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Review

Complement inhibition in cancer therapy

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ABSTRACT

For decades, complement has been recognized as an effector arm of the immune system that contributes to the destruction of tumor cells. In fact, many therapeutic strategies have been proposed that are based on the intensification of complement-mediated responses against tumors. However, recent studies have challenged this paradigm by demonstrating a tumor-promoting role for complement. Cancer cells seem to be able to establish a convenient balance between complement activation and inhibition, taking advantage of complement initiation without suffering its deleterious effects. Complement activation may support chronic inflammation, promote an immunosuppressive microenvironment, induce angiogenesis, and activate cancer-related signaling pathways. In this context, inhibition of complement activation would be a therapeutic option for treating cancer. This concept is relatively new and deserves closer attention. In this article, we summarize the mechanisms of complement activation on cancer cells, the cancer-promoting effect of complement initiation, and the rationale behind the use of complement inhibition as a therapeutic strategy against cancer.

1. Introduction

Cancer is a major public health problem causing millions of deaths worldwide [1]. In the United States, one in four deaths is due to cancer [2]. Breast cancer in females and lung cancer in males are the most frequently diagnosed cancers and the leading causes of cancer death for each sex (Fig. 1). Despite substantial advances in the chemotherapeutic management of cancer, more than half of all cancer patients do not respond to therapy or relapse, dying from metastatic disease. In addition, cancer chemotherapy is usually accompanied by severe side effects. These facts have led to the belief that in some tumor types, traditional therapies have reached a "therapeutic plateau" [3]. More personalized therapies with higher tumor specificity and less toxicity are a clinical need.

A variety of strategies based on the understanding of the molecular events associated with cancer initiation and progression are now under intensive investigation. In fact, some rationally targeted therapies have already shown a remarkable effectiveness in selected populations [4]. Targeted therapy refers to a new generation of cancer drugs designed to interfere with a specific target that is believed to have a critical role in tumor cell proliferation and survival. Most of these strategies are based on the identification of targetable signaling proteins critical for tumor growth or progression. Alternatively, cancer therapies directed at immune modulation have also been pursued, but with only modest advances to date [5,6]. A better understanding of the molecular interactions between tumors and the immune system should lead to better anticancer therapies. In this review we will present emerging data on the relationship between complement, an essential part of the innate immunity, and cancer progression. We will focus on the therapeutic potential of targeting complement activation in cancer, examining the rationale behind this strategy and the aspects that must be investigated before it can be considered an anticancer strategy that is ready for clinical testing.

2. The complement system

Complement has evolved as a first defense against non-self cells or unwanted host elements. The spectrum of complement-mediated functions ranges from direct cell lysis to the control of humoral and adaptive immunity. This system also regulates a number of immunological and inflammatory processes that contribute to body homeostasis [7]. Complement activities are mediated by more than 50 circulating or cell surface-bound proteins. There are three pathways of complement activation: the classical, the alternative, and the lectin pathways (Fig. 2). The three complement pathways differ in their mechanisms of target recognition but

Abbreviations: MAC, membrane attack complex; TGF-β, transforming growth factor β; TLR, toll-like receptor; MDSC, myeloid-derived suppressor cells; Tregs, regulatory T cells; AMD, age-related macular degeneration; C1-INH, C1 inhibitor.

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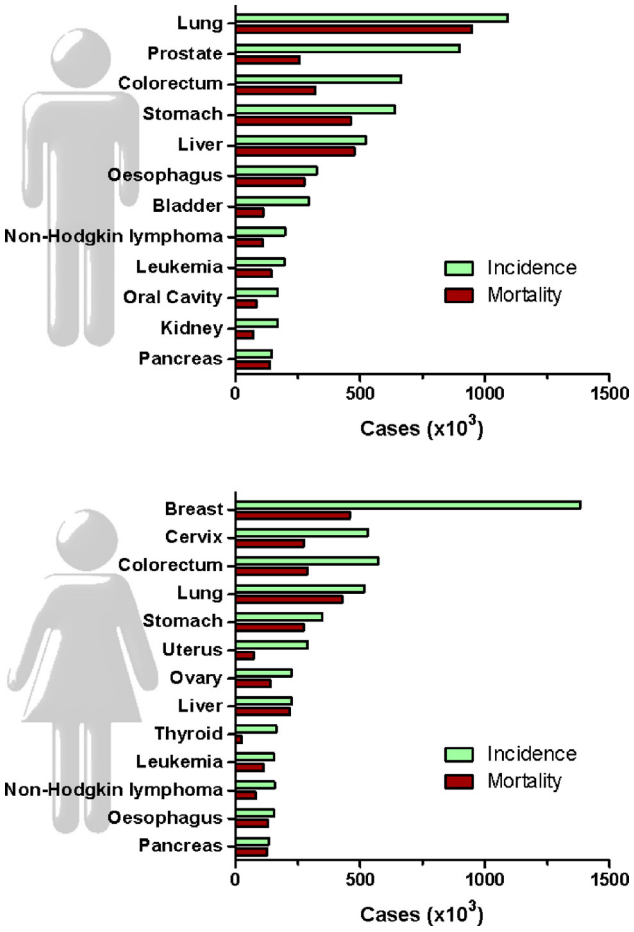

Fig. 1. Estimated new cancer cases (incidence) and deaths (mortality) for the leading cancer types worldwide in 2008.
Source: Globocan 2008 (http://globocan.iarc.fr/).

