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Mitotic catastrophe and cancer drug resistance: A link that must to be broken

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ABSTRACT

An increased tendency of genomic alterations during the life cycle of cells leads to genomic instability, which is a major driving force for tumorigenesis. A considerable fraction of tumor cells are tetraploid or aneuploid, which renders them intrinsically susceptible to mitotic aberrations, and hence, are particularly sensitive to the induction of mitotic catastrophe. Resistance to cell death is also closely linked to genomic instability, as it enables malignant cells to expand even in a stressful environment. Currently it is known that cells can die via multiple mechanisms. Mitotic catastrophe represents a step preceding apoptosis or necrosis, depending on the expression and/or proper function of several proteins. Mitotic catastrophe was proposed to be an onco-suppressive mechanism and the evasion of mitotic catastrophe constitutes one of the gateways to cancer development. Thus, stimulation of mitotic catastrophe appears to be a promising strategy in cancer treatment. Indeed, several chemotherapeutic drugs are currently used at concentrations that induce apoptosis irrespective of the cell cycle phase, yet are very efficient at triggering mitotic catastrophe at lower doses, significantly limiting side effects. In the present review we summarize current data concerning the role of mitotic catastrophe in cancer drug resistance and discuss novel strategies to break this link.

1. Introduction

Proper transfer of genetic information to daughter cells is essential for the successful propagation of any organism. DNA replication, DNA damage repair and chromosome segregation are three key processes involved in the maintenance and transmission of genetic information. Errors in any of these processes might result in either cell death or survival of cells with altered genetic information. Genetic alterations include, for example, various forms of mutations in specific genes, gene amplification, deletions or rearrangements of chromosome segments, as well as gain or loss of an entire chromosome(s). Accumulation of these genomic alterations may cause dysregulation of cell division, imbalance between cell growth and death, in favor of the former, leading to tumor formation.

Genomic alterations throughout the cell cycle lead to genomic instability, a major driving force of tumorigenesis. Continuous alterations in tumor cell genomes promote the acquisition of further DNA alterations, clonal evolution and tumor heterogeneity (Pikor et al., 2013). Genomic instability is inherent in almost all cancers and has been observed at various stages of cancer formation, from pre-neoplastic lesions to advanced malignancies (Gorgoulis et al., 2005).

The resistance to cell death is closely linked to genomic instability, as it enables malignant cells to expand even in a stressful environment (Hanahan and Weinberg, 2011). Genomic instability can originate from different chromosomal aberrations that can eventually lead to the inactivation of essential 'gatekeeper' genes belonging to the p53 family, which are involved in the regulation of several cellular functions, including gene transcription, DNA synthesis, DNA repair, cell cycle arrest, senescence and apoptosis. Importantly, apoptosis-resistant cells are also regarded as resistant to anticancer therapy. It is becoming increasingly clear that cells can also die by multiple mechanisms, and it was suggested that mitotic catastrophe represents a step preceding apoptosis or necrosis, depending on expression and/or proper function of several proteins. Thus, mitotic catastrophe represents an

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important process that might overcome chemoresistance in tumor cells.

2. Genomic instability

2.1. Aneuploidy

Current evidence indicates that aneuploidy is one of the primary causes of the genomic instability of neoplastic and preneoplastic cells (Fig. 1). Aneuploidy destabilizes the karyotype and thus the species, independent of mutation status, hence corrupting highly conserved sets of proteins that synthesize DNA, segregate chromosomes and repair them (Duesberg et al., 2005). Aneuploidy can occur either by chromosome gains and losses due to chromosome segregation errors, a so-called "whole chromosomal" aneuploidy, or due to rearrangements of chromosomal segments, often accompanied by their deletion and amplification, referred to as a "structural" or "segmental" aneuploidy. Frequently, a combination of both structural and numerical chromosomal alterations can be found in cancer cells (so-called composite aneuploidy). Aneuploidy and its association with various pathologies have been known for more than a century (Storchova and Kuffer, 2008). This often reflects chromosomal instability (CIN), which is an ongoing defect in the faithful transmission of chromosomes (Nowell and Croce, 1986). Nearly a century ago, Theodor Boveri contested that aneuploidy might be a cause of tumorigenesis (Boveri, 2008). For example, weakening of spindle-assembly checkpoint triggers CIN and aneuploidy, which appear to be an important stimulus in the initiation and progression of different cancers (Donnelly and Storchova, 2015). Moreover, tumors with a high clinical grade and dismal prognosis are typically associated with greater degrees of aneuploidy. Despite a long history and clinical relevance, it is still debated whether or not aneuploidy is a cause or a consequence of the malignant state (Rajagopalan and Lengauer, 2004). Aneuploidy can occur as a result of aberrant mitotic divisions that create cells entering subsequent division with multipolar spindles (Kops et al., 2005). Such aberrant mitoses can be caused by polyploidization.

