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Mini Review

Mitotic Catastrophe – Role in Programming of Cell Death

and division (Mitotic (M) phase), which are separated by Gap phases (G1 and G2). Mitosis is subdivided into prophase, prometaphase, metaphase, anaphase, telophase and cytokinesis, which together regulate nuclear envelope breakdown, chromosome attachment to spindle microtubules, alignment along the metaphase plate, sister chromatid separation, and finally, the coordinated plasma membrane remodeling and cytoplasmic division to produce two daughter cells [7].

The transition through cell cycle is controlled by the interplay between cyclin dependent kinases (cdks) and their respective cyclin binding partners [7]. cdk1 is vital participant in the mitotic cell cycle. Mitosis begins and ends with the activity of cdk1 with binding partner cyclin B1 [4]. The coordinated activation and inactivation of cdk1 that controls mitotic progression, the fidelity of the process is maintained by an independent and evolutionary conserved checkpoint known as the spindle assembly checkpoint. The spindle assembly checkpoint is a surveillance process at the transition from metaphase to anaphase that monitors the attachment of chromosomes to the kinetochore spindles and halts progression of anaphase until all chromosomes are correctly attached to the bipolar spindle. Upon proper attachment, the spindle assembly checkpoint is switched off and cdc20 activates the E3 ubiquitin ligase, Anaphase promoting complex (APC), leading to ubiquitination and proteolytic degradation of two substrates, cyclin B, which maintains cdk1 in an active form, and securing, the liberated separate target cohesion causing sister chromatid separation and anaphase onset. Furthermore, Anaphase promoting complex-mediated degradation of cyclin B leads to inactivation of cdk1 and signals mitotic exit [8]. Thus the spindle assembly checkpoint is active for a short time during a normal mitosis. A single unattached or incorrectly attached chromosome is sufficient to block progression to anaphase by inhibition of Anaphase promoting complex activity, thereby leading to mitotic arrest [7].

Checkpoints

The cell cycle progression requires a defined sequence of events where every next event depends upon completion of the last event [9]. This dependency of events thus results in complete distribution and accurate replication of the genome to daughter cells [10]. For the accurate functioning of this dependency, cells are equipped with the checkpoints that are set at various stages of the cell cycle.

The DNA damage can occur in cells due to genetic predisposition, carcinogens, irradiation, mutagens, viruses etc. Once the DNA damage occurs, cells activate DNA damage checkpoint that arrests cell cycle and starts the repair process. According to the cell cycle stages, DNA damage checkpoints are classified into at least 3 checkpoints: G1/S (G1) checkpoint, Intra-S phase checkpoint, and G2/M checkpoint. Upon perturbation of DNA replication by drugs that interfere with

Introduction

The incidence of cancer worldwide is on a rise, accounting it to be the second most common disease, first being the coronary heart disease [1]. The losses of cellular regulation that gives rise to most or all cases of cancer are due to genetic damage. Mutations, in two broad classes of genes – proto-oncogenes (eg, ras) and tumor suppressor genes (eg, APC) – play key roles in cancer induction. These genes encode many kinds of proteins that help control cell growth and proliferation. All human tumors have inactivating mutations in genes that normally act at various cell-cycle checkpoints to stop a cell's progress through the cell cycle if a previous step has occurred incorrectly or if DNA has been damaged [2].

The cell cycle checkpoints or mitotic kinases are the rigorous quality control steps of mitosis [3] that function in preserving the fidelity and integrity of DNA and allow mitosis to continue with accurately functioning DNA, spindle assembly, centrosome and kinetochore thus preventing cell death through mitotic catastrophe [4].

Most cancer cells are deficient in G1 checkpoint function and therefore fail to arrest in G1 phase on exposure to genotoxic agents. Instead, they accumulate temporarily in G2 phase. However, given that the G2 checkpoint is also partially impaired in cancer cells, they are unable to maintain G2 arrest and eventually die as they enter mitosis. This process is known as mitotic catastrophe or mitotic death [5].

