CANCER

The tumor as organizer model

Cancer cells are the architects of their primary and metastatic microenvironments

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In 1924, Hans Spemann and Hilde Mangold reported that a small collection of cells taken from a gastrulating newt embryo could, when transplanted into a separate embryo, coax the newly adjacent cells to form a second embryonic axis (*1*). This collection of embryonic cells came to be called the "organizer," and its identification codified the concept of induction—that cells influence their neighbors to change fate, often in dramatic fashion. Importantly, the organizer does not actually "organize" the embryo; rather, it initiates a cascade of sequential induction events that ultimately give the embryo its shape. In the decades since this landmark observation, it has become clear that induction plays a ubiquitous role in both embryonic and adult tissues, and that secreted and/or membrane-associated factors mediate the process. How does the embryonic organizer model apply to the various features of malignant progression, including stroma formation, metastatic spread, and tumor heterogeneity?

Like embryos, tumors are composed of a diverse assortment of cells—a mixture of fibroblasts, leukocytes, and endothelial cells—that together with cancer cells collectively constitute the tumor microenvironment (TME). In contrast to the coherently patterned tissues that emerge during embryogenesis, tumors are highly disorganized. Moreover, the cellular makeup of the TME can vary widely from tumor to tumor, resulting in differences that can profoundly influence responses to therapy. These observations prompt a fundamental question: What is responsible for sculpting the complex ecosystem of a tumor?

Within the TME, different cell types can signal to one another and to tumor cells, resulting in a complex and often redundant cellular cross-talk. Because of this complexity, it has been challenging to unravel the source(s) and recipient(s) of intercellular signals within tumors. For example, transforming growth factor–β (TGF-β) signaling is known to play an important role in cancer progression and metastasis (*2*). However, TGF-β ligands are secreted by, and act on, multiple cell types within the TME, including both stromal cells and cancer cells, making it difficult to distinguish which (if any) of these cells bear primary responsibility for sending or responding to this important signal. This problem becomes even more unwieldy as additional signaling molecules and progressive stages of tumor evolution are considered, creating a multifaceted "chicken and egg" paradox. This complexity poses a challenge for drug development, as signals (such as TGF-β) can have pro-tumor or antitumor activities depending on cellular context.

> ***"...studies suggest that cancer cells reside at the apex of a [tumor microenvironment] signaling hierarchy."***

Despite this complexity, recent studies suggest that cancer cells reside at the apex of a TME signaling hierarchy. These findings can be encapsulated by a "tumor as organizer" model, in which the principal source of signals responsible for establishing the TME is the cancer cells themselves (see the figure). Much of the support for this idea comes from studies of the immune TME. By perturbing specific genes or signaling pathways in cancer cells, investigators have identified cancer cell–intrinsic factors that influence the composition and abundance of tumor-infiltrating immune cells (*3*, *4*). Notably, many of these factors represent oncogenic drivers, including transcriptional regulators or components of signal transduction pathways that are directly involved in cancer cell growth and survival. For example, activation of MYC, KRAS, mammalian target of rapamycin (mTOR), Yes-associated protein (YAP), or β-catenin signaling in cancer cells all prompt a decrease in tumor-infiltrating T cells in the resulting tumors; blocking these driver oncoproteins during tumor formation abrogates these effects (*4*). In some cases, oncogenic signaling modulates the TME by regulating the infiltration of immunosuppressive myeloid cells, whereas in other cases the shift occurs through dysregulation of antigen-presenting dendritic cells, which are needed for effective antitumor immune responses (*4*). Thus, tumor organizers shape their respective microenvironments through diverse programs, each acting under the influence of the unique oncogenic history of the cancer cells.

