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Rethinking Stroma: Lessons from the Blood

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Abstract

Stroma is a largely understudied component of all organs that contributes to stem cell niches. Studies to define stromal components in the bone marrow have led to some unexpected findings that prompt further research.

Search “stroma” and until last year or so, what popped up first in Wikipedia was “an island off the northern coast of Scotland.” But who can blame the Wiki writers when most biologists would have trouble getting beyond connective tissue and vessels? It is a grab-bag term that reflects a lack of precise determination of components and functions because there has been little detailed investigation. Here, I argue that in this era when we know the sequence of every human gene, it is unreasonable to accept persistent ambiguity of stromal cellular and extracellular constituents: not just because stroma is present in virtually every human organ, but because stroma is central to tissue homeostasis, repair, and disease.

Stroma entered the biologic vernacular in the 19th century as microscopists viewed tissues and saw parenchymal cells embedded in a supportive framework. The framework received the name in Latin for a mattress, *stroma*. It is often interchangeably used with *mesenchyma*, which is the structural part of a tissue in support of the functional parenchyma. *Parenchyma* in Greek is literally the “visceral flesh” that as a verb is “poured in” to mesenchyma. That mesenchyma would be viewed as relatively inert support for early microscopists is not surprising, yet it has long been known to be critical for developing tissues.

Mesenchymal interactions with epithelial parenchyma are essential for organogenesis. Mesenchymal cells emerge during gastrulation and become a part of virtually every tissue of metaozoans. They participate in key patterning events determining with precision the identity, number, and organization of cells comprising developing organs and appendages. For example, epithelial-mesenchymal signaling feedback loops involving sonic hedgehog (Shh) and FGF are critical for limb development (Bénazet et al., 2009). Specialized regions of mesenchymal cells form the dermal papillae that regulate hair follicle morphogenesis by β-catenin signaling altering FGF and IGF production (Enshell-Seijffers et al., 2010). Branching morphogenesis, important in multiple organ types, is in part controlled by mesenchymal cell islands producing FGF10 in a Shh-regulated manner (Affolter et al.,

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2003). Yet, in the homeostasis of adult tissues, these critical functional aspects of mesenchymal cells are generally regarded as vestigial and it has only recently been made clear that mesenchyma and stroma are more than architectural support elements.

Mesenchymal stromal cells are increasingly appreciated to be heterogeneous, dynamic, and play a regulatory role in parenchymal cell function in adult tissues. This is evident in the regulatory environment for stem/progenitor cells, particularly in hematopoiesis, and hematopoiesis will be the sole focus hereafter for sake of brevity, though other tissues have been studied by others.

The stroma of bone marrow has historically been a focus in hematopoiesis research, at least in part due to the limited ability to maintain or grow hematopoietic stem cells outside the body. Michael Dexter first demonstrated the importance of stroma in coculture experiments that established the now classic method for in vitro hematopoietic stem/progenitor cell (HSPC) support (Dexter et al., 1977). His laboratory neighbor at the University of Manchester, Raymond Schofield, observed the variable stem cell properties of the spleen colony-forming unit when cultured in isolation and proposed that stroma was also of critical importance in vivo, providing a stem cell “niche” (Schofield, 1978), a term he coined in his landmark paper.

While the hematopoietic cells that represent the parenchyma of bone marrow are the primary interest, it is the stroma that has become a highly prominent focus for trying to understand the behavior of the hematopoietic cells in both health and disease. The stroma is seen as the critical piece, still veiled, that drives the physiology of the hematopoietic stem cell.

In 2003, both my laboratory and that of Liheng Li first reported the presence of regulatory cells in the stroma using in vivo genetic models (reviewed in Mercier et al., 2012). There are now more than 1,000 papers on the topic according to Scopus. What that work has shown is that the participating parts of the stroma are highly complex, far more complex than the first naive reports suggested or than invertebrate models suggested. The invertebrate model of a single cell type governing a single stem cell type is not the case in the bone marrow and likely not in other tissue niches as well. Neural and nonmyelinating Schwann cells, endothelial cells, and mature hematopoietic cells like macrophages and possibly osteoclasts all participate in regulating HSPCs (reviewed in Mercier et al., 2012). Even within the mesenchymal cell pool, multiple candidate populations have evidence of modifying HSPC number, quiescence, and/or localization including those expressing CXCL12, osterix, Nestin, leptin receptor, adipocyte markers, and, perhaps, N-cadherin (reviewed in Mercier et al., 2012). This level of complexity in cell type has created ongoing efforts to discern the overlap or distinction among mesenchymal cells and to organize participants hierarchically, for example, which cell type matters in terms of kit ligand expression (Ding et al., 2012). In addition, it is becoming clear that there is heterogeneity in stem cells and the pairing of stem cell type and niche cell type is undefined. Rationally defining the relationships between cell types and the molecules they produce will require a cataloging process that is likely to take years but offers the potential of giving at least a snapshot view of participants in the orchestra. What will we have at the end? It may well be an assembly without sufficient annotation to know what nodal point can be tweaked to modify how the system behaves as a

