Review

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Is complement good or bad for cancer patients? A new perspective on an old dilemma

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Several studies of human cancers have established that chronic and insidious inflammation promotes the process of carcinogenesis and exacerbates the growth of existing tumors. Conversely, acute inflammation seems to have the opposite effect. Recent discoveries indicate that this dualism in the role of inflammation in cancer is mirrored by the effects of the complement system on this disease process. Previous studies have suggested that complement proteins can contribute to the immune surveillance of malignant tumors. However, a very recent study has indicated that complement proteins can also promote tumor growth. Here, we describe our current understanding of the role of complement in tumor development and progression.

Introduction

Cancer research has historically focused mainly on tumor cells, devoting relatively little attention to the importance of the tumor microenvironment in the initiation, development and progression of malignant lesions. Only in recent years has the role of host-derived factors, such as components of the immune system, been widely appreciated. This lack of interest in the contribution of host-derived factors to the process of carcinogenesis is surprising in light of the discoveries made more than 100 years ago by Rudolph Virchow [1] and William Coley [2].

Virchow observed that various malignant tumors were infiltrated by leukocytes. He termed these infiltrating cells a 'reticular infiltrate' and postulated that their presence indicated that malignant tumors arose at the sites of chronic inflammation [1]. This original discovery created the foundation for a long debate as to whether chronic inflammation can be a factor that increases the risk of cancer. Virchow's theory was soon challenged by Coley's discovery that an acute inflammation, induced by injecting patients with two bacterial strains, *Streptococcus pyogenes* and *Serratia marcescens*, resulted in the regression of malignant tumors in a considerable number of these patients [2]. At first glance, Virchow's and Coley's research would seem to place inflammation on opposite sides in the battle between cancer and the host. However, in view of recent progress in tumor immunology, their discoveries do not seem so contradictory. Virchow's concept defined indolent, long-lasting inflammation as an environment that promotes the initiation and growth of malignancy, whereas

Coley's therapeutic approach demonstrated that acute and brisk inflammation can successfully fight cancer.

Despite these brilliant ideas conceived so many years ago, tumor immunology was largely unexplored for decades and the implications of host-cancer interactions for tumor growth remained obscure. The lack of noteworthy progress in these areas of cancer research can probably be attributed to the traditional view of cancer. Numerous medical textbooks have described malignant neoplasms as autonomously growing tissue that is independent of host-derived control mechanisms. Indeed, malignant tumors do not 'obey' the rules that apply to normal tissues. However, it has become clear that host-derived factors have a tremendous effect on the development of certain malignancies [3–5]. The best example to illustrate the dependence of cancer on the host is the process of angiogenesis in tumor tissue. Although tumor cells can produce pro-angiogenic factors such as vascular endothelial growth factor (VEGF) [6], tumor blood vessels are thought to be of host origin. Therefore, host-derived cells are essential for providing the tumor with an adequate blood supply, which is vital for rapidly growing malignant tissue.

Does inflammation promote cancer?

Virchow's theory that chronic inflammation contributes to carcinogenesis and tumor development was reintroduced after it was observed that several human malignancies were associated with infections and a continuous, indolent inflammatory reaction. These cancers include bladder, cervical, gastric and hepatocellular carcinomas, in addition to certain types of mucosal-associated lymphoid tissue (MALT) lymphomas and Kaposi's sarcoma. In addition, it has been recognized that inflammation induced by factors other than infections can predispose individuals to carcinomas, for example Barret's metaplasia predisposes individuals to esophageal carcinoma, and cigarette smoking or asbestos exposure can predispose individuals to bronchial carcinoma [1,7,8]. The persistent inflammation associated with some autoimmune disorders, such as inflammatory bowel disease (IBD), is also associated with an increased risk of colon carcinoma [9,10].

