INTRODUCTION

Tumors arise as a result of oncogenic transformation, and their progression involves multiple genetic changes, which occur and accumulate in the progeny of the transformed cell over many years [1]. A malignant phenotype established as a result of this series of genetic changes is characterized by uncontrolled growth of transformed cells and their progeny [1]. In parallel, a variety of alterations occur in the surrounding normal tissues, leading to establishment of the tumor microenvironment. These alterations are necessary to accommodate tumor growth and to assure survival of the tumor at the expense of surrounding normal tissue cells. Local tissue response to tumor progression resembles the process of chronic inflammation. Inflammation is a normal component of wound healing or tissue repair. Several years ago, H. Dworak described tumors as wounds that do not heal [2]. Inflammatory reaction is initiated by ischemia, which is followed by the interstitial and cellular edema associated with an appearance in tissue of inflammatory cells, including lymphocytes responsible for mediating an immune reaction and for tissue repair. Finally, a network of blood capillaries and lymphatics necessary for feeding of the repaired tissues is established [3,4]. These phases of inflammatory response progress from an anerobic tissue environment (ischemia) to the development of oxidative metabolism, which uses oxygen to produce energy in the form of ATP [5,6]. Inflammation is a ubiquitous tissue response common to many normal conditions,
including removal of pathogens, embryonic development or tissue re-structuring. It also is a major component of many disease states. Inflammation associated with tumor development is referred to as the “host reaction” to the tumor, and its involvement in shaping the tumor microenvironment has been well recognized.

The tumor appears to be able to attract inflammatory cells early on, and the presence of immune cells in pre-cancerous or benign lesions has been interpreted as an attempt of the host immune system to interfere with tumor development [7–9]. “Immune surveillance” refers to the ability of the host to recognize a danger signal, in this case an incipient tumor, and mount a response designed at its elimination. This implies that the host’s immune system can survey, detect and destroy tumor cells, thus preventing tumor progression. However, it appears that tumors progress despite immune surveillance, and thus considerable skepticism has developed about the role of the immune system in the control of tumor growth. Based on the notion that the developing tumor is not a passive target of immune intervention but rather an active participant, the current view is that tumors take advantage of the host response in order to orchestrate their escape. As tumor cells sensitive to immune effector mechanisms are eliminated, others that are resistant to immune intervention expand and replace the sensitive targets. “Immune selection” of resistant tumor cells is one way to assure that only the fittest (i.e., most resistant) tumor cells survive, and to this end, the host immune system is used as a tool for selection, so that it subserves the tumor and not the host. In addition, once selected for resistance, tumor cells also become adept in using a variety of immunosuppressive mechanisms to engineer an escape from the host-mediated anti-tumor effects, a process termed “immune evasion.” As a result, the tumor either disables the host immune system or manipulates it to create a local microenvironment favorable to tumor progression. To this end, the host becomes a participant in the establishment and maintenance of the tumor by providing structural and trophic elements required for cancer progression. 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.

The objective of this chapter is to review the role of immune cells in the tumor-host interactions. This topic has been highly controversial in the past, because immune cells accumulating at tumor sites or those present in tumor-involved lymph nodes (LN) may be activated to exercise anti-tumor responses or may be profoundly suppressed by tumor-derived factors [10]. The capabilities of these immune cells to eliminate tumor targets or to serve as a source of growth factors for the tumor are likely to depend on the local milieu established by the tumor.

**IMMUNE CELLS IN THE TUMOR MICROENVIRONMENT**

Local or locoregional immune responses to malignant cells are mediated by tumor infiltrating lymphocytes (TIL), which accumulate in many human solid tumors and whose role in tumor progression remains controversial; lymphocytes present in