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The complement system in cancer: Ambivalence between tumour destruction and promotion

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ABSTRACT

Constituting a part of the innate immune system, the complement system consists of over 50 proteins either acting as part of a 3-branch activation cascade, a well-differentiated regulatory system in fluid phase or on each tissue, or as receptors translating the activation signal to multiple cellular effector functions. Complement serves as first line of defence against infections from bacteria, viruses and parasites by orchestrating the immune response through opsonisation, recruitment of immune cells to the site of infection and direct cell lysis. Complement is generally recognised as a protective mechanism against the formation of tumours in humans, but is often limited by various resistance mechanisms interfering with its cytotoxic action, now considered as a great barrier of successful antibody-based immunotherapy. However, recent studies also indicate a pro-tumourigenic potential of complement in certain cancers and under certain conditions. In this review, we present recent findings on the possible dual role of complement in destroying cancer, especially if resistance mechanisms are blocked, but also under certain inflammatory conditions—promoting tumour development.

Contents

1. Introduction

Discovered in 1896 by Jules Bordet and first named “alexine” by Hans Ernst August Buchner as a substance present in the serum to kill bacteria, Paul Ehrlich coined the term “complement” in the late 1890s for substances in serum “complementing” the function of what are now known as antibodies. The complement system is an important component of the innate immune system and is also relevant for the coordination of innate and

Abbreviations: CDC, complement-dependent cytotoxicity; MAC, membrane attack complex; mCRP, membrane-bound complement regulatory protein; siRNA, small interfering RNA; ADCC, antibody-dependent cellular cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; RTX, rituximab; OFA, ofatumumab.

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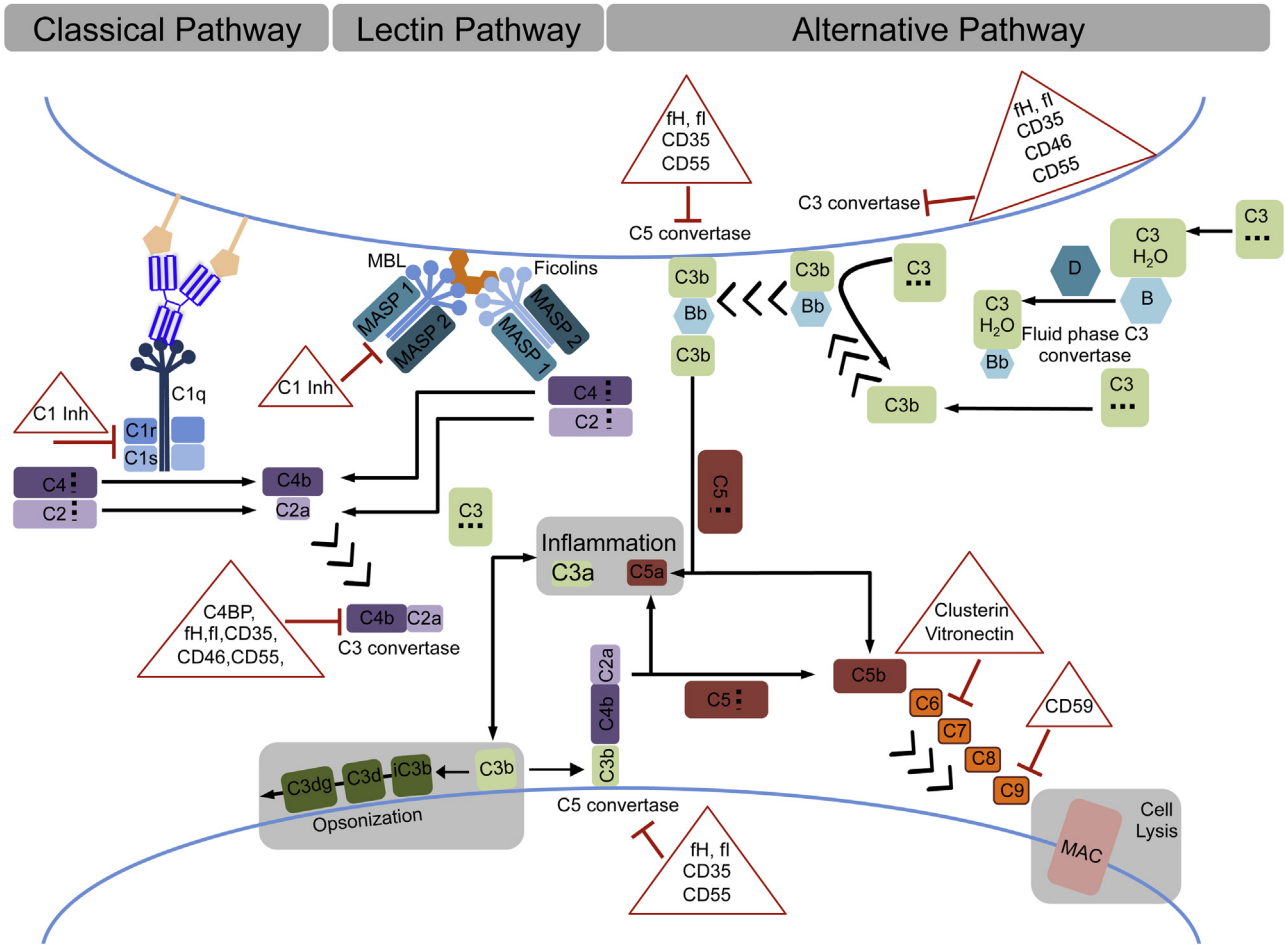

