cells of the patients, are entirely devoided from BRCA expression. In 2005 two groups simultaneously reported that BRCA1 and BRCA2 breast cancers cell models are selectively sensitive to PARP inhibitors [2, 3]. Taking upon a notion initially used by developmental biologists, such a synergic killing was defined as "synthetic lethality". Today, three PARP inhibitors have already been approved by the FDA for treating ovarian, primary peritoneal and fallopian tube cancer: olaparib (Lynparza™, AstraZeneca, Cambridge UK), rucaparib (Rubraca®, Clovis Oncology, Boulder, CO, USA), and niraparib (Zejula™, Tesaro Inc., Waltham, MA, USA). Remarkably, although PARP inhibitors were initially developed as treatments that should be used in precision medicine on specific genetic backgrounds only, clinical trials in ovarian cancers demonstrated that they are effective independently of the BRCA status, perhaps in a manner that is

related to the high rate of BRCAness (Homologous recombination -HR deficiency in the context of BRCA wt status) of ovarian tumors [4-6].

The DDR network is not limited to PARP-dependent signaling and other synthetic lethal combinations have been reported [7]. Some DDR proteins (for example, the tumor suppressor p53) are frequently mutated in tumors [8]; some others, such as the Ataxia telangiectasia mutated (ATR) and checkpoint protein 1 kinase (Chk1), are not mutated in tumors[9]. Different strategies were designed to target either mutant p53 and ATR or Chk1 in vitro and ATR and Chk1 inhibitors have reached clinical trials.[10] ATR and Chk1 kinases are expressed both in healthy and cancer cells and their function is crucial to promote DNA replication when the DNA damage load increases [11]. While ATR and Chk1 are essential molecules in healthy and cancer cells, their selective effect on cancer cells has been ascribed to their increased replication stress [12]. In patients, such inhibitors were tested in monotherapy schemes and in combination with classical chemotoxins already validated in patients. Comprehensive reviews covering the progress in ATR and Chk1 targeting and the use of their inhibitors in the clinic have recently been published, for example [13]. Hence this special issue focuses on other kinases that have received less attention than ATR and Chk1.

SPECIAL ISSUE TOPICS

In this special issue, outstanding reviews written by experts in the field present different key DDR components from the perspective of their relevance as targets for cancer treatment. All reviews first provide a comprehensive introductory overview of the role of each kinase in the DDR; then discussing the potential of the inhibitors that have been designed so far; highlighting the progress of the best candidates into clinical trials.

In this issue, the review entitled "Clinical potential of ATM inhibitors" written by Martin F. Lavin and Abrey J. Yeo, the contribution of the ataxia telangiectasia mutated (ATM) kinase to the cell response to double-strand breaks (DSBs) accumulation is discussed.[14] Similarly to ATR and Chk1, ATM is relevant both for normal and cancer cell survival. Moreover, this review also presents other ATM functions, such as protection against oxidative and nutrient stress, which may also be relevant to the homeostasis of healthy and malignant cells [15-19]. Moreover, the authors also remind us that ATM was initially described as a kinase which loss causes a cancer-prone syndrome, Ataxia Telangiectasia.[20] Thereafter, it may seem puzzling to foresee a therapeutic advantage in eliminating a protein that, when lost, propels cancer genesis. The critical observation is that highly proliferating cells deficient in ATM expression are exquisitely

sensitive to a variety of DNA damaging agents.[21] The authors thoroughly developed this notion, focusing on the relevance of ATM activity both for the nuclear and mitochondrial function. Another subject covered in this review are the 10 ATM inhibitors developed so far, focusing on their effectiveness after transient exposure of cells to treatment, tolerance in mouse models, and capacity to enhance classical chemotherapy [22]. The advantages found when selectively targeting these types of small molecules to cancer tissues and when combining them with other DDR inhibitors such as PARPs are also discussed. The ongoing clinical trials for solid tumors using ATM inhibitors (AZD0156, KU-60019, AZD1390) are also described.