Mitosis

Mitosis is the process of nuclear division and chromosomes distribution in eukaryotic cells [6]. The reproductive cycle of the eukaryotic cell is the cell cycle. The mammalian cell cycle can be divided into distinct phases, DNA replication (Synthesis (S) phase)

DNA synthesis, DNA lesions, or obstacles on DNA, cells activate DNA replication checkpoint that arrests cell cycle at G2/M transition until DNA replication is complete. There are more checkpoints such as Spindle assembly checkpoint and Morphogenesis checkpoint. The Spindle assembly arrests cell cycle at M phase until all chromosomes are aligned on spindle. This checkpoint is very important for equal distribution of chromosomes. Morphogenesis checkpoint or the 'DNA structure checkpoint' detects abnormality in cytoskeleton and arrests cell cycle at G2/M transition [11]. This arrest is in response to unreplicated DNA or DNA damage. The combination of checkpoint deficiencies and specific types of damage like, the pharmacological inhibition or genetic suppression of several G2 checkpoint genes such as ATM, ATR, Chk1, Chk2, polo-like kinase (Plk)1, Plk2, Plk3, Pin1, Mlh1 and 14-3-3- σ would lead to mitotic catastrophe [12].

The checkpoints thus are the surveillance mechanism and quality control of the genomic integrity [13]. Checkpoint failure often causes mutations and genomic arrangements resulting in genetic instability. Genetic instability is the major factor of birth defects and the development of many diseases, most notably cancer [14].

Mitotic catastrophe

The first observations of Mitotic catastrophe were made in the late 1930s and early 1940s when cells in exponential growth phase were exposed to radiation. However, the expression 'Mitotic catastrophe' was not utilized until 1986 [15]. When it was used in an attempt to illustrate the phenotype of a yeast strain *Schizosaccharomyces pombe* as a temperature-lethal phenotype, linked to gross abnormalities of chromosome segregation that was observed in some mutant strains [15].

Mitotic catastrophe is an event in which a cell is destroyed during mitosis. This is believed to be caused through apoptosis as a result of an attempt at aberrant chromosome segregation early in mitosis or as a result of DNA damage later, during the metaphase/anaphase transition. The Mitotic catastrophe which has been described as "Death through a tragedy" is stimulated by ionizing radiations, chemotherapeutic drugs or hyperthermia and is caused by malfunctioning of cell cycle checkpoints and mitotic kinases [15]. Drugs that particularly result in damage further leading to mitotic catastrophe include, microtubule-hyperpolymerizing agents (taxanes, elutherobins, epothilones, laulimalide, sarcodictyins, docodermolide) and microtubule-depolymerizing agents (such as the Vinca alkaloids, cryptophycins, halichondrins, estramustine and colchicine). Other factors inducing Mitotic catastrophe include i) Fusion of mitotic cells with interphase cells in S or G2, as a result of premature induction of mitosis before the completion of S or G2 ii) Overduplication of centrosomes (which leads to multipolar mitosis) iii) Failure of centrosomes to undergo duplication [12].

Defective mitotic cells can engage the cell death machinery and undergo death in mitosis, when cyclin B levels remain high. Alternatively, defective cells can exit mitosis, known as slippage, and undergo cell death execution during G1 in the subsequent cell cycle. Finally, defective cells can exit mitosis and undergo senescence. So, Mitotic catastrophe senses mitotic damage and directs the defective cell to one of the three possible antiproliferative fates i.e, Death in M phase, Death in G1 and Senescence [16,17].

Mitotic catastrophe is associated with several morphological and biochemical changes. The final step of Mitotic catastrophe is almost always characterized by the formation of nuclear envelopes around individual clusters of misaggregated chromosomes. It is also correlated with incomplete DNA synthesis and premature chromosome condensation [18]. On the other hand, in most cases, Mitotic catastrophe leads to death, suggesting that both survival and cell death pathways might be a result of Mitotic catastrophe [15].

Features suggestive of Mitotic catastrophe have also been observed during normal development. Similar sequence of polyploidization events have been described during the development of trophoblast, and of heart myocytes during the first postnatal week, and during reproduction of gland cells and neurons. These observations suggest that Mitotic catastrophe cannot be considered a simple disregulation process activated in response to DNA damage but rather represents a programmed event [15]. There is a consensus that Mitotic catastrophe is the major pathway of tumor cell death activated after treatment with ionizing radiation or certain chemotherapeutic agents. There is also an agreement that Mitotic catastrophe is an outcome of aberrant mitosis that results in the formation of cells with abnormal nuclei [19]. The evidences suggest that cells in Mitotic catastrophe can die in various ways [15].

