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DNA Damage Response and DNA Repair Genes in Cancer Progression: Good or Bad Guys?

Juliana Ferreira de Sousa[1] and Valeria Valente[2,3,4*]

[1]Department of Cellular and Molecular Biology, Faculty of Medicine of Ribeirão Preto, University of São Paulo (USP), Ribeirão Preto, SP, Brazil
[2]Department of Clinical Analysis, Faculty of Pharmaceutical Sciences of Araraquara, University of São Paulo State (UNESP), Araraquara, SP, Brazil
[3]Center for Cell-Based Therapy-CEPID/FAPESP, Ribeirão Preto, SP, Brazil
[4]Center for Integrative Systems Biology (CISBi), NAP-USP, Ribeirão Preto, SP, Brazil

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Description

Cancer researchers around the world are massively working in order to better understand cancer biology and find promising therapeutic targets to attack cancer cells more efficient and specifically. Once increased genomic instability is a remarkable feature of the different types of cancer, several groups are putting efforts in the characterization of alterations in the DNA damage response (DDR) pathway, a specialized genome surveillance mechanism that protects cells of endogenous and exogenous genotoxic stresses. Loss of function mutations or expression alteration in genes of the DDR machinery and in genes involved in DNA repair execution, which are downstream activated, have been extensively associated with cancer development, progression, malignancy grade, and patient's prognosis and survival [1-14].

DDR activation encompasses a phosphorylation cascade in which numerous proteins are involved. Depending on the type of damage, specific DDR signaling is triggered and determines the activation of different pathways mainly coordinated by the PI3K-like kinases ATM (ataxia-telangiectasia mutated) and ATR (ataxia-telangiectasia and Rad3-related). Two major DNA damage sensors undertake the recognition of DNA lesions, the MRE11-RAD50-NBS1 (MRN) complex that detects DNA double-strand breaks (DSBs), and RPA (replication protein A) and the RAD9-RAD1-HUS1 complex that identify persistent single-stranded DNA regions. These complexes recruit the apical kinases ATM/ATR, which in turn phosphorylate several targets including: 53BP1 (p53-biding protein 1), MDC1 (mediator of DNA damage checkpoint 1), TOPBP1 (topoisomerase DNA II binding protein 1), BRCA1 (breast cancer 1, early onset) and the histone variant H2AX. These proteins sustain and amplify DDR signaling and pass-through the signal to effector molecules. ATM is predominantly triggered by DSBs, while ATR responds to the presence of single-stranded DNA generated by DNA replication stress, but there is considerable crosstalk between these pathways in downstream steps. Ultimately, DDR signaling can spread away the DNA lesion site and promotes the engagement of the downstream kinases CHK1 (checkpoint kinase 1) and CHK2 (checkpoint kinase 2), mainly phosphorylated by ATR and ATM, respectively. CHK1 and CHK2 activate two major effectors: p53 and CDC25 (cell division cycle 25) that coordinates cell cycle arrest allowing DNA repair execution by DNA repair proteins also activated in the process. The resume of cell cycle progression occurs only when damage has been completely removed. Otherwise, when extensive damage cannot be properly repaired, DDR can induce senescence or cell death by apoptosis [15].

Therefore, considering the first steps of tumorigenesis, it is classically known that loss of function of genes involved in DDR is a fundamental trigger for cancer development. This multifaceted DDR machinery was shown to be an inducible barrier for cancer establishment by stopping the cell cycle and inducing cellular senescence or cell death in oncogene-transformed cells [3,4]. So far, the activation of DNA repair genes, which are orchestrated by the DDR proteins, functions as the good guys of tumor initiation blockage. Paradoxically, several studies have also shown that increased expression of DNA repair genes is correlated with the incidence of more aggressive cancers in patients with melanoma [16], bladder [17] and breast cancers [18], squamous cell carcinoma of the oral cavity [19], and glioma [20,21]. These data suggested that once the tumor was initiated and progressed to more malignant stages greater competence in DNA repair is required to avoid the collapse of extremely unstable genomes.

