CHAPTER 4

BASIC CONCEPTS IN GLIOMA IMMUNOLOGY

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Abstract: Glioblastomas are the most common primary central nervous system tumor and typically have a dismal prognosis. Immunotherapy has been a promising experimental treatment. Understanding brain tumor immunobiology is critical to designing glioblastoma immunotherapies. In this chapter, we review aspects of basic immunology and neuro-immunology. The antigenic underpinnings of brain tumor immunotherapy including glioma-associated and glioma-specific antigens are discussed. Finally, the molecular and cellular facets of glioma-mediated immunosuppression are outlined. The role of multiple cell types (glioma cells, glioma-infiltrating monocytes, regulatory T cells and myeloid derived suppressor cells) in mediating local and systemic immunosuppression in glioma patients is evaluated.

INTRODUCTION

Glioblastomas are the most common and most malignant primary central nervous system tumors. Despite aggressive treatment with surgery, radiation and chemotherapy, average survival for glioblastoma patients remains only 14 months.1 More effective therapies are urgently needed. Immunotherapy (stimulating the immune system to attack the tumor) is one such promising therapy. Effective immunotherapy requires an understanding of the basic immunobiology of these tumors. In this chapter, we will review basic immunology and neuro-immunology and move on to a discussion of local and systemic glioblastoma immunobiology.

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BASIC IMMUNOLOGY

The immune system made up of the various cellular and visceral components involved in recognizing and eliminating foreign and/or dangerous antigens. Anatomically, it is made up of primary and secondary lymphoid organs. Functionally, it consists of both innate and adaptive immune responses. Innate immunity deals with antigen-nonspecific responses to foreign or dangerous molecules (Fig. 1). Some of this is accomplished at a purely molecular level with the complement system and systemic responses to inflammatory cytokines. At a cellular level, it is made up of macrophages, neutrophils and natural killer cells. Activation of innate immunity is not antigen-specific but is induced in response to molecular factors common to multiple infectious or dangerous agents termed pathogen-associated molecular patterns (PAMP’s) such as cytosine-guanine (CpG)-rich regions of bacterial DNA. Toll-like receptors (TLR’s) are often the receptors for PAMP’s and are key in unleashing innate immune responses.

In contrast to innate immunity, adaptive immune responses are antigen-specific. Foreign and/or dangerous antigens are scavenged from the environment, processed and presented by professional antigen presenting cells (APC’s) of the reticuloendothelial system, including dendritic cells and macrophages. APC’s form an important connection between adaptive and innate immunity. Adaptive immunity is comprised of humoral (antibody) mediated by B cells and cellular immune responses mediated by cytotoxic

Figure 1. Components of the innate immune system. Innate immunity can be defined as the cellular and molecular defenses in place prior to exposure to infection. The innate immune system includes physical barriers such as epithelial surfaces, phagocytic cells like macrophages and neutrophils, blood proteins such as the complement systems and other inflammatory mediators and natural killer lymphocytes. While aspects of innate immunity do respond to shared structures present on or in microbes and absent in mammalian cells, the repertoire of antigens recognized by innate immune mechanisms is relatively limited and there is no true antigen-specificity.