The evidence that cancer cell–intrinsic factors shape the TME is not limited to these types of gain- and loss-of-function studies. For example, mouse pancreatic cancer cell lines give rise to tumors in mice with immune TMEs that reproducibly recapitulate their parental phenotypes, even when implanted at different sites (*5*). In this study, tumors with minimal T cell infiltration were associated with genomic and transcriptomic signatures of increased cell cycle activity compared to tumors with robust T cell infiltration, consistent with the above-noted inverse correlation between oncoprotein-driven proliferation programs and T cell infiltration. Collectively, these findings suggest that targeting driver oncoproteins may promote antitumor effects in two ways: (i) directly, through the inhibition of cell proliferation programs, and (ii) indirectly, through modulation of the immune TME. In the future, it will be important to determine whether the TME-shaping effects of oncogenic drivers are directly tied to their growth-promoting properties or represent correlated but biologically distinct activities.

The activity of such tumor organizers reaches beyond the immune system. Pioneering work on angiogenesis implicated cancer cells as a key source of factors that recruit endothelial cells (*6*), and subsequent studies have confirmed that cancer cells also regulate the recruitment of fibroblasts, neurons, and adipocytes into the tumor, underscoring their critical role in shaping the TME (*7*). Cancer cells derive various benefits from their stromal conscripts, in particular the creation of a favorable metabolic milieu. Given their highly anabolic state, cancer cells have metabolic needs that differ from those of most normal cells. It is increasingly apparent that cancer cells evolve to modify the TME in ways that ensure adequate energy supplies, including fuels obtained through alternative means, such as macropinocytosis and/or paracrine delivery from cancer-associated fibroblasts (*8*, *9*).

Like their embryonic counterparts, tumor organizers act in a stepwise manner that involves a first wave of stromal cell infiltration followed by subsequent waves of induction. Consequently, the TME-shaping signals produced by cancer cells play their most prominent role(s) early in tumorigenesis. Later, once the TME is established, signals from multiple cellular sources may amplify or offset cancer cell–derived signals (see the figure). Thus, although tumor organizers dominate during the formation of the TME,

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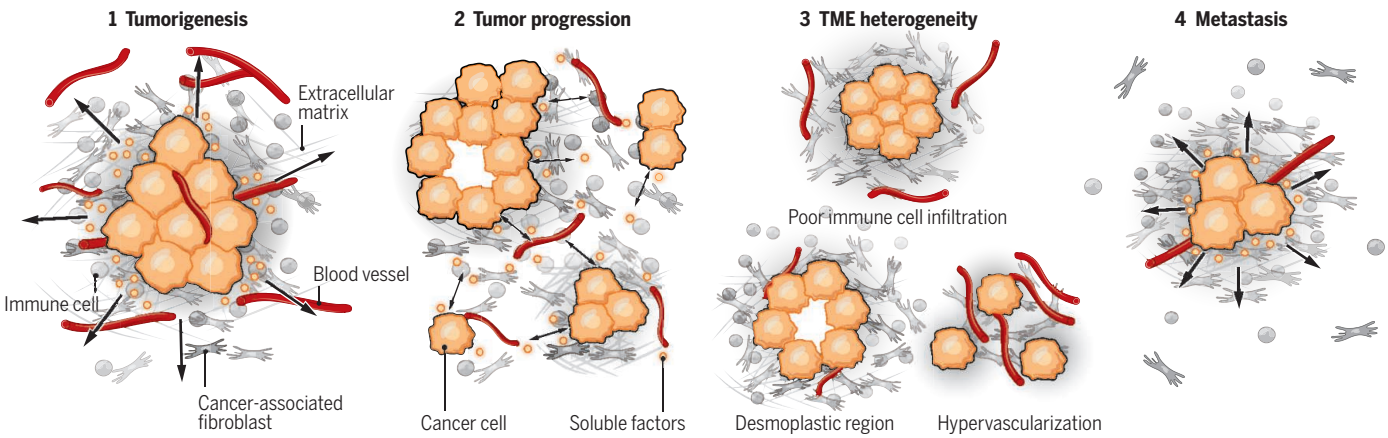
Cancer cells organize their microenvironments

Early in tumorigenesis (1), cancer cells release soluble factors in an organizer-like fashion to recruit supportive stromal cells, forming a tumor microenvironment (TME). Once the TME is established (2), cancer cell–derived signals are superseded by signals from stromal cells, resulting in a complex network of cellular cross-talk. Regions within a tumor exhibit heterogeneity (3) that may be associated with selective pressures in the environment, leading to multiple organizer–like signaling centers. After spreading to a distant organ (4), cancer cells reestablish a supportive stroma through the release of soluble factors.



