Chapter 6

MICROENVIRONMENT AND MESENCHYMAL STEM CELLS IN CANCER

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Introduction

Recent studies of progression, aggressiveness and metastatic ability of solid tumors have shown that genetic disruptions in cancer cells and molecular alterations as well as tumor microenvironment play an important roleInteraction between tumor cells and the microenvironment is key in initiation, progression, and invasiveness of cancer. Mesenchymal stem cells (MSCs) to migrate to the hypoxic regions such as tumor stroma, and settlement takes place depending on the biological feature of the tumor microenvironment (Balkwill et al., 2012, Butcher et al., 2009). MSCs are non-hematopoietic, multipotent cells, which are able to differentiate to bone, adipose and cartilage tissue. Migration of MSCs to the tumor site during carcinogenesis is due to soluble factors released from tumor cells. The most important cause of this migration is thought to be the chemotactic factors released from the tumor. MSCs contain large amounts of chemokine and cytokine receptors on their surface and respond to their ligands in vitro. (McAndrew et al., 2015). An increasing number of studies have reported that MSCs recruited to the tumor microenvironment play various roles in tumor cell development and tumor progression. The development of novel therapeutic approaches targeting the different functions of MSCs in promoting tumor progression as well as the mechanisms underlying their activities could enhance the efficacy of anti-cancer therapies. Furthermore, many studies report the use of MSCs engineered to express different genes or as vehicle to specifically deliver novel drugs to tumors exploiting their strong tropism. Importantly, this approach can enhance local therapeutic efficacy and reduce the risk of systemic side effects (Volarevic et al., 2018, Chulpanova et al., 2018). The communication of cancer cells in the tumor microenvironment with non-cancer cells and the metabolic changes they make in the microenvironment have serious consequences. The purpose of this review is to present the effects of metabolic changes occurring in this environment of communication pathways and interactions between cancer and MSCs in the tumor microenvironment.

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or suppressive effects of MSCs have led to discussions over the past decade. Although there are some studies suggesting that MSCs increase tumor formation (Galie et al., 2008, Yan et al., 2012), other studies report that MSCs can inhibit the progression of tumor (Khakoo et al., 2006, Cousin et al., 2009, Secchiero et al., 2010) This contradiction can be explained by the use of different tumor models, MSCs' functional heterogeneity, the MSCs derived from different sources (bone marrow-derived MSCs versus tissue-derived MSCs), the dose and timing of MSC injection, and the use of various mechanisms such as chemokine signals, vascular support, and immunomodulation (Klopp et al., 2011).

Although the presence and function of MSCs in the tumor microenvironment has not yet been fully understood, available information suggests that MSCs play an important role in the construction of the microenvironment, in the feeding of CSC/ Tumor-initiating cells, and in the support of epithelial cancer cells. Based on this information, targeting stromal components while targeting cancer cells may also enhance the effectiveness of cancer therapy. It is thought that it can be both a metabolic and stromal phenomenon that can be overcome by targeting the mitochondrial function in chemoresistant epithelial cancer cells. Therefore, targeting both tumor stroma and epithelial cancer cells at the same time may be a successful approach to anti-cancer therapy. This general strategy for such combination therapy to come from the top of the drug resistance may be applicable to many different types of cancer.

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