Chromosomal instability promotes metastasis through a cytosolic DNA response

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Background: Chromosomal instability (CIN) is a hallmark of cancer and it results from ongoing errors in chromosome segregation during mitosis. While CIN is a major driver of tumor evolution, its role in metastasis has not been established.

Methods: We use genetically engineered tumor cells that have been engineered through genetic means to modulate the rate of chromosome missegregation rates thereby enabling the selective probing of the role of CIN in tumor evolution and tumor-microenvironment interaction.

Results: Here we show that CIN promotes metastasis by sustaining a tumor-cell autonomous response to cytosolic DNA. Errors in chromosome segregation create a preponderance of micronuclei whose rupture spills genomic DNA into the cytosol. This leads to the activation of the cGAS-STING cytosolic DNA-sensing pathway and downstream noncanonical NF-▪B signaling. Genetic suppression of CIN significantly delays metastasis even in highly aneuploid tumor models, whereas inducing continuous chromosome segregation errors promotes cellular invasion and metastasis in a STING-dependent manner. Using single-cell RNA sequencing, we uncover a CIN-induced transcriptional switch from a proliferative and metabolically active state to a mesenchymal phenotype associated with inflammatory pathways, offering an opportunity to target chromosome segregation errors for therapeutic benefit.

Our work reveals an unexpected link between CIN, cytosolic DNA sensing pathways, and metastasis. The use of an isogenic system has enabled us to dissect the role of CIN from that of aneuploidy. Unlike normal cells, chromosomally unstable cells are awash with cytosolic DNA and have adapted to coexist with a chronically active cGAS-STING pathway by suppressing downstream type I interferon signaling and instead upregulating the alternative NF-▪B pathway.

Conclusions: The emergence, and subsequent tolerance, of CIN represents an important bottleneck during tumor evolution. Our single-cell analysis revealed that CIN induces a transcriptional switch whereby cells shift from a proliferative and highly metabolic state, ideally suited for primary tumor growth, to a chromosomally unstable and mesenchymal state associated with upregulation of inflammatory pathways. These two largely mutually exclusive states likely account for the reversibility in chromosome missegregation rates seen in primary tumors and metastases, and provide an explanation for the negative effect of aneuploidy during early tumorigenesis. Interestingly, this mutual exclusivity was recently observed in a pan-cancer genomic analysis of metastatic tumors, and it leads us to suggest that CIN underlies the subset of metastases that are characterized by EMT and inflammation. By providing a mechanistic link between CIN and metastasis, our work opens new avenues to target chromosomally unstable tumors for therapeutic benefit.

COI: Patent on the role of cGAS-STING in metastasis. Consulting for Sanofi