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Review

Recent progress in the understanding of complement activation and its role in tumor growth and anti-tumor therapy

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ABSTRACT

The complement system is indispensable in immune response, responsible for the wide range of immune surveillance, clearance and defense. Its activation, regulated by several crucial factors, is an important prerequisite for its role in tumor growth and anti-tumor therapy. Membrane attack complex (MAC) and anti-tumor anaphylatoxins like C5a have significant effects on promoting tumor, such as upregulation of oncogenic growth factors, activation of mitogenic signaling pathways and breakage of normal cell cycle. Complement cascades, initiated by anti-tumor antibodies, also play a pivotal role in anti-tumor therapy to suppress the tumor growth. Our review focuses on the recent progress in the understanding of complement activation and the role of it in tumor growth and anti-tumor therapy, in the context of rapid development of monoclonal antibodies and nanomaterials for cancer treatment.

Contents

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1. Introduction

The complement system contains a series of serum proteins that is important in innate immunity. Under different circumstances, the system can be activated in three pathways: the alternative pathway (AP), the lectin pathway (LP) and the classical pathway (CP). The genomic study showed that the original complement system, composed of the primitive alternative pathway, emerged 1300 million years ago, followed by the emergence of the lectin pathway after 400 million years. Their main role is characterized in triggering inflammation and opsonization. The classical pathway might occur 600 million years ago [1,2]. Previously, it is considered that the complement system was merely a proteolytic cascade, aiming to remove pathogenic microorganism. With more and more studies into the conformation and structure of its component and the interaction with homeostasis, cancer progression, autoimmune disease on physiological and pathological basis, the versatility of complement has aroused more and more attention. The complement system is an intricate machine terminating at the formation of MAC, inflammation, opsonization and the release of anaphylatoxins. There have been several reviews focusing on the relationship between complement components and the tumor or anti-tumor therapy [3,4]. This review will give an overview of the recent progress in complement activation and its effects on tumor growth and anti-tumor therapy.

2. Recent progress in complement activation

The activation of complement is mediated by more than 40 proteins in tissues, plasma, and even inside the cells [4]. Through the proteolytic cascades operated by regulatory factors, cellular receptors and co-factors, the structures of these molecules are changed. Thereby, the cleavage of subsequent molecules by enzymes is induced, finally forming anaphylatoxins, opsonin as well as other components to activate phagocytosis, regulate adaptive immune response and take part in the regulation of T/B cells [5].

2.1. Progress in structure studies of classical pathway

The recognition molecule of CP, C1q, is composed of six heterotrimeric copies of three polypeptide chains (A, B and C). Each of chain is made up of a C-terminal globular (gC1q) and an N-terminal triple-helical collagen like region (CLR) [6–8]. Ca^{2+}, the ion that binds at the top of the C1q heterotrimer, is considered to have primary influence on the target recognition properties of C1q toward its target molecules (such as IgM, IgG, CRP and PTX-3) through the modification in directing the electric movement of the C1q globular domain [9]. The signal that induces the auto-activation of C1r is transmitted from the gC1q via the CLR after conformation change of C1q [10]. Besides immune complex and antibody cluster, some distinct molecules on the surface of apoptotic cells, such as double stranded DNA, the calreticulin, glyceraldehyde-3-phosphate dehydrogenase can also be recognized by the gC1q domain [11,12].

Recently, researches have made dramatic progresses on the relationship between the structures of the antibodies and complement, giving a new view to consider the complement activation from the biophysical aspect. The most significant theory proved is that IgG antibodies can form ordered hexamers after binding to the antigen [13]. Diebolder and his research group found that the ordered IgG hexamers on the antigen surface are the key part in activating C1 and that these hexamers are formed by Fc segments which interact with each other non-covalently. This breakthrough serves as an explanation of the strong antigen and epitope dependency of complement activation, despite the low affinity of a single IgG binding to the C1q head pieces. In this hexamer model, each IgG has two Fab arms with one bound to membrane-associated antigen and the other at the height of IgG Fc platform [11,13]. Additionally, neighboring Fc segments can interact through specific noncovalent chemical bond and achieve the regulation of complement activation. After the test on whether the non-Ag-bound Fab domain might take an effect on IgG hexamer stabilization or complement activation, Wang et al. found that deletion of Fab arms led to a decrease in the fractional mass of IgG present as hexamers by 30%, but it did not completely abolish hexamerization [14]. Intriguingly, complement activation is increased by deletion of a single or both Fab arms because the increase in soluble C4d production was observed in incubating human serum with either single-Fab-antibodies or no-Fab-antibodies. From the above, Fab domains can contribute to the stabilization of IgG hexamer, but are dispensable for C1q binding and they restrict the activation of C1 to a certain extent, leading to a suggestion that Fab segments can affect the downstream Fc-mediated events. Since experiments have showed that Fab arms have little impact on the C1q binding, one speculation of this finding is that the conformation change occurs in the IgG: C1q complex that transmits a signal to the Fc domain [14]. But it needs to be clarified that these results by Wang et al. may not be indiscriminately used in anti-tumor therapy because the effect of deletion of Fab parts has not ever be explored on the existing antibodies for anti-tumor therapy. In addition, some other molecules were found to have a critical role in the activation of the classical pathway in the latest studies. The role of C-terminal lysine of IgG didn't arouse much attention as the C-terminus chain is situated in a distance with effector site such as antigen binding domain and Fcγ receptors, while study shows that the removal of C-terminal lysine optimizes the Complement-Dependent Cytotoxicity (CDC) and complement activation. One possible explanation is that IgG hexamers was destabilized due to electrostatic repulsion caused by charged lysines. This explanation confirms other discoveries that IgG molecules with one heavy chain C-terminal lysine form IgG hexamers with IgG molecules without C-terminal lysine in an alternating way, in which electrostatic repulsion decreases. What's more, Ig hexamers with oppositely charged C-terminus mixed together fully restore the potential of CDC. In a word, the C terminal lysine serves as a down regulatory molecule in avoiding the uncontrolled activation [15]. Modulation of glycosylation at the Fc fragment of IgG has long been known to influence the complement activation and this idea has been applied into clinical study in treating complement-mediated autoimmune disease [16]. Some scientists speculate that IgG deglycosylation has an impact on the IgG hexamerization and C1q binding. In their experiment of deglycosylation, lessened binding affinity of C1q is detected among all IgG mutants and those with relatively low hexamerization ability to show a significant decrease in hexamer abundance. This result indicates glycan's role in the IgG Fc: Fc interactions since it serves as a bridge between the heavy chain CH2 domain and stabilizes the structure [14].

When it comes to the applications to anti-tumor therapy, it is interesting to find that antibodies which effectively form hexamers can induce CDC effectively, even when they are under complement limiting conditions [17], showing that the anti-tumor antibodies