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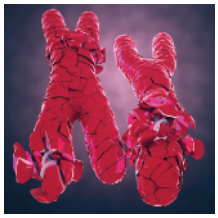
Mitosis

Major finding: Defective assembly of the nuclear envelope and nuclear pore complex in micronuclei may underlie chromothripsis.

Mechanism: Spindle microtubules disrupted assembly of non-core nuclear envelope proteins on lagging chromosomes.

Impact: The lack of a chromosome separation checkpoint may explain the high frequency of chromothripsis in cancer.

DEFECTIVE NUCLEAR ENVELOPE ASSEMBLY MAY PROMOTE MITOTIC ERRORS



Chromothripsis is a catastrophic mutational process resulting in chromosome fragmentation that occurs frequently in cancer and can arise from micronuclei after they spontaneously lose their nuclear envelope integrity. However, the underlying cause of micronucleus nuclear envelope fragility remains unknown, prompting Liu, Kwon, and colleagues to investigate the assembly of nuclear envelopes on lagging chromosomes in micronuclei compared with primary nuclei. During normal nuclear envelope assembly two groups of proteins transiently assemble on different parts of the chromosomes: "core" proteins concentrate near the spindle and "non-core" proteins concentrate away from the spindle. The core nuclear envelope proteins were recruited to lagging chromosomes at equivalent or higher levels compared with the main chromosome mass, whereas nuclear pore complex proteins and other non-core proteins failed to assemble almost completely. This defect in nuclear envelope and nuclear pore complex assembly in micronuclei resulted in defective import and accumulation of nuclear proteins. Spindle microtubules irreversibly blocked assembly of nuclear pore complexes and other non-core nuclear envelope proteins on lagging chromosomes independent of aurora B, and positioning missegregated chromosomes away from the spindle corrected the defective nuclear envelope assembly and suppressed DNA damage in micronuclei. These findings were inconsistent with a previously proposed "chromosome separation checkpoint." Instead, these finding suggest that chromosome segregation and nuclear envelope assembly are loosely coordinated by the timing of mitotic spindle disassembly. The lack of a precise checkpoint may underlie errors during mitotic exit and the irreversibility of nuclear assembly defects during mitotic exit may explain the frequency of chromothripsis in cancer. ■

Liu S, Kwon M, Mannino M, Yang N, Renda F, Khodjakov A, et al. Nuclear envelope assembly defects link mitotic errors to chromothripsis. Nature 2018;561:551–5.

Immunology

Major finding: LC3-associated phagocytosis (LAP) in TAMs results in the immunosuppression of TILs.

Mechanism: Apoptotic tumor cells activate STING-dependent type I interferon signaling in the absence of LAP.

Impact: Targeting LAP-associated proteins may be a potential immunotherapy strategy.

NONCANONICAL AUTOPHAGY IN MYELOID CELLS DRIVES TUMOR IMMUNE TOLERANCE

Canonical ATG-driven autophagy, which results in the degradation of cellular components by the formation of autolysosomes, paradoxically inhibits the outgrowth of malignant cells during early tumorigenesis and promotes tumor progression during the later stages of tumorigenesis. Recently, LC3-associated phagocytosis (LAP) was identified as an autophagosome-independent noncanonical autophagy pathway in phagocytic cells such as macrophages. Given that LAP defects in macrophages were shown to result in the elevation of proinflammatory cytokines, Cunha and colleagues sought to ascertain the effects of myeloid LAP in the tumor microenvironment. Loss of LAP, but not canonical autophagy, in macrophages suppressed syngeneic and autochthonous tumor growth and was shown to drive M1 polarization of tumor-associated macrophages (TAM). Further, single-cell RNA sequencing revealed that loss of LAP in TAMs resulted in impaired phagocytosis of dying tumor cells and induced a type I interferon response. Ablation of type I interferon signaling restored tumor growth in mice with LAP-deficient macrophages. Similarly, transfection of DNA to activate stimulator of interferon genes (STING), which drives type I interferon production in non-phagocytosing cells, resulted in expression of type I interferon in LAP-deficient macrophages, and ablation of STING restored tumor growth in mice with LAP-deficient macrophages. Ablation of LAP in macrophages resulted in increased $CD4^+$ and $CD8^+$ tumor-infiltrating lymphocyte (TIL)–mediated type I interferon production and effector function, and depletion of interferonγ or either $CD4^+$ or $CD8^+$ T cells resulted in reduced tumor growth in LAP-deficient mice. Taken together, these findings provide further insight into the role of noncanonical autophagy in myeloid antitumor immune response and suggest that inhibition of LAP may promote the repolarization of immunosuppressive TAMs. ■

Cunha LD, Yang M, Carter R, Guy C, Harris L, Crawford JC, et al. LC3-associated phagocytosis in myeloid cells promotes tumor immune tolerance. Cell 2018;175:429–41.e16.

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