OncoImmunology 3, e27897; January 2014; © 2014 Landes Bioscience

Role of the complement system in NK cell-mediated antitumor T-cell responses

Valérie Janelle and Alain Lamarre*

Immunovirology Laboratory; Institut national de la recherche scientifique; INRS-Institut Armand-Frappier; Laval, QC Canada; Biomed Research Center; Department of Biology; Université du Québec à Montréal; Montréal, QC Canada

Keywords: cancer, complement, immunotherapy, melanoma, NK cells

The role of the complement system in oncogenesis and tumor progression remains poorly understood. We have recently demonstrated that the induction of a tumor-specific CD8+ T-cell response is improved upon transient inhibition of the complement system, which is coupled to an increased availability of natural killer cells. The complement system may therefore turn out to constitute a promising target for the development of novel anticancer therapeutics.

More than simply "complementing" innate immune responses, complement proteins play a role in cellular turnover, growth and regeneration. Moreover, activated complement proteins have been shown to mediate antineoplastic effects by promoting complement-dependent cytotoxicity (CDC) as well as antibody-dependent cell-mediated cytotoxicity (ADCC). Yet, a growing body of evidence suggests a dichotomic role for the complement system in tumorigenesis. In fact, the complement anaphylatoxins C3a and C5a have been shown to promote the overexpression of potentially oncogenic proteins such as phosphoniositide-3-kinase (PI3K), AKT1 and mammalian target of rapamycin (mTOR).[1] Moreover, overexpression of CD59, a membrane-bound regulator of the complement system found on various

becoming activated and producing pro-inflammatory cytokines.[3] NK cells mediate cancer immunosurveillance by killing MHC class I-deficient cells, which cannot be recognized by T lymphocytes, and by limiting the metastatic dissemination of malignant cells.[4] Furthermore, NK cells can crosstalk with dendritic cells (DCs) resulting not only in their own activation but also in DC maturation.[5]

Although a number of studies have explored the function of the complement system in various pathophysiological settings, its impact on oncogenesis and tumor progression remains unclear. We have recently set out to investigate the role of the complement system in a mouse model of melanoma, finding that transient decomplementation at the time of T-cell priming with cobra venom factor

secretion of transforming growth factor β1 (TGFβ1), which facilitates angiogenesis, invasion and metastasis, as well as to limit the expression of the β chain the interleukin-2 (IL-2) receptor and the secretion of interferon γ (IFNγ) by NK cells.[7] It has also been shown that the induction of complement component 5a receptor 1 (C5AR1) signaling in Toll-like receptor (TLR)-activated macrophages selectively inhibits the transcription of genes that encode IL-2 family cytokines. These cytokines play an important role in the activation and differentiation of distinct subsets of T cells as well as of NK cells. On the other hand, the clearance of apoptotic cells upon iC3b opsonization, which promotes phagocytosis upon binding to complement component 3 receptor (C3R), can be accompanied