DNA Damage Response

Subjects: Oncology

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Genomic instability is responsible for the progression of acute leukemia, caused by the dysfunction of the DDR genes and activation of certain oncogenes

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1. Introduction

DNA damage leads to changes in the DNA double-helical structure [1]. Under normal physiological conditions, the DNA repair mechanism is activated in response to DNA damage in an attempt to correct the defected DNA and restore normal cell function [2]. This is crucial to cell cycle as it ensures that any genetic mutations are corrected before mitosis and not passed onto daughter cells [3]. Hematological malignancies (HM) account for approximately 10% of all newly diagnosed cancers and are usually characterized by genetic defect in the form of chromosomal translocation or breakpoint/fusion [4]. Many HM run a chronic relapsing course, culminating in therapy resistance with multiple lines of therapy [5]. Development of resistance to DNA-damaging chemotherapy agents such as cisplatin, cyclophosphamide, chlorambucil, and temozolomide can be somewhat mitigated with concurrent inhibition of DNA repair pathways, increasing cytotoxicity [6] and hence therapeutic efficacy [7]. The field of hematology-oncology is considered to be at the forefront of utilizing genomic tools to aid diagnosis, stratification of patients into treatment groups, and infer prognosis. Genetic testing is an integral part in classification of diseases with various techniques employed in the development of diagnostic workflows [8].

Genomic instability is one of the main drivers of hematological malignancy and is associated with inherited and acquired leukemias. The maintenance of genomic stability depends on the amount of continuous exposure to DNA-damaging agents and integrity of the immune system. Eighty percent of patients with chronic lymphocytic leukemia (CLL), a type of HM, display chromosomal anomalies, whereas this is seen in 50% of patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [9][10]. CLL along with AML/MDS exhibit genomic instability. It is also important to note that lymphoma is associated with hereditary diseases such as ataxia-telangiectasia (A-T), Nijmegen breakage syndrome (NBS), and bloom syndrome, which also exhibit genomic instability. Particular mutations such as ataxia telangiectasia mutated (ATM) gene are associated with the defects in DNA repair mechanisms and are present in various cancers including acute leukemia [11]. Several hematological cancers such as CLL and AML have a poor prognosis and therefore the use of PARP1 inhibitor, an inhibitor of the DNA repair pathway, has shown promising results in chemosensitization when treating with cytotoxic agents [12][13].

2. Source of DNA Damage

The agents causing DNA damage can be endogenous or exogenous [14]. Reactive oxygen species (ROS) or ionizing radiation are some examples of DNA damaging agents [15]. Persistent exposure to genotoxic agents may cause disruption of covalent bonds between nucleotide sequences [16]. Resultant changes in the nucleotide sequences may lead to changes in genome replication, transcription, and hence aberrant expression of dysfunctional proteins, causing carcinogenesis [17][18].

Ionizing irradiation (IR) is one of the familiar sources of DNA damage, particularly during radiotherapy. IR leads to increased nuclear instability which causes direct and indirect DNA damage [19]. Several types of IR exist, such as alpha or beta particles and gamma radiation [20]. The energy released from the irradiation has the ability to damage proteins and nucleic acids resulting in double strand breaks (DSB) at the phosphodiester backbone of DNA [21][22]. The irradiation dose determines the level and complexity of DNA damage and the type of damage is influenced by the cancer therapy used [23].

DNA damaging agents are broadly categorized into two categories: clastogens and aneugens. Clastogens are mutagenic agent stimulating disruption or breakages of chromosomes, while aneugens are substances that cause a daughter cell to have an abnormal number of chromosomes. Chromosomal breaks are caused by clastogens and result in acentric chromosomal fragments, while aneugens causes aneuploidy, which impacts cell division and the mitotic spindle apparatus [24].

3. The DNA Damage Response (DDR)

Thousands of single strand breaks (SSBs) and approximately 10–50 DSBs occur in each cell daily, requiring correction by cellular mechanism of DDR [25]. Therefore, DDR plays a crucial role in maintaining genomic integrity. DDR comprises a group of pathways involved in detecting DNA damage, identifying their location, and promoting their effect. Disruption of DDR can lead to disease pathogenesis, including immune dysfunction, neurological deterioration, progeria, and predisposition to cancer [26]. Cell survival or replication is affected by genetic alterations, particularly when it occurs in oncogenes, tumor-suppressor genes, and genes that regulate cell cycle [27]. The sites of DNA damage are identified by DNA repair proteins that are part of the cell cycle checkpoints leading to activation of repair or apoptosis pathways [28].