How chronic inflammation specifically contributes to carcinogenesis is not completely clear. However, it is known that inflammatory cells migrating to the sites of inflammation produce large quantities of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [11]. Additionally, the inhibition of endogenous anti-oxidant

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mechanisms further contributes to reactive species overload during chronic inflammation [12]. ROS and RNS induce DNA damage and produce genetic instability in proliferating cells. The presence of these highly reactive species, combined with the repeated tissue damage induced by microbes or inflammation, then leads to permanent genetic alterations, such as point mutations, deletions or gene rearrangements, in regenerating epithelial cells [3]. In addition, oncogenic viruses that induce chronic inflammation directly transform epithelial cells by inserting active oncogenes into the host genome. Several oncogenic viruses have been identified for humans including human papilloma [13], hepatitis B [14] and Epstein–Barr [15] viruses. The irreversible alterations occurring in the genome of host cells initiate the process of malignant transformation [16].

To form malignant tumors, transformed cells must undergo cycles of proliferation that are associated with specific alterations in their differentiation. Proliferation of transformed cells, together with the altered differentiation program, finally leads to the creation of tumor cells [16]. The microenvironment, which is rich in inflammatory mediators such as cytokines and chemokines, facilitates the proliferation of transformed cells, thereby contributing to the process of cancer promotion [17]. It is also well established that inflammatory cells such as activated macrophages and their products can facilitate remodeling of the extracellular matrix [18], a process that is required for local tissue invasion and subsequent metastases; they also contribute to angiogenesis, which is essential for the rapid growth of malignant tumors [19].

This relatively straightforward view of the role of inflammation in cancer initiation, promotion and progression is, however, complicated by data that are not in accord with this theory. For example, the noticeable inflammatory infiltrate that is seen in psoriasis is not associated with an increased risk of skin cancer [20]. Furthermore, although rheumatoid arthritis is associated with an increased risk of lymphoproliferative disorders, including non-Hodgkin lymphomas, this autoimmune disease also seems to be associated with a reduced risk of gastrointestinal malignancies [21]. In the case of some tumors, the presence of a large number of infiltrating leukocytes indicates a more favorable prognosis [22]. These observations indicate that in some types of malignancy, inflammation impairs tumor growth instead of promoting it. This hypothesis has been confirmed in clinical practice by the successful use of *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) for the treatment of superficial bladder carcinoma [23]. Although the exact mechanisms of BCG-induced tumor regression have yet to be explained in detail, it is likely that this therapy induces appropriately polarized inflammation, in which inflammatory anti-tumor properties prevail.

Thus, there is no simple answer to the question of whether inflammation promotes cancer. Furthermore, tumor-associated immune responses have unique characteristics that distinguish them from immune reactions occurring in the absence of malignancy [24]. It seems that the effect of inflammation on the growth of malignant tumors depends on both tumor- and host-derived factors;

the type of tumor, the kinetics and location of the malignant growth and the overall clinical condition of the cancer patient all influence the quantity and quality of the inflammatory and immune responses to malignancy, and consequently the effects of these responses on tumor growth. For example, fast-growing cancers are likely to undergo necrotic changes as a result of the inability of the host to provide an adequate blood supply to rapidly growing neoplastic tissue. Although for a long time it was thought that dying tumor cells do not induce a noticeable immune response, recent investigations have challenged this concept, by demonstrating that dead tumor cells provide danger signals which trigger the infiltration of leukocytes and the induction of both an innate and adaptive immune response [25]. Although these immune reactions might not effectively reduce tumor growth, they are certainly directed against tumor cells [26] and, in conjunction with additional forms of immunotherapy, can be used to fight cancer.

Host-derived factors that determine the influence of inflammation on tumor growth are relatively well characterized. The deciding factor in terms of whether they promote or impair tumor growth is the quality of the tumor-associated inflammatory infiltrate [4,27,28]. Tumor-associated macrophages (TAMs) polarized towards an M2 phenotype, myeloid-derived suppressor cells (MDSCs) [28] and T regulatory (Treg) cells [29] are known to promote tumor growth through various mechanisms, such as stimulation of angiogenesis and suppression of the anti-tumor immune response. By contrast, M1 macrophages, natural killer (NK) cells, natural killer T (NKT) cells and CD4$^+$ and CD8$^+$ T cells contribute to tumor immune surveillance [27].