Also in this issue, the manuscript entitled "Targeting DNA-PK in cancer", Giovanna Damia reviews the contribution of the DNA-dependent protein kinase (DNA-PK) to DDR [23]. Similarly to ATM, DNA-PK has a primary role in the repair of DSBs. DNA-PK has a crucial role in non-homologous end joining (NHEJ), a DSBs repair pathway that is highly error-prone but nevertheless essential outside the S and G2 phases [24]. Similarly to ATM, DNA-PK has other DNA repair-independent functions, such as regulating the transcriptional machinery, the function of various transcriptional factors, and histones [25, 26]. The role of DNA-PK in protecting telomeres, promoting immune diversity, and generating innate immune response when dealing with foreign pathogens is presented [27-29]. The association between the dysregulation of DNA-PK expression and cancer and metastasis risk is also discussed [30]. Given its role in NHEJ, it has been hypothesized and demonstrated that acute downregulation of DNA-PK causes hypersensitivity to γ irradiation. Likewise, encouraging results were obtained when combining DNA-PK inhibitors with genotoxins and γ irradiation in pre-clinical models [31]. Ongoing and completed clinical trials are summarized, with the discussion focused on the unfortunate toxicity resulting from the systemic delivery of DNA-PK inhibitors. Strategies that could alleviate such toxicity, for example, identifying genetic backgrounds that are exquisitely sensitive to DNA-PK inhibitors, are debated as well [32-34].

In the manuscript entitled "WEE1 kinase limits CDK activities to safeguard DNA replication and mitotic entry ", which is part of this issue, Camille Elbæk, Valdemaras Petrosius and Claus Sørensen discuss the central role of Wee1 in the control of the signals that shut down the S phase [35]. While working in coordination, Wee1 and Chk1 have different roles. Wee1 phosphorylates and regulates the activity of CDKs, controlling the timing of S phase finalization. Wee1 can delay mitosis onset, but it also functions within S phase. Wee1 loss causes an intra-S-phase replication catastrophe, characterized by increased origin firing, reduction in the nucleotide pool, accumulation of forks with augmented regions of single-stranded DNA, and dysregulated nucleases which pulverize chromosomes [36-38]. The interaction of Chk1

and Wee1 functions is discussed, focusing on the nature of the synthetic lethality between their inhibitors. The challenges faced by researchers during the design of specific Wee1 inhibitors are also debated [39]. Moreover, the review also discusses novel approaches to the design of inhibitors such as the use of Proteolysis-Targeting Chimeras, which may boost the therapeutic potential of Wee1 inhibitors due to their specificity [40]. The evolution of clinical strategies involving Wee1 inhibitors is also put into the spotlight, and current clinical trials focused on the combination and sequential therapies that circumvent toxicity are presented [41-45].

In the review entitled "Therapeutic opportunities for PLK1 inhibitors: Spotlight on BRCA1-deficiency and triple-negative breast cancers" which is part of this special issue, Gastón Soria and coworkers concentrate their analysis on the DDR events regulated by the master polo-like mitotic kinase (PLK1) [46]. Antimotitic agents or mitotic kinases have received much attention as a target of cancer treatment;[47] however, a high toxicity of PLK1 inhibitors has been demonstrated in the clinic. Such a disappointing outcome might have to do with the crucial role of PLK1 in the survival of both healthy and cancer cells. In fact, the authors highlight the extremely sporadic frequency of PLK1 mutations in human cancers and the striking lethality observed after PLK1 ablation in more than 700 cell lines. The authors also remind us that, even in the most successful clinical trials, the dosage limitations imposed by the toxicity issues have allowed only moderate disease stabilization in a limited number of patients (for example, [48-50]). Such a modest success has demonstrated that the only way to profit from these FDA-approved inhibitors is to find a genetic background that is particularly sensitive to PLK1 inhibition. The authors propose two potential niches for PLK1 inhibitors. The tumor cell killing capacity of PLK1 inhibitors is augmented in triple-negative breast cancers (TNBCs) and BRCA1 deficient cancers [51-54]. The authors emphasize that a retrospective analysis of human breast tumors demonstrated that BRCA1 deficient tumors had augmented levels of PLK1. In this review, they include a similar analysis demonstrating a similar scenario for TNBCs. An increase reliance of these types of cancers on PLK1 function may decrease the PLK1 inhibitor doses, reducing the toxicity issues observed in the healthy cells of patients.