Chromosome cohesion defects might also contribute to aneuploidy in human cancer cells. Resolution of sister-chromatid cohesion at the onset of anaphase depends on separase, a protease that is inhibited by securin (also identified as the pituitary tumor transforming gene 1 (PTTG1)). Inactivation of the securin or separase homologues in the budding yeast (Pds1p and Esp1p, respectively) or fission yeast (Cut2p and Cut1p, respectively) results in chromosome loss (Karra et al., 2012). Consistently, overexpression of separase or securin is a key regulator that controls the loss of chromatid cohesion, as well as promotes aneuploidy and cellular transformation. Moreover, it has been demonstrated that inactivation of stromal antigen 2 (STAG 2) in human cell lines results in defective sister chromatid cohesion and in an increase in aneuploidy (Solomon et al., 2007). Chromosome missegregation might also arise from the impaired attachment of kinetochores to spindle microtubules. This can occur when a single kinetochore attaches to microtubules that emanate from both poles of the spindle, a situation known as merotelic attachment (Holland and Cleveland, 2009).

Another important source of aneuploidy arises from errors in chromosome partitioning during mitosis. A surveillance mechanism known as the mitotic checkpoint (also identified as spindle assembly checkpoint, SAC) is a primary guard against chromosome missegregation (Holland and Cleveland, 2009). Components of SAC, such as Bub1, Bub3, BubR1, Mad1, Mad2, Mad3, Mps1 and CENP-E, recognize incorrectly attached or empty kinetochores and trigger cell cycle delays until all chromosomes are properly attached to microtubules and aligned at the metaphase plate (Han et al., 2014; Storchova and Kuffer, 2008). The cell cycle delay is executed via inhibition of the anaphase promoting complex cyclosome (APC/C), whose activity is required for the metaphase-to-anaphase progression (Sivakumar and Gorbsky, 2015). Together, checkpoint proteins contribute to the formation of a checkpoint effector complex, named the mitotic checkpoint complex (MCC). MCC protects cyclin B and securin from ubiquitination, preventing their destruction by the proteasome, resulting in maintenance of the mitotic state (Musacchio, 2011). However, if checkpoint signaling is compromised, cells can initiate anaphase before all chromosomes have established proper spindle attachments, leading to chromosome missegregation and subsequent aneuploidy.

Aurora B has been directly implicated in checkpoint signaling, independently from its established function in error correction (Musacchio, 2011). Furthermore, evidence that Aurora B controls kinetochore recruitment of most checkpoint components (in the absence of microtubules, i.e., under conditions of lack of attachment), including Mps1, and that it is important for their phosphorylation suggests that it might act near (or at) the apex of the checkpoint signaling pathway (Hewitt et al., 2010).

Aneuploidy has also been proposed as a cause of cancer, based on the fact that it is a strikingly common characteristic of tumors (Holland and Cleveland, 2009). It is now clear that the effects of aneuploidy are more complex than initially proposed (Weaver and Cleveland, 2008). However, it remains unclear whether or not aneuploidy arises early in tumorigenesis and plays a role in tumor development or whether it arises late and reflects a general breakdown of cell-cycle control. Studies using a mouse model of CIN have now clearly shown that aneuploidy is not merely a by-product of tumor cell formation but plays a direct role in tumor cell formation (Gordon et al., 2012). So far, conventional gene knockouts have been constructed for almost all known mitotic checkpoint genes, including those encoding MAD1 (also known as MAD1L1), MAD2 (also known as MAD2L1), BUB1, BUB3, BUBR1 and centromere-linked, kinesin-linked motor protein (CENP-E) or BUBR1 (Han et al., 2014). In addition, hypomorphic alleles that express dramatically reduced levels of BUB1 and BUBR1 have also been generated (Jeganathan et al., 2007). Complete loss of these gene products in most cases leads to embryonic lethality, whereas mice with genetically reduced levels of mitotic checkpoint components have an increased level of aneuploidy and CIN in embryonic fibroblasts and tissues (Jeganathan et al., 2007). Recent data suggest that overexpression of MAD2 (mitotic arrest deficient 2), an essential spindle checkpoint protein, causes a large number of chromosome breaks, chromosome fragmentation and fusion, in addition to whole chromosomal aneuploidy. Consequently, the overall combination of DNA damage, MAD2 overexpression and aneuploidy lead to tumor formation (Kato et al., 2011). In order to test the direct effects of aneuploidy, Wever and Cleveland introduced a model in which reduced levels of CENP-E caused chromosome missegregation due to a weakened mitotic checkpoint, thereby leading to failure of interaction between the chromosome and the microtubules of the mitotic spindle. The consequences of aneuploidy are often multifaceted and it is likely that, depending on the context of other genetic alterations, aneuploidy can both promote and inhibit immortalization, transformation and tumorigenesis (Weaver and Cleveland, 2008). Not surprisingly, the effects of aneuploidy are likely to be dependent on the specific chromosomes that have been gained and lost. Thus, aneuploidy due to reduction in CENP-E promotes spontaneous spleen and lung tumors, but inhibits genetically- and chemically-induced tumors (Weaver and Cleveland, 2008). Downregulation of one of the mitotic checkpoint components, BubR1, enhanced chromosome missegregation in animals expressing the Multiple Intestinal Neoplasia allele of APC, and increased the rate of colon tumors, but decreased the rate of small intestine tumors (Rao et al., 2005). More recent studies have demonstrated that