On Leukocytes in Mammary Development and Cancer

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That cancer is development gone awry is not a new concept. Most of the “hallmarks” ascribed to cancer—proliferation, invasion and induction of blood vessel growth—also occur during organogenesis and development. Therefore, tumors are not necessarily learning new tricks during their development, but how about when they metastasize? In colonizing a new organ, often with some degree of specificity, tumor cells may simply be copying a program that is executed during development by hematopoietic stem cells (HSCs)—the stem cells that ultimately generate all of the cells in our blood and maintain its homeostasis. One family of cells generated by HSCs—leukocytes—is the focus of the work by Coussens and Pollard (2012). These two scientists have woven together several studies that revolutionized the way we think of immune cells. As pointed out by the investigators (whose respective laboratories are responsible for much of the seminal work on this subject), immune cells also have a variety of trophic functions, and it is these functions that are used rationally during development, and recklessly during tumor growth.

This leads us back to metastasis. There is so much to learn about why a tumor travels from one organ to another, how it does so, and the manner by which it adapts to and ultimately flourishes (or fails) in a foreign microenvironment. And as stated above, immune cell precursors,

HSCs, do the same. In the mouse, HSCs have originated in one tissue (the dorsal aorta), traveled to another (the placenta) via the circulation, and matured somewhere else (the liver)—all before birth. Finally, HSCs make their way to the bone marrow, where they reside postnatally. Specialized niches in the bone marrow are thought to mediate HSC dormancy as a means to preserve the “stemness” of this population, and there are mechanisms in place that allow these cells to rapidly exit these environs and proliferate in response to injury. Therefore, it should not come as a surprise that a common site where micrometastases are found is the bone marrow for many cancers (including that of the breast).

Uncovering whether the same niches that control HSC expansion in the bone marrow are also responsible for maintaining quiescence of tumor cell populations is an exciting prospect, as is deciphering the precise components of these niches. Such work could explain the seemingly incongruous observation that despite an absence of clinically detectable disease, circulating tumor cells are present in the blood of post-treatment cancer patients sometimes even *decades* later! Perhaps the niches that regulate prolonged dormancy of tumors are dynamic and inhibit tumor proliferation while allowing them to mobilize periodically, much like for HSCs. It also stands to reason that loss of the same controls

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that prevent HSC expansion until systemic damage occurs could awaken dormant tumors.

Shiozawa et al. (2011) have demonstrated that prostate cancer cells do in fact compete with HSCs for niches within the bone marrow, and that tumor cells are mobilized from HSC niches by similar mechanisms as for HSCs. Whether this is the case for other cancers and whether these similarities can be exploited therapeutically remain to be seen.

So what more is there to be learned about immune cells? By furthering our understanding of how solid cancers mimic and hijack components of our immune system, we may not “cure”

cancer, but we very well may uncover a means to suppress some cancers into a state of permanent dormancy.

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