In this issue, the review entitled "Aurora kinases and DNA damage response" by Hoi Tang Ma and Randy Y.C. Poon, the mitotic aurora kinases A (AURKA) and B (AURKB) are discussed [55]. Their contribution to mitosis progression, cell differentiation events, stem cell maintenance, chromatin remodeling, and telomeres preservation is presented. The review thoroughly discusses the role of AURKA and AURKB (AURKs) in guarding against chromosome segregation mistakes [56-58]. DDR dysregulation after AURKs overexpression is also discussed, highlighting that AURKs augmentation is frequently observed in solid

tumors [59-61]. Alterations in the function of AURKs causes the transmission of DNA damage to the subsequent G1, impacting on the activation of the tumor suppressor p53 in G1, which in turn downregulates AURKs [62]. Likewise, AURKs dysregulation modulates HR, NHEJ, and PARP activation, and in turn, DNA repair pathways downregulate excess AURKs activation [63, 64]. Such observation suggested clinical benefits after AURK inhibition. Aurora kinase inhibitors, specific for either AURKA and AURKB, are currently available and were successfully combined with DNA damaging agents in Phase II clinical trials designed to treat neuroblastoma and acute myeloid leukemia [65, 66]. However, the authors remind us that AURKA and AURKB inhibitors per se trigger DDR [67, 68], and AURKA and AURKB are turned off by DNA damage. Hence sequential rather than combined therapies may be a better choice, which should be tested shortly.

The review entitled "Targeting AKT/PKB to improve treatment outcomes for solid tumors" from this issue is authored by Mahmoud Toulany and coworkers [69]. They focus the manuscript on the current understanding of the role of protein kinase B, also known as AKT, from the perspective of its interaction with the DDR response. Most known AKT functions are related to its activation at the cellular membrane by receptor tyrosine kinases (RTK) and other proteins [70-72]. However, AKT can also be activated in the nucleus by DSBs associated kinases, ATM and DNA-PK, and perhaps other kinases to promote the DNA damage tolerance event (TLS) and the DSB repair pathway (HR and NHEJ) [73-75]. They also devote a section to discuss the dysregulation of AKT and its relevance for cancer genesis as AKT hyperactivation is frequent and is considered a marker of poor prognosis (for example, [76]). The fact that conventional chemo- and radio-therapy induce the activation of the nuclear fraction of AKT is also discussed, exploring as well its link with the blockage of apoptosis and the augmentation of resistance events in different cancer models [77, 78]. Specific AKT inhibition and compounds that block AKT activity, such as perifosine and nelfinavir [79, 80] are also discussed in this review. The clinical trials involving AKT inhibitors, the most successful combinations found so far, and the challenges associated with toxicity and resistance events are also analyzed.

CONCLUSIONS:

The fast proliferation of cancer cells and their incapacity to arrest when facing increased levels of DNA damage has encouraged the development of therapeutic agents that increase the load of DNA damage. The limited success of those treatments has prompted the exploration of DDR as a therapeutic target, which may reduce the cancer cell capacity to complete DNA replication in the face of DNA damage. Several DDR kinases were successfully targeted by specific inhibitors; and those compounds have been tested

with a certain degree of success in clinical trials. Those results also indicate options which should be explored: 1) identifying genetic backgrounds which are more sensitive to the treatment, 2) identifying treatment combinations, possibly involving immune checkpoint therapy, which may be more effective in cancers when compared to highly proliferating normal cells, 3) attempting selective delivery of those agents to tumor cells. It is highly likely that inhibitors of kinases or other DDR factors will follow PARP inhibitors' successful path in the years to come.

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