More recently, this dual role of DDR in tumorigenesis (tumor suppressive) and cancer progression (tumor promoting) has been proposed as a mechanism by which cancer cells escape of checkpoint imposed senescence or death and adapt to advanced stages presenting higher levels of replicative stress and genetic instability [22]. Thus, after tumor establishment, the activation of DNA repair genes becomes the bad guy that allows cancer progression. The elevated resistance to radio and chemotherapies observed in highly malignant tumors could be, at least in part, related to this phenomenon [16,23].

Glioblastoma multiforme (GBM), the most common and malignant primary brain tumor affecting adults, is extremely aggressive and resistant to current therapies, which usually include maximal surgical resection, radiotherapy and chemotherapy with the alkylating agent temozolomide (TMZ) [24-26]. The median survival of GBM patients is 14.6 months and the percentage of individuals who lives for five years or more is less than 10% [27,28]. It has been widely demonstrated that the activation of DDR acts as an oncogene-induced biological barrier against GBM development [29-32]. Bartkova et al., showed that DDR is aberrantly and constitutively activated in low-grade astrocytoma and in GBM samples, but not in normal brain or in brain tissues adjacent to the tumor area. More importantly, although GBM presents higher degree of proliferation, the levels of DNA damage were greater in the low-grade astrocytoma than in GBM. These results indicate that somehow DDR seems to be more effective in more aggressive lesions than in low-grade tumors.

***Corresponding author:** Valeria Valente, Department of Clinical Analysis, Faculty of Pharmaceutical Sciences of Araraquara, University of São Paulo State (UNESP), Araraquara, SP, Brazil, E-mail: valenteval@gmail.com

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In this context, we have recently showed an independent correlation between the overexpression of HJURP, a novel protein involved in DNA repair and centromeric chromatin assembly, and the worse survival prognosis of GBM patients. Interestingly, we observed that the more aggressive the tumor is, the higher the levels of HJURP expression. We also demonstrated that HJURP function is essential for GBM cell lines survival while non-tumor cells were not significantly affected, suggesting a potential synthetic lethal effect for HJURP silencing in GBM cells [33]. HJURP overexpression was also included in a four-gene signature associated with poor clinical outcome of high-grade gliomas patients [34]. Additionally, XRCC2 and XRCC4, both related with the homologous recombination DNA repair pathway, are also overexpressed in GBM and the knockdown of these genes sensitizes GBM cell lines to radio and chemotherapies [35].

Therefore, if we consider the initial steps of precancerous lesions development, DDR has the important roles of inhibiting uncontrolled proliferation and activating senescence or apoptosis when DNA damage accumulates. Not a coincidence, in the majority of low-grade cancers the pathway of ATM/ATR, the apical kinases that mediates DNA damage signaling, are compromised by loss of function mutations, mainly in TP53 but frequently also in other downstream genes. In contrast, after establishment of early lesions, it seems that along with tumor evolution the activity of these pathways are recovered and exacerbated in order to defend tumor cells from the replicative stress, high mutation rates and severe genomic instability [3,4,22,33,36,37]. Thus, the competence acquired in the DDR pathway, in part through the overexpression of DNA repair genes, allows the survival of progressively more malignant cancer cells despite the excessive genomic instability accumulated.

This scenario highlights the fundamental role DDR presents in cancer progression and points out the potential of this pathway for the identification of promising therapeutic targets. Further research is necessary to elucidate the mechanisms by which endogenous replicative stress and genomic instability accumulation impose a selection pressure over tumor cells for the acquisition of higher competence in DNA repair and also to identify the genetic targets associated with this competence. The characterization of the genetic alteration repertoire related to the enhanced DNA repair capacity could permit the developing of adjuvant therapies that sensitizes tumor cells to the genotoxic agents or even boost the design of novel therapeutic strategies based on synthetic lethal effects for GBM cells.

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