Thus, whether the immune system limits or promotes tumor growth seems to depend on the balance between opposing forces previously described [30]. However, the distinct line separating pro- and anti-tumor immune cells has largely been drawn on the basis of animal studies involving the use of various experimental models, which in many cases do not appropriately reflect human malignancies. Therefore, conclusions regarding human cancer should be made rather carefully. In addition, an acute inflammatory response to tumors, which probably includes M1 macrophages, is rarely observed in humans. The majority of human malignancies grow for years without inducing a grossly visible acute inflammatory reaction. Therefore, it is probable that tumor-associated inflammation in humans, which is chronic and insidious in nature, has more tumor-promoting, rather than immune surveillance, properties.

Does complement contribute to the immune surveillance of cancer?

The complement system is traditionally recognized as a key player in innate immunity, which defends the host against microbes [31]. This defense depends on the coordination of various steps during the development of an inflammatory reaction, the opsonization of pathogens and the direct killing of certain species of bacteria by lysis. It has also been demonstrated that complement acts as a bridge between the innate immune response and the

Box 1. Complement activation

The complement system can be activated through several distinctive pathways. The classical pathway (CP) is initiated when C1q binds to antibody–antigen complexes, proteins and membrane fragments associated with tissue damage (damage-associated molecular patterns [DAMPs]), molecules bound to pathogen-associated molecular patterns (PAMPs) such as C-reactive protein or serum amyloid protein, and receptors expressed by marginal zone macrophages (SIGN-R1). Bound C1q activates C1r and C1s, and C1s then cleaves C2 and C4. The lectin pathway (LP) begins with the binding of mannose-binding lectin (MBL) or ficolins to PAMPs or apoptotic host cells. This binding activates MBL-associated serine proteases, which cleave C4, generating C4a (which is released) and C4b. As a result of C2 and C4 cleavage by the CP or LP, C4b combines with C2a to form the CP C3 convertase, which cleaves C3 into C3a and C3b. The alternative pathway (AP) is initiated by spontaneous hydrolysis of C3 ('tickover') to C3 (H$_2$O), which binds to factor B (fB). Bound fB is cleaved by factor D (fD) into Ba and Bb. This cleavage leads to formation of the 'initial' AP C3 convertase, which, like CP convertase, cleaves C3 into C3a and C3b. C3a is released, and C3b binds to activating surfaces. Surface-bound C3b binds additional fB, which is cleaved within this complex by fD, leading to the formation of the 'final' AP C3 convertase, which is stabilized by properdin. The AP C3 convertase can amplify complement activation induced by the CP or LP. C3b can bind to C4b2a or C3bBbP to form the CP or AP C5 convertase, respectively, which cleave C5 into C5a and C5b. C5a is released, and C5b contributes, together with C6–C9, to the formation of the terminal complement complex (TCC).

subsequent activation of adaptive immunity [32]. The anti-infectious properties of complement are supplemented by various other functions of this system, including clearance of immune complexes and apoptotic cells [32], involvement in tissue regeneration [33], mobilization of hematopoietic progenitor cells [34] and angiogenesis [35]. The diverse functions of the complement system are reflected in the high complexity of its organization: it consists of more than 30 proteins circulating in the plasma or bound to cellular membranes [32]. Circulating complement components are activated by various forms of cleavage to generate active effector complement proteins or complexes of proteins (see Box 1 and Figure 1). Several novel mechanisms activating complement have been described in recent review articles [32,36,37].