whole. Returning to the orchestra analogy, we will know who is in the chairs and may be even what instruments they can play, but we will not know how to make music. That would take more of a systems biology approach, investigating multiple components simultaneously over time to define just how the components are hierarchically related and integrate their activity to provide physiologic outputs.

Such a systems-like approach would be enormously demanding in time and resources that could only be worth it if highly distinctive applications might result. The possibility of distinctive applications is suggested by unexpected outcomes of experimental work noted below that was initially intended to address other questions.

Dexter taught that stroma was needed to keep cells happy ex vivo and investigation into the niche that followed generally focused on assessing what is needed for homeostasis. However, perturbing stromal cells resulted in odd hematopoietic phenotypes in at least two instances. For example, genetic perturbations of primitive mesenchymal cell subsets (altering RNA processing or ribosomal genes) or more undefined populations (deleting RARg) disordered the regulatory environment of the hematopoietic system sufficiently to cause a dysplastic and frank malignant state or a hyperproliferative one, respectively (Raaijmakers et al., 2010; Walkley et al., 2007). This disorganization of the hematopoietic parenchyma by mesenchymal dysfunction reveals how critical the relationships are. Those relationships do not just maintain the localization or number of parenchymal stem cells, but also the integrity of parenchymal organization and function. Moreover, the effect was driven by particular mesenchymal cells. Cells expressing osterix altered hematopoietic function, while those expressing osteocalcin did not (Raaijmakers et al., 2010). Perhaps most interesting about the parenchymal malignancy (acute myeloid leukemia) arising in one of the studies (Raaijmakers et al., 2010) is that molecular characterization of the few leukemias that could be studied indicated that they had multiple, new genetic lesions. These data argue that the alteration of stromal function imposes a new set of rules on the parenchymal cells. It changes the way they function, as evident in dysplasia, and it changes what cells thrive. The emergence of malignant cells was presumably due to selection: a selection that seemed to be persistent when the cells were secondarily transplanted. Altered stroma may impose new determinants of “fitness” on the parenchymal cells with which it interacts. It could then enable and perhaps facilitate outgrowth of a neoplastic clone. This model would argue that the multihit hypothesis of cancer could include a hit outside of the cancer cell itself: a cell nonautonomous participant in the emergence of malignancy.

Stroma participating in the invasiveness or growth characteristics of malignancy is a longstanding concept about which much has been published, but a model whereby it can be a primary driver of cancer emergence adds a different dimension and enhances the rationale for learning more about just what stroma is and how it works. This is further fueled by the recent recognition that osteoline-age cells participating in bone marrow stroma are highly dynamic (Park et al., 2012). They turn over with rapidity not unlike the hematopoietic system and they are replaced by a stem/progenitor pool much like other tissues of rapid cell turnover. Further, the cells can translocate both interstitially and intravascularly so they could theoretically be a population that could acquire a genetic lesion, and propagate that lesion to a large number of descendent cells and distant sites. They could create a “field” of

stroma imposing different selection pressures on parenchymal cells. Such a scenario may not be a commonplace basis for neoplasia emerging, but it raises the issue of whether stroma might change with age in a way in which acquired genetic lesions within parenchymal cells might be given a competitive edge, providing them a niche in which previously they would not have thrived. It is a hypothesis worth testing particularly as it might provide insight into new vulnerabilities of cancer cells.

If stroma is a part of the ecosystem in which cancer emerges, understanding how its dysfunction could lead to the selection of malignant cells raises another possibility. There are few settings where cancer biology focused on the cancer cell as an autonomous unit have provided opportunities for prevention. Perhaps defining how targeted alterations in specific stromal cells select for dysplastic and neoplastic cells will offer such an opportunity. Even the somewhat odd models such as those cited above may give us insight into the signals at work between mesenchymal and parenchymal cells that enable a malignant prone condition to proceed.

Stroma has shown itself in the bone marrow to be far more than just the stuff that holds tissues together and it may hold greater secrets still. Teasing stroma apart in other tissues as well as bone marrow, testing its components as disease participants, and defining whether it can be therapeutically targeted is worth our attention, particularly in the context of tissue stem cells.

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