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Tumor microenvironment: a mechanical force link

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The tumor microenvironment is created by tumor cells and molded by infiltrating immune cells. Both adaptive immune cells like T cells and B cells and innate immune cells such as macrophages, dendritic cells (DC), NK cells, granulocytes, mast cells and immature myeloid cells are brought together to form a tumor immune microenvironment [1]. Although it is virtually taken for granted that the entry of immune cells to tumor microenvironment is a mechanistic process involving chemotaxis and extravasation, blood vessels are indeed a matter. And their real role in this process is much complex than what we generally think at present [2].

Tumor blood vessels formed by angiogenesis or vasculogenesis show marked differences from normal blood vessels with respect to both their structure and function [3]. Structurally, tumor blood vessels are tortuous and dilated, and they are distributed very heterogeneously with many areas lacking vasculature [4]. Moreover, tumor blood vessels lack adequate pericytes coverings. Pericytes are located around endothelial cell junctions and form umbrella-like structures that cover endothelial gaps and maintain endothelial integrity. Functionally, blood vessels are hyperpermeable and blood flow is at times insufficient due to patchy hypoperfusion and leakage out of the blood vessels. Structural and functional abnormalities of tumor blood vessels result in hypoxia, acidity and high interstitial fluid pressure [5]. The hypoxic microenvironment stimulates the release of VEGF and the latter in turn further exacerbates the endothelial permeability, leading to more blood leakage and worsening interstitial hydrostatic pressure. Tumor interstitial pressure inevitably becomes a strong external force to prevent immune cell entry. Therefore, an alternative strategy of targeting tumor vasculature, different from the current blockade one, is to ameliorate the formation of tumor vascular networks, with normalized tumor blood vessels [6]. Normalized blood vessels will likely permit more cytotoxic immune cells to leave vessels and access to tumor parenchyma. A greater awareness of the concept of vessel normalization will further stimulate interests in studying this process.

Interstitial fluid homeostasis is normally maintained by lymph vessels collecting and transporting extracellular protein-rich fluid back to the hematic circulation [7]. High interstitial pressure plus hypoxia significantly up-regulates the expression of VEGF-A, C and D in tumor microenvironment. In turn, all these growth factors have the ability to induce tumor lymphangiogenesis. Compared to hematic flow, lymph flow may be much friendlier for tumor cell survival, due to its slow speed and absence of shear stress. Accordingly, lymphangiogenesis in tumor microenvironment is thought to promote tumor metastasis, leading to the adaptation of blockage of lymphangiogenesis as a new weapon against tumor metastasis [8]. Although it may well inhibit, blocking lymphangiogenesis may also aggravate the interstitial fluid pressure. Thus, a too strong interstitial pressure may seriously prevent the extravasation of cytotoxic CTLs, NK cells and other immune cells that attack tumor cells. Even higher increased interstitial fluid pressure might facilitate tumor cells to intravasate tumor vessels for hematogenous metastasis. Chronic inflammation drives tu-

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mor initiation, progression and metastasis. Targeting tumor inflammatory microenvironment by non-steroid anti-inflammatory drugs, neutralizing antibodies of inflammatory cytokines and small compounds against inflammation pathways have shown promise in tumor therapeutics. Blocking lymphangiogenesis may impede inflammation resolution, leading to worsened inflammation and tumor-promoting results. In other words, targeting tumor lymphangiogenesis may well increase lymphangiogenesis rather than decrease it.

Interstitial fluid pressure not only influences immune cell infiltration and tumor inflammation, but also changes tumor physical microenvironment. Tissue stiffness profoundly affects tumor cell behavior via biomechanical signaling pathways. This mechanical force is generated by the interaction between the extracellular matrix and cells and transduced by integrins on the cells and their downstream microfilaments. It has been demonstrated that soft matrices (low density) are required for tumor stem maintenance and promotion of tumor-repopulating cell growth; and stiffness matrices may promote the proliferation of differentiated tumor cells [9]. Interestingly, tumor tissue stiffness is very heterogeneous. Solid tumors are usually stiffer than their normal counterparts, also stiffer than immune organs such as bone marrow, spleen and lymph nodes. When immune cells migrate from soft immune organs to stiff tumor tissues, whether and how the altered mechanical signaling influences those immune cell functions remain unclear. We found that different matrix stiffness indeed conferred different phenotype and function in macrophages (unpublished data). When looking at tumor physical microenvironment, besides tissue stiffness, there are also compressive forces that need to be considered. In fact, tumor compressive forces are probably mainly generated by interstitial fluid pressures. Because of the heterogeneous distribution of tumor blood vessels, interstitial fluid pressures vary in different parts of tumor tissue, leading to heterogeneity of compressive forces in a tumor. Because of the effect of compressive forces on neighboring matrix stiffness, interstitial fluid pressure may influences both compressive forces and tissue stiffness, thus remodeling the tumor physical microenvironment. Intriguingly, the application of compressive forces to embryonic stem cells results in auxetic nuclei [10]. Although the underlying mechanism is unclear, it is reasonable to speculate that compressive forces induce DNA from condensed form to a loosened form, leading to auxetic nuclei. If it is true, asymmetric compressive forces also regulate gene expression. Therefore, interstitial fluid pressure is not a simple physical barrier for immune cell infiltration and inflammation resolution. It also affects tumor cells and immune cells through regulating their pulling and compressive forces. To date, understanding the influence of tumor physical microenvironment on tumor-infiltrating immune cells remains completely unclear. Probably, now is the time to pilot this new area of tumor immunology.

Currently, adaptive cell therapy (ACT) against cancer is an emerging field that shows promise in clinical trials. Advances in cell engineering and culture approaches make it to become a reality that chimeric T cell antigen receptor (CAR) T cells and tumor-specific T cells from TILs and PBMCs can be generated abundantly *in vitro*. However, these tumor-killing cells have to face high tumor fluid pressure-mediated entry barrier after adoptive transfer. Nevertheless, although normalizing tumor vasculature by low dose either anti-VEGFA antibody or radiation enhances the entry of adoptively transferred T cells, it is possible the combination of lymphangiogenesis-promoting method further supports T cell entry into tumor. On the basis of the above analysis, we propose that the tumor vasculature is at the center of tumor microenvironment and act as a link between the tumor immune microenvironment and tumor physical microenvironment. The reciprocal interactions among tumor vasculature, immune microenvironment and physical microenvironment are summarized in a schematic (Figure 1). Elucidation of their cellular and molecular mechanisms must provide deep insight into new strategies on tumor therapeutics.

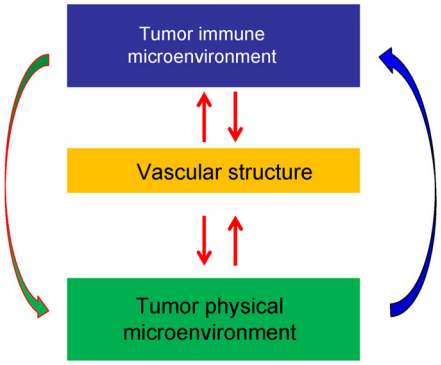

Figure 1 Interactions of vasculature, immune microenvironment and physical microenvironment in tumor.

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