Fig. 1. Activation pathways of complement system. Activation of the complement cascade comprises the classical, lectin and alternative pathways. The classical pathway is induced upon binding of C1q to antibody-opsonised target cells. The lectin pathway is activated by MBL or by ficolins. The alternative pathway is induced by infections agents including bacteria, virus, and fungi. All pathways converge on the level of C3 and initiate the terminal pathway, which leads to the formation of the membrane attack complex (MAC), C5b-9. The anaphylatoxins C3a and C5a recruit immune cells to the site of inflammation. The complement cascade is tightly controlled by soluble and membrane-bound complement regulatory proteins (mCRPs) (triangles). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

adaptive immune reactions (Carroll, 2004; Ricklin et al., 2010; Walport, 2001a). As one of the most ancient parts of the immune system, present in evolution long before the development of adaptive immunity, it efficiently protects the host from pathogenic microorganisms, contributes to immune complex regulation and represents an important link between the innate and the specific immune system (Carroll, 2004; Kemper and Atkinson, 2007). Activation of the complement system occurs in a cascade *via* cleavage of inactive zymogens by serine proteases. Three activation pathways that are commonly distinguished are the antibody-dependent classical pathway as well as two phylogenetically older antibody-independent pathways, the alternative and the lectin pathways (Fig. 1). Apart from these well-characterised pathways, various modes of activation have recently been described (Doni et al., 2012; Huber-Lang et al., 2006; Spitzer et al., 2007). All three pathways converge on the level of C3 and continue with the formation of the terminal complement complex, either as fluid phase sC5b-9, or as pore-like membrane attack complex (MAC), when formed on the cell surface (Muller-Eberhard, 1986). During MAC formation, the C5b-9 complex is inserted into the cell membrane, leading either to cell destruction or, in sublytic doses, to cell activation (Morgan, 1989). Complement activation elicits a number of biological effects, such as cytotoxicity, opsonisation, phagocytosis, recruitment and degranulation of leukocytes, smooth muscle contraction, and an increase in vascular permeability (Walport, 2001b). Complement activation also induces proinflammatory conditions that affect cell surface molecules on both leukocytes and on endothelial cells. Thus, effector functions arising from complement activation may harm the host by inducing inflammatory tissue destruction. Complement activation links to antibody-dependent cellular cytotoxicity (ADCC) through the interaction of cell bound iC3b with complement receptor-3 (CR3, CD11b/CD18) on immune effector cells enabling complement-dependent cellular cytotoxicity (CDCC) (Elvington et al., 2012; Gelderman et al., 2004). The primary objective of this review is to discuss the role of complement in mAb-based immunotherapy of cancer. Here, we focus on complement resistance on tumour cells and discuss strategies for possible therapeutic intervention. We will also address the recent hypothesis on the role of complement cascade proteins in tumourigenesis.

2. Complement activation

The complement system has three main activation pathways the antibody-dependent classical pathway as well as the two phylogenetically older antibody-independent pathways, the lectin and the alternative pathway (Fig. 1). All three activation pathways con-