Chapter 14

DNA Repair Based Therapy in Oncology and Neurodegeneration

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1. Introduction

There are various types of DNA damages as well as the presence of sophisticated processes utilized by the cells to maintain the integrity of genome. It has been shown that DNA damage is a usual event which is also underlying cause of many disorders such as cancer and other inherited or acquired pathologies. There are many endogenous and exogenous sources which cause DNA damages interfering with genome [1].

In response to genotoxic stress which can be mainly caused by various chemicals, reactive cellular metabolites and ionizing/UV radiation, DNA repair pathways and cell cycle checkpoints can be activated, allowing the cell to repair and prevent the transmission of damaged and/or incompletely replicated chromosomes. The balance between cell cycle arrest, DNA repair and the initiation of cell death can determine whether DNA damage is compatible with cell survival or require elimination of the damaged cell by apoptosis. Defects of DNA repair pathways and cell cycle checkpoints may cause susceptibility to DNA damages, genomic defects, hypersensitivity to cellular stress and resistance to apoptosis, which all characterize cancer cells [2].

Repair of DNA is critical for cell growth, proliferation and for organ development. Genome stability and maintenance require several biochemical pathways involving many different proteins that are having roles in specific DNA repair pathways. Loss of function in these repair proteins may lead to pathologies including growth and developmental defects, like immunodeficiency, cancer and neurodegeneration [3]. As known, cancer is a disease of excessive cell

proliferation, whereas neurodegeneration is a disease of excessive cell dysfunction and death. Those opposite cellular effects can arise from defects of common and/or related processes [4]. DNA repair enable cancer cells to additively accumulate genomic alterations and change into more aggressive phenotypes. As DNA repair pathways are frequently altered in cancer; during anticancer therapies alterations in DNA repair should also be considered [5]. So it may therefore be most effective to search primarily for genetic alterations in those pathways first.

Genomic integrity is important for the survival and is controlled by DNA damage response (DDR) network, this is a complicated signal transduction system sensing DNA damage and recruit repair factors; DDR senses different types of damages and coordinates the responses including cell cycle, apoptosis, senescence and DNA repair processes [6,7]. As it is now known, aging, dementia, and cancer share altered cellular functions in response to DNA damage and/or genotoxic stress. The molecular machinery involved in neural function in neurodegenerative diseases may be shared with oncogenic pathways; so both may be affected by common signaling pathways regulating the balance of cell survival and death [3]. For those regulations to occur, cell cycle check point proteins are extremely important, among those p53 is the most significant because of its role in stopping cell cycle in G_0/G_1 and G_2/M phases, it helps to determine whether the cell will go to apoptosis or DNA repair will occur. Those prevent inappropriate DNA replication, whereas the G_2/M checkpoint prevents cells with DNA damage from entering mitosis. Loss of p53 may increase risk of carcinogenesis, whereas specific gain-of-function in its alleles reduces the incidence of cancer but accelerate aging [3]. The p53 is only one of the targets that may involve in both cancers and aging-related neurological diseases. For instance, in mouse models, experiments showed that the withdrawal of the important myc oncogene was resulting in regression of osteosarcomas, epidermal papillomas and lymphomas [8,9]. As those kinds of gene therapies are now usual for experimental area, in this chapter, we aimed to focus on the current therapeutic approaches focusing on the DNA repair in cancer and neurodegenerative diseases.

DDR is related to a pair of related protein kinases called ATM and ATR and both are activated by DNA damage. ATM works with its regulator MRN complex (MRE11, Rad50-NBS1) by sensing the double-strand breaks (DSBs) [10]. ATR has also its regulator ATRIP (ATR-interacting protein) sensing single-strand DNA (ssDNA). Both of them has many common substrates including Chk1 and Chk2 initiating a cascade that results in cell cycle arrest and DNA repair. Chk1 and Chk2 are serine/threonine kinases; Chk1 is responsible for initiating cell cycle arrest to allow time for DNA repair. After its activation, Chk1 prevents cells from entering S phase [11,12]. Chk2 has a similar effect and is activated by phosphorylation by ATM after DSB [13,14]. In this cascade, phosphorylation of histone H2AX on Ser139 by ATM and ATR leads to the accumulation of repair proteins on DSBs sites [15-17]. Many proteins involved in DDR contain specific H2AX-recognition domains such as BRCT domains (C-terminal domain of BRCA1) [18,19].

Depending on the phase of the cell cycle, there are two major intracellular DNA DSB repair pathways: homologous recombination (HR) or non-homologous-end joining (NHEJ) [1,20]. As chromosomes are duplicated during S-phase of the cell cycle, double strand breaks (DSBs) during S/G_2 can be repaired without any loss of information, by recombination between the

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damaged and its homologous undamaged counterpart. This process is known as homologous recombination (HR), and requires the activity of a number of proteins including BRCA1, BRCA2, XRCC2, XRCC3, and RAD51 [21]. Homozygous HR mutants are rarely survive to birth. Patients carrying such mutations usually have developmental disorders like Fanconi anemia [22]. Homologous recombination uses a sister chromatid in S and G_2 phases as a template; NHEJ is an error-prone method of directly ligating the DSB ends in G_0 and G_1 phases. HR involves BRCA1, BRCA2 and Rad51 proteins and NHEJ involves Ku70/80, the DNA-PK, and DNA ligase IV [1]. During migration and differentiation, there is dependence on NHEJ pathways, so mutations in the NHEJ pathway can result in loss of neuroprogenitor cells, cortical neurons and finally results in microcephaly.

