Chapter 5

THE ROLE OF IMMUNE CELLS IN THE TUMOR MICROENVIRONMENT

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Abstract: Interactions between tumor infiltrating leukocytes and tumor cells have been of great interest because of the possibility that immune cells either interfere with tumor progression or actively promote tumor growth. The tumor microenvironment is shaped by cells entering it, and their functions reflect the local conditions. Successive changes occurring at the tumor site during tumor progression resemble chronic inflammation. This chronic inflammatory reaction seems to be largely orchestrated by the tumor, and it seems to promote tumor survival. Molecular and cellular mechanisms linking the inflammatory reaction and cancer are emerging, and this review summarizes the current understanding of interactions between inflammatory and cancer cells in the tumor microenvironment.

Keywords: TIL; immune evasion; immune surveillance; inflammation; cancer
1. INTRODUCTION

Tumor development involves multiple genetic changes, which occur in the progeny of the transformed cell over many years, accumulate and result in the establishment of a malignant phenotype characterized by uncontrolled growth (Zhang et al., 1997). In parallel, a variety of alterations occur in surrounding normal tissues, leading to establishment of the tumor microenvironment. These changes are necessary to assure survival of the tumor at the expense of surrounding normal tissue cells. To meet tumor requirements and sustain its growth, several successive stages of changes have to occur in the tumor microenvironment. In many respects, the tissue changes arising in response to tumor formation resemble the unfolding process of chronic inflammation. Inflammation is a normal component of wound healing or tissue repair. In fact, tumors have been described as wounds that do not heal (Dworak, 1986). Inflammation, when it occurs, generally consists of the initial ischemia, resulting in the interstitial and cellular edema (an immune reaction associated with appearance in tissue of immune cells) and, finally, the appearance of blood capillaries and lymphatics necessary for feeding of the repaired tissues (Ribatti et al., 2003; Aller et al., 2004). These phases of inflammatory response progress from an anaerobic tissue environment (ischemia) to the development of oxidative metabolism, which uses oxygen to produce energy in the form of ATP (Mareel and Leroy, 2003; Balkwill and Mantovani, 2001). Inflammation appears to be a ubiquitous tissue response common to many normal conditions, including embryonic development, as well as disease states. Its involvement in shaping the tumor microenvironment has been recognized, and it has been referred to as the “host reaction” to the tumor.

The tumor appears to be able to induce an inflammatory response in the host early on, because the presence of immune cells has been noted even in pre-cancerous or benign lesions (Kornstein et al., 1983; von Kleist et al., 1987; Vacarello et al., 1993). This has been interpreted as an attempt of the host immune system to interfere with tumor growth, otherwise referred to as “immune surveillance”. However, the developing tumor is not a passive participant in this interplay. On the contrary, it takes advantage of the host response in order to: (a) use immune cells for elimination of sensitive tumor cells and their gradual replacement by those resistant to immune intervention (“immune selection”) and (b) use the host as a participant in creating the microenvironment favorable to tumor progression (“immune evasion”). To this end, lymphocytes, macrophages and dendritic cells (DC) infiltrating the tumor, together with fibroblasts and extracellular matrix forming a scaffold supporting its expansion, contribute to establishing an inflammatory milieu that nourishes the tumor. Thus, the host becomes a participant in the