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The cornucopia of cancer biology

Cancer biology is the cornerstone on which much of modern cancer research is based. Continuing to explore the intricacies of this multilayered foundational scientific area is essential.

Understanding the changes that set healthy cells on the path to becoming cancerous by deregulating normal molecular and cellular process to trigger tumor initiation, fuel tumor growth and promote the seeding of metastases to distal sites is the core endeavor of cancer biology. Over the past decades, this simplified view of tumorigenesis has been enriched by the ever-more-complex layers of biological insight provided by fundamental discovery studies. A wealth of knowledge has been gained through investigation of the interactions of tumor cells with components of their surrounding extracellular space and with normal cells of the same tissue and other tissue-residing or recruited cell types, and the systemic effects triggered by tumors. Cancer biology has expanded and evolved into a vast interdisciplinary field that goes beyond classic cell and molecular biology to intersect with and integrate knowledge from many other areas, including genetics, immunology and translational research. Four papers published in this issue of *Nature Cancer* elucidate different but overlapping aspects of cancer biology, highlighting the richness of the field.

Kang and colleagues explore the regulation of PD-L1, one of the key immune checkpoint proteins expressed on cancer cells, and delineate an intricate mechanism that involves phase-separation-mediated gene expression. The authors employed genome-wide CRISPR–Cas9 screens to identify regulators of PD-L1 in cancer cells exposed to the cytokine IFNγ and focused on the histone acetyltransferase KAT8, demonstrating that its depletion downregulated PD-L1 expression, enhanced T cell killing and reduced tumor growth. Exploring the molecular underpinnings of these effects in various cancer cell types, they discovered that KAT8 interacts with the IFNγ effector transcription factor IRF1, forming condensates that promote acetylation and activation of IRF1 at the promoter of the gene encoding PD-L1 to subsequently induce transcription of this gene. To establish the translational potential of these findings, Kang et al. designed a peptide that disrupts the interaction and condensate formation of KAT8 and IRF1, thereby enhancing anti-tumor immunity and reducing tumor growth. In an accompanying News & Views article, Kubelick and Garcia Quiroz discuss the reported molecular mechanism and implications of these findings in greater depth.

Focusing on a different aspect of cancer immunobiology — namely, inflammation in the tumor microenvironment — Erez and colleagues delineate the dynamic interplay between primary tumors and the brain metastatic niche through systemic factors and the interactions of brain-resident astrocytes and recruited immune cells. Using melanoma and breast cancer models of experimental mouse metastasis, together with human tumor specimens, they show that secretion of the glycoprotein LCN2 by primary tumor stromal cells is associated with brain metastasis and that, acting systemically, LCN2 activates brain-resident astrocytes. The resulting neuroinflammation leads to the activation of other cells, such as granulocytes, that further secrete LCN2 locally in the brain to enhance pro-inflammatory responses. Among these is infiltration by immunosuppressive myeloid cells that subsequently facilitates metastasis. Although the contributions of other tumor-microenvironmental cell types and potential tumor-type-specific differences await further study, these findings highlight the rich biology that underpins metastatic seeding.

In a separate study centering on the metastatic niche, Fendt and colleagues report on the organ-specific manner in which lipid metabolism promotes metastasis formation. They show that although both mouse lung and mouse liver have high levels of certain fatty acids, such as palmitate, a high-fat diet further increases palmitate levels specifically in the lung by signaling to lung alveolar type II cells. Tumor cells that reach the lung metastatic niche oxidize the excess palmitate into acetyl-CoA through the action of the enzyme CPT1A. This acetyl-coA is subsequently utilized by the histone acetyltransferase KAT2a to acetylate the p65 subunit of the transcription factor NF-κB, resulting in the induction of NF-κB target genes encoding molecules that support metastasis formation. The authors discuss these findings further in an accompanying Research Briefing, with additional perspective provided by Pinheiro and Wellen in a News & Views article published in *Nature* (L. V. Pinheiro and K. E. Wellen, *Nature* 615, 224–225; 2023).

Continuing the theme of metastasis, but centering on outgrowth, Yang and colleagues elucidate a previously unappreciated cellular process through which the nuclear expulsion of chromatin and associated proteins from dying breast cancer cells promotes metastatic growth of neighboring cells by acting in a paracrine signaling capacity. They show that apoptotic breast cancer cells expel decondensed, citrullinated chromatin in a manner reliant on calcium-dependent peptidylarginine deiminase 4. The subsequent interaction of expelled chromatin with S100a4 permits the latter to bind RAGE, its receptor, on nearby surviving cancer cells, to trigger their outgrowth. Inhibiting this process through the general approach of degrading DNA with DNAse I, or by targeting specific pathway nodes with a PADI4 inhibitor, a neutralizing antibody to S100a4 or a soluble RAGE decoy receptor, reduces metastatic tumor growth in the lung. The authors present evidence of nuclear expulsion products in human tumor samples and the association of a relevant gene-expression signature with a poor prognosis for patients with breast cancer, which indicates that further exploration of the underlying biology and translational potential of this pathway is warranted.

In attempting to understand and treat cancer, context is key. In turn, biological investigation is one of the most powerful means at our disposal to inform context. In our efforts to devise innovative and more efficacious anti-cancer therapies, it is essential to continue strengthening foundational discoveries through interdisciplinary cancer biology studies.

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