Although complement activation also occurs in the fluid phase, biologically relevant complement activation is often associated with the deposition of complement proteins on microbial or other suitable cell surfaces (Figure 1). Therefore, the observation that complement components are deposited in various tumors indicates that complement is activated in the tumor tissue or in its vicinity (Figure 1). Consequently, complement effectors generated through this process might contribute to the immune surveillance of malignant tumors. For example, complement proteins,
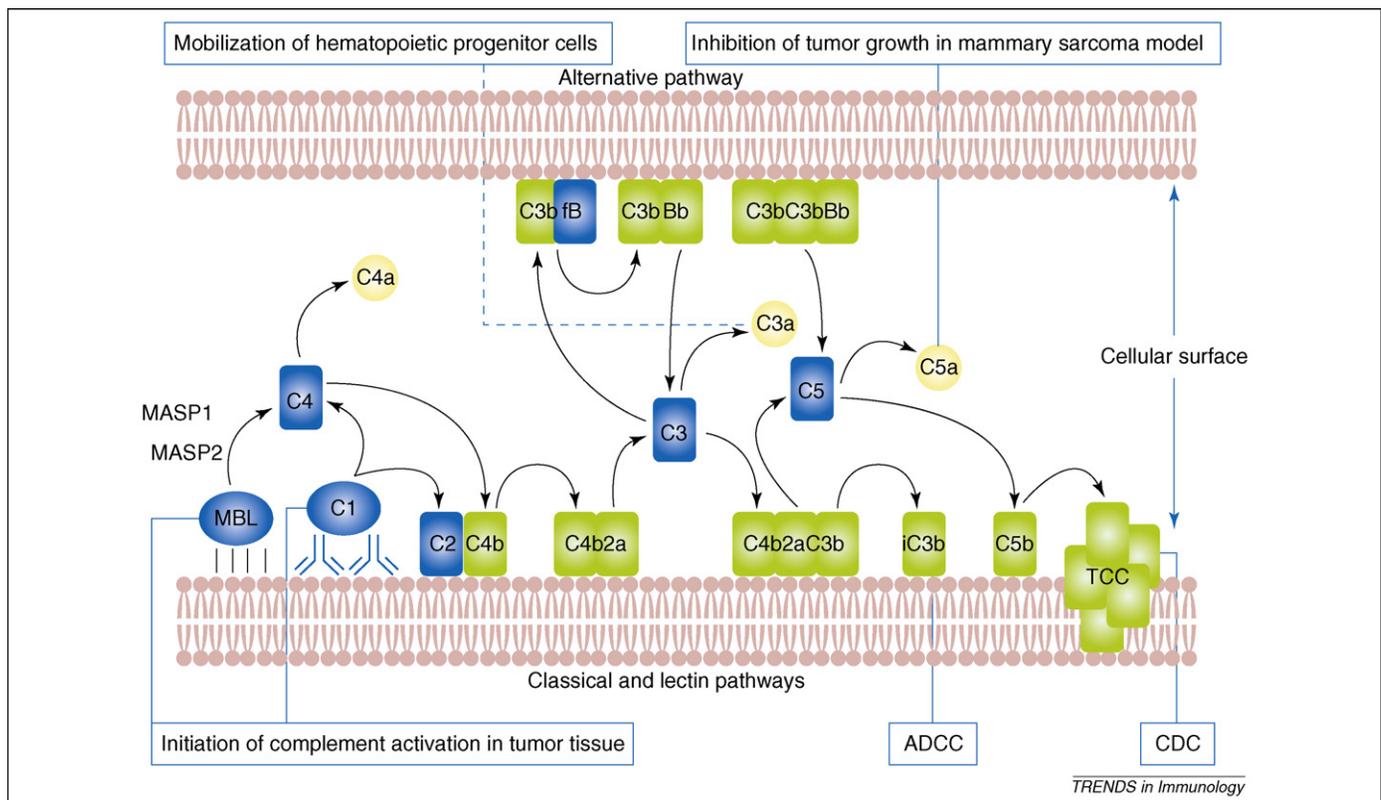