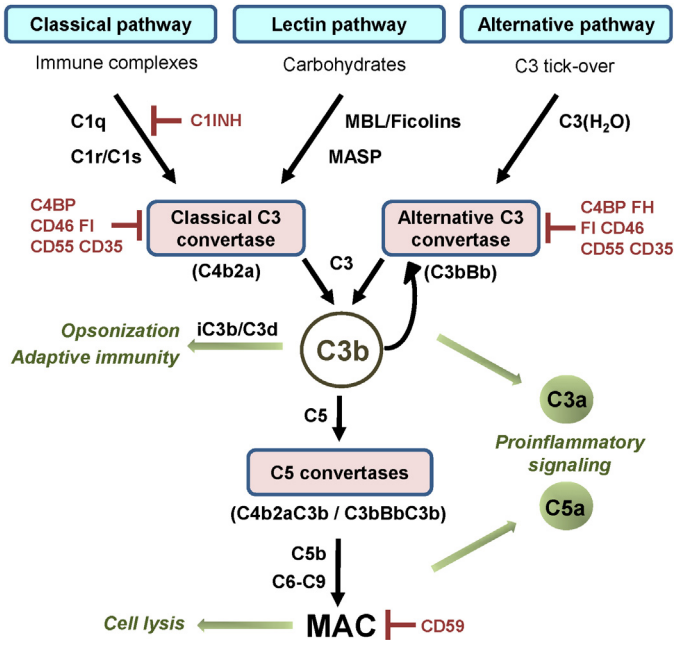

Fig. 2. Simplified scheme of the pathways of complement activation. Pattern-recognition molecules such as C1q, MBL (mannose-binding lectin), or ficolins bind to surface structures and initiate the formation of the classical C3 convertase. The alternative C3 convertase results from spontaneous hydrolysis of C3 (tick-over). C3 convertases cleave C3 into C3b and C3a. Deposition of C3b leads to the generation of additional C3 convertases (self-amplification) and the C5 convertase, which cleaves C5 into C5a and C5b. In the terminal pathway, interactions between components C5b, C6, C7, C8, and C9 lead to the formation of the lytic membrane attack complex (MAC). C3b and its degradation fragment iC3b participate both in phagocytosis and in adaptive immune response; the C3dg fragment is only involved in adaptive immune. The anaphylatoxins C3a and C5a trigger immune reactions upon binding to their receptors (C3aR, C5aR, and C5L2). Complement regulators prevent unwanted complement activation (C1INH: C1 inhibitor; C4BP: C4 binding protein; FI: Factor I; FH: Factor H).

converge in the activation of the central component C3. After this activation, C5 is cleaved, and the assembly of the pore-like membrane attack complex (MAC) is initiated. The enzymatic cleavage of C3 and C5 leads to the production and release of anaphylotoxins C3a and C5a, two important inflammatory mediators and chemoattractants [8]. Complement is tightly controlled by several proteins whose main function is to prevent activation. Complement inhibitors are grouped into two categories, soluble regulators and membrane-bound regulators. These regulators naturally protect self cells and tissues from unwanted complement activation [9].

3. Complement activation in cancer cells

Malignant transformation is accompanied by the acquisition of genetic and epigenetic alterations that distinguish the transformed cells from their normal counterparts. This process dramatically changes cell-surface proteins, glycosylation, and phospholipid patterns [10–15]. Cancer-related membrane modifications can be recognized by innate and adaptive immune mechanisms that protect the host against the development of cancer [16]. This is the basis of the immune surveillance hypothesis, which proposes that the immune system surveys the body for tumor-associated molecules, eliminating many, if not most, emerging tumors [17]. The immune surveillance activity is one of the three phases proposed in the inmmunoediting theory: elimination (immune surveillance), equilibrium, and escape [18]. If tumor cells are able to get pass the elimination phase, they enter an equilibrium period during which surviving tumor cells keep dividing and acquiring genetic and epigenetic abnormalities under the immunological pressure. This pressure contributes to the selection of tumor cell variants that are resistant to immune effectors. During the escape phase, tumor cells effectively evade the immune system.

There is no direct evidence to support the contention that complement can eliminate nascent tumors. However, considering that complement is designed for the recognition of non-self elements, it is logical to assume that changes in the composition of tumor cell membranes make these cells a target for complement recognition. Consistent with this assumption, a number of clinical studies have reported an activation of complement in cancer patients [19–23]. Indirect evidence for a role of complement in immunosurveillance also comes from the fact that cancer cells develop a variety of strategies to avoid complement-mediated damage [24]. Their best-known escape mechanism is the overexpression of complement regulatory proteins, a subject that has been extensively reviewed [25–29]. According to the immunoediting hypothesis, this overexpression is indicative of a selective pressure created by complement activation in the tumor microenvironment that sculpts cancer cells to evade the harmful effects of complement.

Other indirect evidence of complement activation by cancer cells comes from the increased complement activity found in biological fluids from cancer patients [30–34]. Complement activation has also been observed in *in vitro* studies of cancer cell lines. Lung cancer cells deposit C5 and generate the active product C5a more efficiently than do non-malignant bronchial epithelial cells [35]. However, the antigens responsible for this activation and the pathway/s involved are not yet known. The classical pathway has been identified as the main contributor to complement activation on