Chapter 16
The Tumor Microenvironment

Regulation of Antitumor Immunity
and Implications for Immunotherapy

George Coukos
and Jose-Ramon Conejo-Garcia

SUMMARY

After more than 30 yr of crusading against cancer, targeting mostly the tumor cell cycle, the need for novel therapeutic strategies has become increasingly clear. Survival and expansion of tumor cells cannot be achieved in the absence of a favorable microenvironment, the main components of which are leukocytes, vascular cells, and fibroblasts. This tumor microenvironment critically provides growth factors and survival signals for tumor cell proliferation, secretes angiogenic factors that control tumor vascularization, and directs invasion and metastasis through adhesion molecule interactions. In addition, a successful antitumor immune response is prevented by multiple mechanisms of evasion orchestrated by nontumor cells. Understanding how the tumor microenvironment modulates the immune response is vital to designing new potential ways of boosting anticancer immunity. This chapter is focused on providing a rationale for new prospects of manipulating the tumor microenvironment to minimize escape from natural anticancer immune response and targeted immunotherapies.

Key Words: Neoplasm; vascular endothelial growth factor A; lymphocytes; tumor infiltrating; cytokines; immunotherapy.

1. INTRODUCTION

It is now generally accepted that tumor cells express unique antigens that are recognized by the immune system (1–3). These can be differentiation antigens, also expressed by embryonal cells but not by adult normal cells; overexpression/amplification antigens, also expressed by normal cells but at levels that are too low to induce an immune response under physiological conditions; and newly acquired mutational antigens, resulting from mutations associated with the oncogenic process. In addition, select tumors express viral xenoantigens. CD45+ leukocyte infiltration is detectable in most tumors. The presence of tumor-infiltrating T-lymphocytes has been shown to correlate with clinical outcome in vertical-growth-phase melanoma, as well as in ovarian, breast, prostate, renal cell, esophageal, and colorectal carcinomas (4–10). In ovarian cancer, for example, CD45+ cells represent up to 45% of total cells in many specimens (11), and T-cells are detectable
within tumor cell islets, in surrounding stroma, or both (4). Yet, established cancers represent failures of immune surveillance (12). A number of soluble, as well as membrane-bound, molecules have been isolated by tumor cells and have been postulated to mediate immune evasion, including immunosuppressive growth factors and cytokines such as vascular endothelial growth factor (VEGF)-A, transforming growth factor (TGF)-β, interleukin (IL)-10, prostaglandin E2, death ligands to the tumor necrosis factor (TNF) receptor family, such as Fas (CO95) ligand and TNF-related apoptosis-inducing ligand (TRAIL), ligands to the negative regulator cytotoxic T-lymphocyte-associated molecule (CTLA)-4, and the programmed death receptor ligand 1 (DD-L1) (12,13).

In addition to the presence of tumor cells, solid cancers are composed of host cells including inflammatory leukocytes, a variety of stroma cells, and vascular endothelial cells and pericytes. This microenvironment influences in a critical manner tumor growth, invasion, and metastasis. Emerging evidence indicates that it also plays a central role in regulating immune recognition and attack of tumors.

As tumors establish themselves, complex interactions are developed between tumor cells and the host. It has been proposed that antitumor immune mechanisms edit the tumor (12), promoting the expansion of tumor clones that can survive—and benefit—from the surrounding inflammation. In turn, tumor cells edit their microenvironment by influencing the expression of growth factors, cytokines, and chemokines that establish combinatorial signals in the tumor, which ultimately regulates the pattern of infiltration of inflammatory cell subtypes and endothelial cell precursors. Tumor cells also modify the function of host cells, inducing the production of factors that promote tolerance and angiogenesis. Until recently, “nontumor” host cells were thought to be normal diploid cells that do not acquire mutations. This concept has been recently challenged by reports showing the presence of the same chromosomal aberrations in endothelial cells and surrounding tumor cells in lymphomas (14), as well as loss of heterozygosity in stromal cells from solid tumors (15–17). These new findings, together with a revival of the immunosurveillance theory and the failure of antitumor therapies focused exclusively on inhibiting the proliferation of tumor cells, have made the role of the tumor microenvironment the subject of intensive research in the last few years. Understanding how the tumor microenvironment modulates the immune response is vital to designing new potential ways of boosting anticancer immunity. This chapter is focused on new prospects of manipulating the tumor microenvironment to minimize tumor escape from anticancer immune response.

2. EFFECTS OF THE TUMOR MICROENVIRONMENT ON ANTIGEN PRESENTATION

Dendritic cells (DCs) are viewed as critical regulators of adaptive immune responses, including those against tumors. DCs take up, process, and present antigens to naïve T-cells in major histocompatibility complex (MHC) class I- and/or class II-restricted fashion (18). DCs are now recognized as a diverse population of cells with remarkable plasticity, which exhibit different phenotypes that can elicit potent type 1 T-cell stimulation, promote type 2 responses, or induce T-cell tolerance, depending on lineage and environmental instructions (18–20). Although DC-based vaccine therapies are generally viewed as systemic, it is now understood that the antigen-presenting function of DCs is severely compromised in patients with cancer, not only within the tumor microenvironment, but also systemically (21–23).