HOW BURSTING MICRONUCLEI PROMOTE CANCER

Micronuclei have fragile nuclear envelopes that often rupture, causing chromosomes to spill out into the cytoplasm. There, they encounter nucleases that can digest the DNA into small fragments that can be lost, randomly linked, or looped into circles known as circular extrachromosomal DNA. This process, known as chromothripsis, produces complex rearrangements that can drive cancer.

At the same time, the presence of DNA in the cytoplasm triggers the cGAS-STING inflammatory pathway thought to have evolved as a form of immune defense against viral infection. The enzyme cGAS binds DNA from the ruptured micronucleus, catalyzing the formation of 2’3’-cyclic GMP-AMP (cGAMP), which subsequently activates STING and downstream inflammation. When chronically activated due to abundant micronuclei in cancer, this inflammation can drive tumor growth and metastasis.

Instability and inflammation

Focusing on the role of CIN in cancer metastasis, we were surprised to learn how CIN drives cancer’s spread. In particular, we made the surprising observation that cancer cells with CIN displayed activation of pathways related to inflammation, causing these cells to produce and secrete many inflammatory molecules known to be involved in cancer metastasis. This was puzzling at first, given that these cancer cells were being cultured in the lab and had not yet been introduced into animals—and thus had not encountered any immune cells. So what was the source of this inflammation?

After spending many hours looking through the microscope, we observed not only that cells with CIN had a preponderance of micronuclei, but that those containing ruptured micronuclei harbored an immune-related enzyme called cGAS. Discovered by James Chen at University of Texas Southwest Medical Center in 2013, cGAS is a sensor of double-stranded DNA in the cytoplasm. We thus wondered if the rupture of micronuclei and the subsequent exposure of chromosomes to the cytoplasm might be interpreted by the cancer cells as a danger signal, in much the same way that cells might react to the DNA of an invading pathogen. Sure enough, we found that ruptured micronuclei were potent activators of cGAS and its partner protein STING, leading to innate immune activation. But unlike acute viral infection, which only lasts for a few days before it’s cleared, the cancer cell cytoplasm is continuously exposed to bursting micronuclei, leading to persistent pathway activation and chronic inflammation.

The link between chronic inflammation and cancer is well established. In fact, all the cardinal signs of inflammation first described by the Roman encyclopedist Aulus Cornelius Celsus—blush, heat, pain, and swelling—apply to cancer, and clinicians through the ages have often referred to tumors as non-healing wounds due to their persistent and unremitting inflammation. What role inflammatory signaling plays in cancer progression is yet to be fully elucidated, but by linking intrinsic genomic abnormalities such as CIN with ongoing inflammation in cancer, we have shown that CIN not only drives genetic heterogeneity but also fuels cancer spread through mechanisms other than genetics inheritance.

Targeting chromosomal instability

Unlike cancer cells, normal cells do not tolerate errors in chromosome segregation. The importance of safeguarding against chromosome instability to prevent cancer was illustrated by the late Angelika Amon at MIT has revealed that aneuploidy is associated with multiple cellular defects, including metabolic and mitochondrial dysfunction, as well as cellular stress induced by protein misfolding. In fact, humans have evolved various mechanisms that ultimately lead to the clearance of aneuploid cells. Work done by Duane Compton and colleagues at the Giesel School of Medicine at Dartmouth revealed that normal cells rapidly activate p53, a master tumor suppressor, in response to chromosome segregation errors, thus halting future cell division and the propagation of aneuploid cells. These important safeguards

It has therefore become apparent to Cantley and myself, among others, that cancer cells must have coopted a protective immune pathway to their own advantage. While activation of innate immune signaling might play a protective role during early tumor development by preventing many cancers from arising in the first place, at some point tumor cells override these safeguards, develop tolerance to CIN-driven inflammation, and chronically leverage these pathways to drive tumor growth. The ability of cancer cells to sustain ongoing levels of inflammation is critical to their spread from one organ to another. Immune cells are some of the most mobile cell types in the body; within hours of sensing an infection or a wound, they can travel through the vasculature and migrate against elevated hydrostatic pressures present in inflamed tissues to reach the site of injury. This process, which is vital for organismal survival, is mimicked by cancer cells during metastatic progression and is enabled by ongoing CIN and the genomic abnormalities it produces.

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