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Review Article

DNA damage checkpoint recovery and cancer development

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ABSTRACT

Cell cycle checkpoints were initially presumed to function as a regulator of cell cycle machinery in response to different genotoxic stresses, and later found to play an important role in the process of tumorigenesis by acting as a guard against DNA over-replication. As a counterpart of checkpoint activation, the checkpoint recovery machinery is working in opposition, aiming to reverse the checkpoint activation and resume the normal cell cycle. The DNA damage response (DDR) and oncogene induced senescence (OIS) are frequently found in precancerous lesions, and believed to constitute a barrier to tumorigenesis, however, the DDR and OIS have been observed to be diminished in advanced cancers of most tissue origins. These findings suggest that when progressing from pre-neoplastic lesions to cancer, DNA damage checkpoint barriers are over-ridden. How the DDR checkpoint is bypassed in this process remains largely unknown. Activated cytokine and growth factor-signaling pathways were very recently shown to suppress the DDR and to promote uncontrolled cell proliferation in the context of oncovirus infection. In recent decades, data from cell line and tumor models showed that a group of checkpoint recovery proteins function in promoting tumor progression; data from patient samples also showed overexpression of checkpoint recovery proteins in human cancer tissues and a correlation with patients' poor prognosis. In this review, the known cell cycle checkpoint recovery proteins and their roles in DNA damage checkpoint recovery are reviewed, as well as their implications in cancer development. This review also provides insight into the mechanism by which the DDR suppresses oncogene-driven tumorigenesis and tumor progression.

Contents

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Introduction

The cell cycle maintains normal cell growth, and loss of control of the cell cycle is found in many cancers. Checkpoints are the most important cell cycle regulatory machinery, which act as a brake when there is an abnormal processing of DNA replication. In response to genotoxic stress, by activating checkpoint machinery, cells stop cycling, thus allowing DNA repair systems to correct replication errors. If the DNA errors can be repaired successfully, checkpoint signals will be attenuated and the cell cycle will be restarted. If the DNA damage cannot be properly repaired, cell fate may be permanent senescence or apoptosis, or cells will continue to divide with aberrant DNA. Therefore, the complete checkpoint system is a vital cellular component guarding the integrity of genetic information [1].The DNA damage checkpoint network contains sensors, transducers and effectors: the MRN complex and RPA for example are typically considered sensors, Ataxia telangiectasia-mutated (ATM), ataxia telangiectasia and Rad3-related(ATR) and DNA-PK are referred to as transducers or mediators, and their main downstream transducers are Chk1, Chk2 and p53, which regulate several substrate effectors and propagate the checkpoint signal [2]. Cdc25A is also a major effector, whose degradation results in inactivation of Cdk1 and Cdk2, leading to intra-S or G2 phase arrest. ATM and DNA-PK respond mainly to DSBs, whereas ATR is activated by single-strand DNA and stalled DNA replication forks [3]. As a key regulator of the G1/S checkpoint, the role of p53 in cancer development has been studied in depth. Here, we discuss the roles of intra-S and G2/M checkpoint activation and recovery pathways in cancer development, and their relevance for clinical outcomes.

DNA damage checkpoints work as a barrier to cancer initiation

The DDR is activated in response to oncogenic activation

Tumorigenesis is a multi-step process and disruption of cell cycle checkpoints is one of the underlying factors [4]. Oncogenic stress triggers both the DDR and the alternative reading frame (ARF) tumor suppressor, which activate the p53 pathway and provide intrinsic barriers to tumor progression. The DDR has been shown to have a lower activation threshold than the up-regulation of ARF, and is activated earlier in response to oncogenic stimuli [5]. Senescence and apoptosis are two important mechanisms that inhibit genetically aberrant cell proliferation. In cultured cells, introducing an activated oncogene evokes a DNA damage response. Forced expression of the c-myc or H-ras oncogenes drives cell proliferation initially and then causes permanent cell cycle arrest, [6] which is termed oncogene induced senescence (OIS). The DDR and OIS are intrinsically related as DDR markers are found in OIS cells. In oncogenic RasV12 induced senescence cells, ATM, Chk1, Chk2 were activated and protein foci accumulated. [7] DDR pathway activation was also observed in cells in which senescence was induced by overexpression of E2F, Cyclin E and Cdc6 [8,9].

The DDR pathway protects cell from malignant transformation

The ATM/ATR-Chk1/Chk2-p53-p21 axis forms the key elements that regulate the cellular DNA damage response, and defend against malignant transformation. Accumulating data show that compromised components of this axis will impair the DDR and facilitate tumorigenesis [10,11]. In the neoplastic transformation of murine embryonic fibroblasts (MEF), deregulation of the DDR and the G1/S checkpoint precedes G2/M checkpoint abrogation [11]. ATM is the initiating kinase which controls both the G1/S and G2/M checkpoints. Studies have also reported that when cells were depleted of ATM by introducing specific siRNA, OIS was inhibited [10]. As a result, the senescence barrier can be broken by inactivation of ATM, and cells will gain the potential for neoplastic transformation. Recent studies in murine models indicated that under conditions of systemic replication stress, animals doubly mutant for Chaos3 and components of the ATM-Chk2-p21 DDR pathway had decreased tumor latency and/or increased tumor susceptibility [12]. Replication stress response is another type of tumorigenesis barrier coordinated by ATR and Chk1 [13,14]. Haploinsufficiency of Chk1 fosters benign to malignant tumor progression [15]. Modulating the activity of DNA damage checkpoints can either accelerate or decelerate carcinogenesis. However, little is known about how the intensity of DNA damage checkpoint responses is modulated in reaction to oncogenic activation [16].

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