Important proteins can be activated in response to DNA damage and are essential in controlling the rate of cell growth. These proteins are considered as the main components of DDR-signaling in mammalian cells, which include protein kinases ATM and ATR, which play a crucial role in repair of DNA damage [29]. These components are stimulated by DSBs and replication protein A (RPA) that attach to single-stranded DNA (ssDNA) [30]. ATM/ATR are responsible for targeting protein kinases called checkpoint kinase, CHK1 and CHK2T, as both functionally facilitate replication fork stabilization during DNA replication and repair. Inhibition of CDKs by cell cycle checkpoints leads to cell arrests or reduction of cell-cycle progression in G1-S, intra-S, and G2-M. DNA repair pathways are controlled by cell-cycle checkpoints before the cell enters the stage of mitosis. Furthermore, ATM/ATR cell signaling plays a role in the enhancement of transcription of DNA repair proteins and post-translational modification by phosphorylation, acetylation, or ubiquitination [31].

Proteomic studies have shown that DDR is involved in regulating various cellular processes in order to identify abnormal ATM/ATR-mediated phosphorylation sites [32]. The stimulation of oncogenes or dysfunction of tumor-suppressors genes are responsible for abnormal cell proliferation. ATR/ATM-mediated signaling activated following exposure to stress, initiates cell apoptosis, but also causes cell progression in vivo [33][34]. Within the context of cancer, DDR is stimulated at an early stage of tumor growth to prevent cancerous cells from proliferating [35]. However, inactivation of DDR pathways due to mutagenesis or epigenetic changes leads to proliferation of malignant cells, causing tumorigenesis.

When the level of DNA damage exceeds the ability of the repairing mechanism to fix the damaged site, DDR signals stimulate cell apoptosis, leading to activation of checkpoints resulting in reduction of the activity of cyclin-dependent kinase (CDK) and therefore, cell death or cell-cycle arrest. Activation of p53 transcription is one of the possible anti-tumor response strategies [33][36]. Moreover, chromatin controls DDR and structural changes occur in response to DNA damage [37]. An example of the actions that occur on the site of DNA damage is the phosphorylation of serine-139 of the histone H2A variant H2AX by ATM/ATR/DNA-PK, on chromatin. The ubiquitin-adduct formation in the DNA damaged regions, the recruitment of DDR factors and chromatin-modifying components are responsible for the enhancement of DSB repair and improve DSB signaling [31]. Unusually, activation of ATM also leads to chromatin relaxation at sites of DSBs [38]. Furthermore, H2AX tyrosine-142 phosphorylation is an example of activated DDR [39].

Several metabolites induce DNA damage and impair genomic stability including ROS, nitrogen species, carbonyl species, and lipid peroxidation products, such as 4-hydroxynonenal. Genomic alteration can also occur under normal physiological condition. Somatic recombination through V(D)J recombination and somatic hyper-mutation are important processes which occur in B and T-cells. This results in production of diversity of immunoglobulins and T-cell receptors, required for antigen recognition or through DNA topoisomerase 2 in order to control the integrity and structure of DNA within the nucleus [40].

Aging has been linked to telomere shortening [41]. Epithelial cancer cells, which have a rapid mitotic rate, result in shedding and high turnover of the epithelium, particularly in elderly patients [42]. In early cancerous lesions, the stimulation of epithelial carcinogenesis is caused by critical shortening of telomeres or abnormality in telomere function, leading to induction of tetraploidization, which plays a role in chromosomal instability (CIN) and tumorigenesis [43][44][45][46]. In tetraploidy, there is a tendency to lose chromosomes gradually when the chromosomes are disturbed randomly through division to daughter cells, leading to CIN [47]. Several cancers display some form of CIN suggested to be caused by the shortening of telomeres and, as consequence, chromosomal fusions [48].

DSB exposes the genome, especially oncogenes, to various DNA-damaging metabolites causing a constant accumulation of CIN [49]. Genomic instability and dysfunction of DDR pathway in later stages of cancer development are associated with severe hypoxia. When inherited, DDR abnormalities can contribute to the “mutator phenotype” of many cancers. Together, these evidences highlight that a deficient DDR system is associated with increase of defected DNA in human cancerous cells. Therefore, DDR is an essential anti-cancer component and a potential target for anti-cancer therapy [49].

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