Cells that fail to execute an apoptotic program in response to mitotic failure are likely to divide asymmetrically with the consequent generation of aneuploid cells. This implies that disabling of the apoptotic program may actually favor chromosomal instability, through the suppression of mitotic catastrophe. Mitotic catastrophe thus may be conceived as a molecular device that prevents aneuploidization, which may participate in oncogenesis. It is controlled by cell-cycle-specific kinases (such as the cyclin B1-dependent kinase Cdk1, polo-like kinases and Aurora kinases), cell-cycle checkpoint proteins, survivin, p53, caspases and members of the Bcl-2 family [12].

It is clear that mitotic catastrophe is an important anticancer strategy that is achieved by a variety of mechanisms that target the cell cycle. Although these approaches target proteins that are upregulated in cancer cells, thereby providing a therapeutic window to preferentially kill the cancer cells, they are not specific to cancer cells and are likely to be accompanied by some side effects. New approaches may provide more effective strategies to exploit mitotic catastrophe in cancer prevention and treatment [21].

References

1. Jemal A, Seigel R, Ward E, Murray T, Xu J (2006) Cancer statistics. *CA Cancer J Clin* 56: 106-130.
2. Lodish, Berk, Matsudaira, Kaiser, Kreiger, et al. (2005) *Molecular cell biology*. 5th ed.
3. Butcher N, Britten CD (2008) G2 checkpoint abrogation and checkpoint kinase-1 targeting in the treatment of cancer. *Br J Cancer* 98: 523-528.
4. Singh R, George J, Shukla Y (2010) Role of senescence and mitotic catastrophe in cancer therapy. *Cell Division* 5: 4.
5. Nitta M, Kobayashi O, Honda S, Hirota T, Kuninaka S, et al. (2004) Spindle checkpoint function is required for mitotic catastrophe induced by DNA-damaging agents. *Oncogene* 23: 6548-6558.



6. Prescott LM, Harley, Klein (2002) Microbiology. 5th ed.
7. Mc Gee MM (2015) Targeting the mitotic catastrophe signaling pathway in cancer. *Mediators of Inflammation* 1-13.
8. Sacristan C, Kops GJ (2015) "Joined at the hip: kinetochores, microtubules and spindle assembly checkpoint signaling." *Trends in cell biology* 25: 21-28.
9. Hartwell LH, Weinert TA (1998) Checkpoints: controls that ensure the order of cell cycle events. *Science* 246: 629-634.
10. Russell P (1998) Checkpoints on the road to mitosis. *Trends Biochem Sci* 23: 399-402.
11. Thompson SL, Bakhom SF, Compton DA (2010) Mechanism of chromosomal instability. *Current Biology* 20: 285-295.
12. Castedo M, Perfettini JL, Roumier T, Andreau K, Medema R, et al. (2004) Cell death by mitotic catastrophe: a molecular definition. *Oncogene* 23: 2825–2837.
13. Bartek J, Lukas J (2007) DNA damage checkpoints: from initiation to recovery or adaptation. *Current opinion in cell biology* 19: 238-245.
14. Aguilera A, Gomez-Gonzalez B (2008) Genomic instability: a mechanistic view of its causes and consequences. *Nature Reviews Genetics* 9: 204-217.
15. Vakifahmetoglu H, Olsson M, Zhivotovsky B (2008) Death through a tragedy: mitotic catastrophe. *Cell Death and Differentiation* 15: 1153–1162.
16. Molz L, Booher R, Young P, Breach D (1989) Cdc2 and the regulation of mitosis: six interacting mcs genes. *Genetics* 122: 773-782.
17. Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, et al. (2012) Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death. *Cell Death Differ* 19: 107–120.
18. Vitale I, Galluzzi L, Castedo M, Kroemer G (2011) Mitotic catastrophe: a mechanism for avoiding genomic instability. *Nat Rev Mol Cell Biol* 12: 385–392.
19. Mackey MA, Morgan WF, Dewey WC (1988) Nuclear fragmentation and premature chromosome condensation induced by heat shock in S-phase Chinese hamster ovary cells. *Cancer Res* 48: 6478–6483.
20. Castedo M, Kroemer G (2004) Mitotic catastrophe: a special case of apoptosis. *J Soc Biol* 198: 97–103.
21. Kessler JD, Kahle KT, Sun T, Meerbrey KL, Schlabach MR, et al. (2012) A SUMOylation dependent transcriptional subprogram is required for Myc-driven tumorigenesis. *Science* 335: 348–353.

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