

## Commentary

# Defining microenvironments within mouse models that enhance tumor aggressiveness

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In 1889, Stephen Paget surmised that tissue microenvironment impacts tumor cell behavior in his “seed and soil hypothesis”.<sup>1</sup> Here he speculated that particular cancers (the seed) exhibit distinctive affinity for the *milieu* of particular organs (the soil) during metastatic spread. In doing so, he essentially proposed that the different anatomic sites possess or lack growth and survival advantages for tumor cells and thus can actively shape their phenotype. Since then, the components thought to contribute to the tumor microenvironment have grown to include fibroblasts, inflammatory cells, vasculature, growth factors, cytokines, chemokines, proteases and a host of other molecules.<sup>2</sup> Tumor cells actively shape this environment, participating in a complex and bidirectional interaction with these elements.

The balance between innate cancer cell traits and their tissue microenvironment can profoundly alter malignant behavior. Specifically, this crosstalk can determine whether a given tumor becomes highly invasive and metastatic, remains confined to local growth, stays dormant or regresses altogether. An early illustration of this microenvironment-based plasticity came in 1975 when Mintz and Illmensee used a mouse embryonic blastocyst environment to suppress the malignancy of teratocarcinoma cells, reprogramming them to give rise to normal tissue.<sup>3</sup> Such embryonic *milieus* provide striking experimental examples of how a microenvironment can imprint a new phenotype on neoplasms.<sup>4</sup>

Cancer cell lines grown in inbred mouse strains are a mainstay in the study of malignancy, but such models do not faithfully mimic some aspects of the tumor-microenvironment interaction. These models belong to two broad groups: ones using syngeneic mouse tumor cells in immunocompetent mice and those based on xenografted human cells in immunodeficient mice. Following the first

xenografting into athymic nude mice in 1968,<sup>5</sup> immunodeficient mouse strains have become heavily utilized for the pre-clinical testing of cancer therapies. Xenograft tumors retain many biologic features of human cancers; for instance, they can better mimic the gene expression profiles of their human *in vivo* counterparts relative to their *in vitro* cell lines of origin.<sup>6</sup> However, xenograft models also fail to recapitulate certain important aspects of human cancer. The murine host environment produces numerous molecular incompatibilities with human tissues whose overall impact on tumor behavior is difficult to quantify. Another source of error is absence of a specific immune system, which may alter the subpopulations of tumor cells which predominate. For such reasons, therapeutic interventions showing efficacy in preclinical xenograft models are frequently ineffective in clinical application.

Murine syngeneic models provide more compatible microenvironments than xenografts but lack other key features of human tumors, including the constellation of oncogenic mutations seen in patients. Furthermore, both xenograft and syngeneic models are derived from established cell lines and not primary tumor tissues and thus have accumulated additional genetic abnormalities conducive to rapid *in vitro* growth. A final limitation common to both model types is that the subcutaneous microenvironment is most commonly used instead of other sites that might better reflect a tumor's original growth and metastatic features.

In this issue of *Cancer Biology & Therapy*, Speroni et al. explore the question of the engraftment site as a determinant of tumor histology and biologic behavior.<sup>7</sup> Here the mouse dorsal foot is compared to the more conventional flank subcutaneous site using syngeneic mouse tumors derived from MC-C fibrosarcoma and B16F0 melanoma cell lines. For both tumors, the dorsal foot microenvironment conferred a greater inflammatory response and decreased local growth relative to the less reactive subcutaneous site. Foot implantation also increased tumor vascularization, decreased necrosis, produced a more aggressive histologic pattern, facilitated lung metastasis and decreased survival. The authors conclude that the microenvironment of the dorsal foot is a useful experimental tool in allowing tumors to display their whole biologic potential.

An established basis exists for the combined association of increased inflammation, angiogenesis and enhanced tumor progression seen in this model. Inflammation and angiogenesis are closely related processes, sharing growth factors, cytokines, adhesion molecules, proteases and other factors in common.<sup>8</sup> Furthermore, the

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recruitment of inflammatory cells is well known to support aggressive tumor behavior. In particular, macrophages play a physiologic role in wound healing by participating in matrix remodeling and tissue repair, in addition to secreting pro-angiogenic factors. In the tumor microenvironment, these functions are exploited by malignant cells to support growth, angiogenesis and invasion. Despite the lack of specific immunity in immunodeficient models, their preserved macrophage function raises the possibility that the dorsal foot has properties as tumor microenvironment for xenografts similar to those shown in the syngeneic models here.

Ultimately, the dorsal foot may prove a valuable surrogate to orthotopic implantation, which has also been shown to facilitate tumor progression and metastasis but comes with greater technical challenge in accessing and monitoring the implant site.<sup>9</sup> If so, greater experimental use of this site for tumor grafting may prove a valuable tool in modeling the biologic behavior of a variety of malignancies and assessing their responses to therapies.

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