Preface

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We hereby present an additional collection of reviews dealing with regulatory mechanisms that are operative in the tumor microenvironment. This collection deals with facets of the tumor microenvironment that have not yet been discussed in the reviews series of Cancer Microenvironment. Vogt Sionov et al., discuss the heterogeneous neutrophil subsets in the malignant process. Traditionally, neutrophils have been associated with promotion of inflammation and concomitantly with increased progression and metastasis. However, under certain conditions, neutrophils were shown to kill breast cancer cells that metastasized to the lungs. This group described two major subpopulations of neutrophils with opposing activities: N1 neutrophils manifest anti-tumor activity mediated through tumor cell killing and N2 neutrophils show pro-tumor activities. These two neutrophil subsets jointly operate in the tumor microenvironment; understanding the conditions and mechanisms of their recruitment and activation are discussed. Vannucci describes changes in the fibrous collagen stroma that occur during carcinogenesis and highlights their importance in the malignant process. As a 3D structure, the fibrous stroma serves as a scaffold for cell-to-cell and cell-to-matrix interactions. Understanding the relationship of structure/function of collagen matrices lead to a better understanding of the interactions among the various cellular components of the microenvironment, among themselves and with the matrix. Rigoni et al., have discussed the role of mast cells in shaping the tumor microenvironment. Mast cells have been best

characterized in the context of allergies; in the context of the tumor microenvironment they are considered as relatively newly-described “plays”, with pleiotropic functions affecting the outcome of the malignant process. Mast cells affect the tumor microenvironment through interactions with immune cells, the malignant cells and the ECM. Better understanding the role of mast cells in the tumor microenvironment, may lead to mast cell-based therapies aimed at directly killing tumor cells or sensitizing vulnerable tumor cells to other therapies. Giakoustidis et al., have described the role of myeloid cells, especially tumor-associated macrophages (TAMs) and also myeloid-derived suppressor cells in the metastatic pathways of primary colorectal cancer to the liver. The distinct function of TAM subsets, such as M1 and M2, in the malignant process is emphasized. Theresa Whiteside’s review describes the state of the art knowledge on T regulatory cells (Tregs) in human cancer and in HIV infection. In the milieu of tumors, Tregs inhibit the differentiation/function of adaptive immunity cells and retain tolerance against tumor-associated antigens. Tregs are also plastic cells in their differentiation pathways, which is interconnected to that of Th17 precursor cells and the direction of differentiation depends on the local cytokine milieu in the tumor microenvironment. Thus, this review focuses on the diverse and very potent effects of Tregs in the malignant process. Better characterization of human Treg cells and understanding their diverse biological functions should facilitate the development of pharmacological means to intervene in their function. Lastly, Voronov and Apte have discussed the role of the IL-1 agonistic molecules in colon inflammation and its progression to colorectal cancer (CRC). It was shown that IL-1 α is constitutively expressed in colon epithelial cells in its unprocessed precursor form (Pro IL-1 α), which is released into the microenvironment upon necrotic tissue death, as occurs during colon inflammation, when the epithelial barrier of the colon is destroyed.

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Subsequently, Pro IL-1 α acts in the microenvironment as an alarmin and activates IL-1R signaling in diverse cells in the microenvironment. This leads to the secretion of pro-inflammatory cytokines, cell infiltration and amplification of the local inflammatory response. On the other hand, IL-1 β activates healing of the damaged epithelium; in its absence, a non-healing colitis develops. Studies are in progress to characterize how these major IL-1R agonists act during distinct phases of colon carcinogenesis or invasiveness of colorectal cancer (CRC). Understanding the mechanisms of action of the major IL-1 agonists in different phases of the malignant process may lead to the use of IL-1 neutralizing agents for cancer therapy. IL-1 neutralizing agents are already FDA-approved

and are used in the clinic for Rheumatoid arthritis and other diseases with an inflammatory component.

Altogether, these reviews provide important data on cells, cytokines and structures in the tumor microenvironment. In addition, they present the functional complexity of these entities, which is possibly context dependent. Further understanding how the different components of the tumor microenvironment interact among themselves to create specific growth patterns of the tumor is a challenge that still lies ahead of us.

We hope the readers will benefit from this collection of reviews.

Ron N. Apte and Elena Voronov