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Tumor microenvironment, a dangerous society leading to cancer metastasis. From mechanisms to therapy and prevention

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Abstract Cancer is no longer considered by scientists just a jumble of mutated cells. To grow, invade and metastasize, a treacherous society between cancer and host cells must be formed, and this association provides novel and effective clinical targets for cancer control and prevention. This collection of reviews at the front-edge of scientific knowledge focuses on host–tumor cell interactions, the disastrous consequences they can produce and approaches the ways to break up these cellular conspiracies, to leave the tumor cells unattended and vulnerable.

1 Introduction to the special issue

The success of Bevicuzimab in the clinic has contributed to change the traditionally tumor cell oriented focus of the clinical oncologist, having demonstrated that tumors need host components in order to grow. This paradigm is basically true for many targeted therapies reaching clinical practice. Novel regimens, as well as novel side effects to be taken in account, foster the knowledge that "there is a body surrounding the tumor" and that we are entering a new era. For many years the pathologist looked at the tumor mostly as a proliferative mass without paying a great deal of attention to the surrounding tissues, cellular components and stroma. Over recent years it has became increasingly clearer that the tumor microenvironment plays a pivotal role in cancer development and progression.

In particular, components of innate immune system are one of the driving forces during tumor angiogenesis. They release several chemokines and cytokines that on one hand promote the immune-response against the tumor, while on the other hand they can lead to the stimulation of endothelial cells and consecutively to tumor angiogenesis.

Host cells, including endothelial and the pericytes that surround the vasculature, are required by the expanding tumor tissue, and the inflammatory infiltrate components more recently have been recognized as providing support and immune-suppression that favour the constant tissue remodeling within the tumor site.

Recent studies have shown how several anti-inflammatory agents may have remarkable results in cancer prevention. Our laboratory, for instance, while investigating the effect of chemopreventive compounds noticed how their activity was tightly correlated with inflammatory processes, angiogenesis and the microenvironment. Several of these agents are able to affect the nuclear factor B pathway that is known to be a main molecular hub in inflammation. Now that it is widely recognized that tumor microenvironment and its inflammatory components are crucial in cancer progression it has become more evident that targeting the microenvironment is a promising therapeutic approach in cancer treatment.

In this issue we take this topic well beyond vessels and inflammation and delve into the reasons and risks of the principal clinical problem of metastasis. Several articles, in particular the review of *Lisa Coussens*, provide overviews on the evidence that cancer subverts much of the immune system to its own favor, from tumor angiogenesis to metastases formation. Here we describe a close synergy between cancer cells, leukocytes (as commented by *Douglas Noonan*) and receptive niches in distant sites, where it becomes clear that tumor cells alone are not sufficient to form metastases. *Isaac Witz*, the founder of the TUMIC-International Cancer Microenvironment Society, introduces the role of selectin–

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selectin ligand interaction as an "axis of evil" in the promalignant factors, while *Paolo Comoglio* describes and example of tyrosine kinase-growth factor dangerous alliance.

The article of *Marie-France Poupon* suggests that metastases could occur in waves of tumor cell colonizations, where "non-metastatic" tumor cells may mix with their metastatic cousins in the prepared niche, perhaps again creating subversive societies of mutual gain at the expense of the host. *Francesco Bertolini* discusses how circulating endothelial markers may provide a key insight into monitoring tumor therapy efficacy host microenvironment. Insights into the complexity of select specific weapons such as tissue inhibitors of metalloproteinase are provided by *Bill Stetler-Stevenson*. We also know that certain organs have a microenvironment more "appealing" than others for metastatic seeds: this is the topic addressed by *Andrea Mastro*.

Genetic analyses delve into genes potentially regulating metastasis and the close relationship of these gene products in modulating cancer–host information exchange. Metastasis signatures regulating the microenvironment are reviewed by *Ulrich Pfeffer* while *Carrie Rinker-Schaeffer* reports on metastasis suppressor genes, as controllers of tumor–host relationships.