As an example to neurological disorders caused by DSB repair, the severity of the disease in ataxia telangiectasia usually correlates with the nature of the mutation, the amount of active ATM protein within the cells of the patient; as it is a disease with the symptoms of immunodeficiency, sterility, radiosensitivity, cancer predisposition [23,24]. In those cases, loss of ATM results primarily in neuronal dysfunction and ataxia rather than microcephaly. If ATM signal fails, neurons may escape apoptosis and with their unrepaired DSBs they will stay in a dysfunctional state causing juvenile neuropathology. Late-onset progressive neuropathologies, like ataxia telangiectasia, are under debate yet probably depending on the cumulative effects of DNA damages [25].

Single-strand breaks (SSBs) are 3 orders of magnitude more frequent than DSBs. SSBs are usually repaired by the SSBR and NER pathways. Nucleotide-excision repair (NER) is mainly responsible for repairing pyrimidine dimers having important roles during G_1 phase to remove bulky lesions, caused for example by ultraviolet irradiation [1]. But if those pathways are defective, they can trigger apoptosis by blocking the progression of RNA polymerases [26]. The defects in the repair of SSBs are less likely to cause developmental defects, but they are related to neurodegeneration and premature ageing. Deficiencies in single-strand break repair (SSBR) may lead to cellular sensitivity to radiation, oxidative stress and base damaging agents. As poly-ADP-ribose polymerase (PARP1) is the sensor of chromosomal SSBs, it hauls SSBR proteins to the sites of DNA damage [27]. Neuronal cells seem to be particularly sensitive to PARP-induced cell death as shown in cerebral ischaemia experiments [28].

DNA-damaging agents are the corner-stones for the treatment of solid tumors. It is now known that tumors that do not respond to DNA-damaging treatment had proficient DNA repair processes [29,30]. DNA damaging genotoxic therapeutics can be divided into groups due to their mechanism of action and type of damage induced. Alkylating agents and platinum-based agents directly effect DNA to induce bulky DNA damage and those are repaired by the nucleotide excision repair pathway (NER) [1,31,32]. Direct methylating agents cause damages that are repaired mainly via the base excision repair pathway (BER) [31]. DSBs are considered as most toxic forms of DNA damages, induction of DSB via radiation or radio-mimetics is an effective method to induce cellular death. DNA metabolism can also be targetted and DNA intercalating agents, topoisomerase poisons and antimetabolites can be used for this purpose [32].

ATM kinase has been a target for the development of novel anticancer agents. The disease associated with ATM mutation is known as ataxia telangiectasia, an autosomal recessive neurological disorder characterized by cerebellar ataxia and oculocutaneous telangiectasia [33]. This disease has symptoms of growth retardation, premature aging and insulin resistance; patients are known to exhibit hypersensitivity to ionizing radiation. So ATM inhibitors are thought to act as radiosensitizer and/or chemosensitizer [34]. Several ATM and ATM/ATR specific inhibitors have been recently developed: LY294002, KU-55933, KU-60019, CP466722, aminopyrazines [35-37]. As p53 is one of the major substrates for ATM, targetting p53 function also enhances cell sensitivity to ATR disruption.

Inhibitors of poly-ADP-ribosepolymerase (PARP) enzyme, that is normally involved in DNA repair, are also used in DNA repair-based therapies. PARP1 inhibitors are used in the treatment of BRCA1- or BRCA2- defective cancers. ADP-ribosylation is also important in DNA repair and genome stability [5]. As it is known, the BRCA1 and BRCA2 genes play essential roles in HR-mediated DSB repair, PARP1 inhibition induces DNA damages. BRCA1/2- defective cells are sensitive to PARP1 inhibition, but BRCA1/2-proficient cells are resistant [38]. However, although there are main hypotheses, the precise mechanism through which PARP1 inhibition leads to cytotoxicity in HR-defective cells is not exactly known yet. As it is found that PARP1 inhibitors were active against HR-defective tumors, it was thought that their effect could be increased by combination therapies with other genotoxic drugs.

miRNAs are also promising agents to improve efficacy of cancer therapy due to their ability to target DDR components and control cellular responses to DNA damaging agents. For instance, it is known that inhibition of ATM by miR-101, miR-100 and miR-421 or inhibition of DNA-PKcs by miR-101 may cause increased cellular sensitivity to IR [39,40]. It is known that some miRNAs can target multiple genes involved in DDR, so it is thought that modulating endogenous miRNA expression may be a promising way to overcome chemoresistance in cancer treatment [41].

2. Conclusion

Cancer and neurodegeneration are diseases occured because of genomic instability accumulated in large regions of the genome. Many of these abnormalities are eligibilities of inaccurate joining of double-strand break ends, resulting from disruption of DNA repair mechanism [42]. These defects are defined such as single nucleotide polymorphisms, mutations, copy number changes or chromosomal realignments causes inactivation of DNA-repair, tumour-suppressor and proapoptotic genes, leading to defects in the repair of DNA damage. Accordingly, there is a need for diagnostic tests of DNA repair deficiency in clinical trials. Recent studies indicated correlation between a DNA repair profiling methods and prognosis [43]. Clinical development of DDR inhibitors will be expedited in the future by use of next-generation sequencing of key and novel genes included as well as molecular and functional assays for DDR proficiency to identify phenotypes is likely to respond to this approaches and strategies.

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