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cross-talk between stromal cells may supersede these cancer cell–derived signals once the TME is established. It will be important to distinguish which cancer cell–intrinsic factors are involved in the maintenance of the TME, as such factors hold the greatest therapeutic promise.

When tumors metastasize, cancer cells again adopt a central role, shaping the surrounding tissue in a manner that supports metastatic outgrowth (see the figure). Because the properties that allow cancer cells to thrive in their primary TME may or may not have the same effect at a new location, cancer cell–intrinsic factors are likely to constrain which disseminated cells are competent for metastatic outgrowth in a given tissue. In this reframing of the classic "seed and soil" model of metastasis (*10*), the organizer-like properties of cancer cells determine the degree to which they can interact with and regulate the microenvironment of a foreign tissue, thereby defining the feasibility of metastatic colonization. In other words, disseminated cancer cells may exhibit different properties depending on the nature or aptitude of the receiving tissue—a phenomenon that developmental biologists call the "competence state" of the surrounding cells (*11*). Such properties may allow disseminated cancer cells to circumvent immune surveillance and/or create a favorable metabolic milieu in what would otherwise be a hostile environment. In a model of metastatic breast cancer, for example, some disseminated tumor cells can adopt a dormant state, thereby reducing natural killer (NK) cell recruitment and allowing metastatic progression (*12*). Moreover, data regarding the premetastatic niche, whereby cancer cells optimize conditions at future metastatic sites, raise the possibility that tumor organizers act at much greater distances than their embryonic counterparts (*13*). These studies suggest that cancer cells navigate the selective pressures imposed by dissemination in part by adaptively (re)organizing their new environments.

The tumor as organizer model has important implications for intratumoral heterogeneity—the marked histological and molecular variation found within a single tumor. As they grow, tumors evolve multiple subclones with divergent genetic and epigenetic features and distinct repertoires of stromal-recruiting factors. But, unlike embryonic organizers, which are evolutionarily preprogrammed, tumor organizers are shaped by genetic and epigenetic events selected during tumor progression. As such, the histological variation observed in a given tumor—regions that are hyper- versus hypovascular, fibroblast-rich (desmoplastic) versus fibroblast-poor, or leukocyte-infiltrated versus noninfiltrated—may result from geographic variation in the expression of cancer cell–derived factors. That is, tumor evolution may lead to the emergence of "secondary" tumor cell organizers, analogous to the ancillary organizers that arise following gastrulation in the embryo, each with its own inventory of inductive factors (see the figure). Nonetheless, other environmental factors such as hypoxia—which may vary from one region of a tumor to another—are also likely to affect the composition and function of the TME. Likewise, commensal microbes may control the differentiation of T cells and activation of antigen-presenting cells in tumors, which in turn can influence sensitivity to some therapies. Thus, intratumoral heterogeneity likely reflects an interplay between the TME-shaping effects of tumor cell organizers and tumor-independent environmental factors.

Strategic manipulation of the TME can have a profound impact on clinical outcome, and this has made the stroma an appealing target for cancer therapy, including immunotherapy (*14*). As these efforts continue to show promise, a deeper understanding of how cancer cells shape local environments becomes increasingly important. Future insights may come from ongoing phenotyping of TMEs across human cancer types and a correlation of TME composition with molecular features of the cancer cells. Progress in imaging methodology and single-cell profiling make such deep phenotyping possible and provide further opportunities to characterize TME components and cancer cell–intrinsic features that determine therapy responsiveness (*15*). The application of these techniques to patient samples, taken at different stages of disease in a high-throughput manner, will enable a comprehensive understanding of cellular cross-talk within the TME. ■

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