Figure 1. Complement effectors generated during activation contribute to various mechanisms that limit tumor growth. The complement system can be activated through several distinctive pathways. The classical pathway is initiated when C1q binds to its various targets. The lectin pathway begins with the binding of mannose-binding lectin (MBL) or ficolins to pathogen associated molecular patterns (PAMPs) or apoptotic host cells. This binding activates MBL-associated serine proteases (MASPs). Finally, the alternative pathway is initiated by low-grade cleavage of C3 in plasma and the generation of small amounts of C3b. The C3b cleavage product iC3b binds to tumor cells and through the interaction with complement receptor 3 (CD11b/CD18) on mononuclear phagocytes and natural killer (NK) cells enhances antibody-dependent cellular cytotoxicity (ADCC). C5a inhibits growth of tumors in a mammary sarcoma model in mice. The terminal complement complex (TCC) is thought to contribute to complement-dependent cytotoxicity (CDC), which is one of the mechanisms for eliminating tumor cells by therapeutic antibodies. C3a, which contributes to the mobilization of hematopoietic progenitor cells, probably contributes to tumor immune surveillance. Unbroken lines connect complement proteins to functions which inhibit tumor growth, whereas broken lines connect complement proteins to functions that can currently only be hypothetically linked to inhibition of tumor growth.

including the C5b–9 terminal complement complex (TCC) (Figure 1), are deposited on the surface of breast cancer cells [38] and in papillary thyroid carcinoma [39,40]. Complement has also been shown to be activated in patients with colorectal carcinoma [41], and the data indicate that this activation is initiated through the lectin pathway (Figure 1) [42]. In another study, complement activation products were detected in the ascitic fluid of ovarian carcinoma patients, and tumor cells isolated from this fluid were found to bear C1q and C3 cleavage products (Figure 1) but not TCC [43]. However, the evidence from studies of human malignancies that suggests a role for complement in the immune surveillance of cancer is still circumstantial. More direct support for such a hypothesis has come from a study indicating that mammary sarcoma cells expressing C5a exhibited slower tumor growth in a syngeneic mouse model than did cells lacking C5a [44] (Figure 1).

Cancer cells are protected from attack by complement

Although the activation and deposition of complement in tumor tissue has been demonstrated, the functional implication of these observations remains unclear. The contribution of complement to the immune surveillance of cancer is disputable. The failure of complement to destroy tumor cells can be partially attributed to their resistance to complement attack, including complement-mediated lysis [45]. This resistance can result from various

mechanisms, including the expression of membrane complement regulatory proteins (mCRPs) [46], which normally protect host cells from complement-mediated destruction, and the secretion of soluble complement inhibitors by tumor cells [47]. mCRPs, including CD35 (complement receptor type-1 [CR-1]), CD46 (membrane cofactor protein [MCP]) and CD55 (decay-accelerating factor [DAF]) control the activation of complement at the level of C3, which is a central molecule of the complement cascade. By contrast, CD59 interferes with the assembly of the TCC [48]. Soluble complement inhibitors, such as C1 inhibitor, factor H, factor-H-like proteins, factor I and C4b-binding protein (C4BP) are secreted by tumor cells into the local microenvironment [49–52]. C1 inhibitor binds to and inactivates the C1r and C1s proteinases [53], which contribute to the activation of complement through the classical pathway. Factor H is a cofactor for factor-I-mediated cleavage of C3b and accelerates the decay of the alternative pathway C3 convertase [54]. C4BP acts as a cofactor for factor I in the degradation of C3b and C4b. Importantly, the presence of factor H in the urine of patients with bladder carcinoma is a useful diagnostic test for this type of malignancy [55].

A large number of studies have demonstrated that various cancer cells express at least one of the mCRPs (Figure 2). Tumor cells most often express CD46, CD55 and CD59 [45,56–58] but relatively few human cancers express
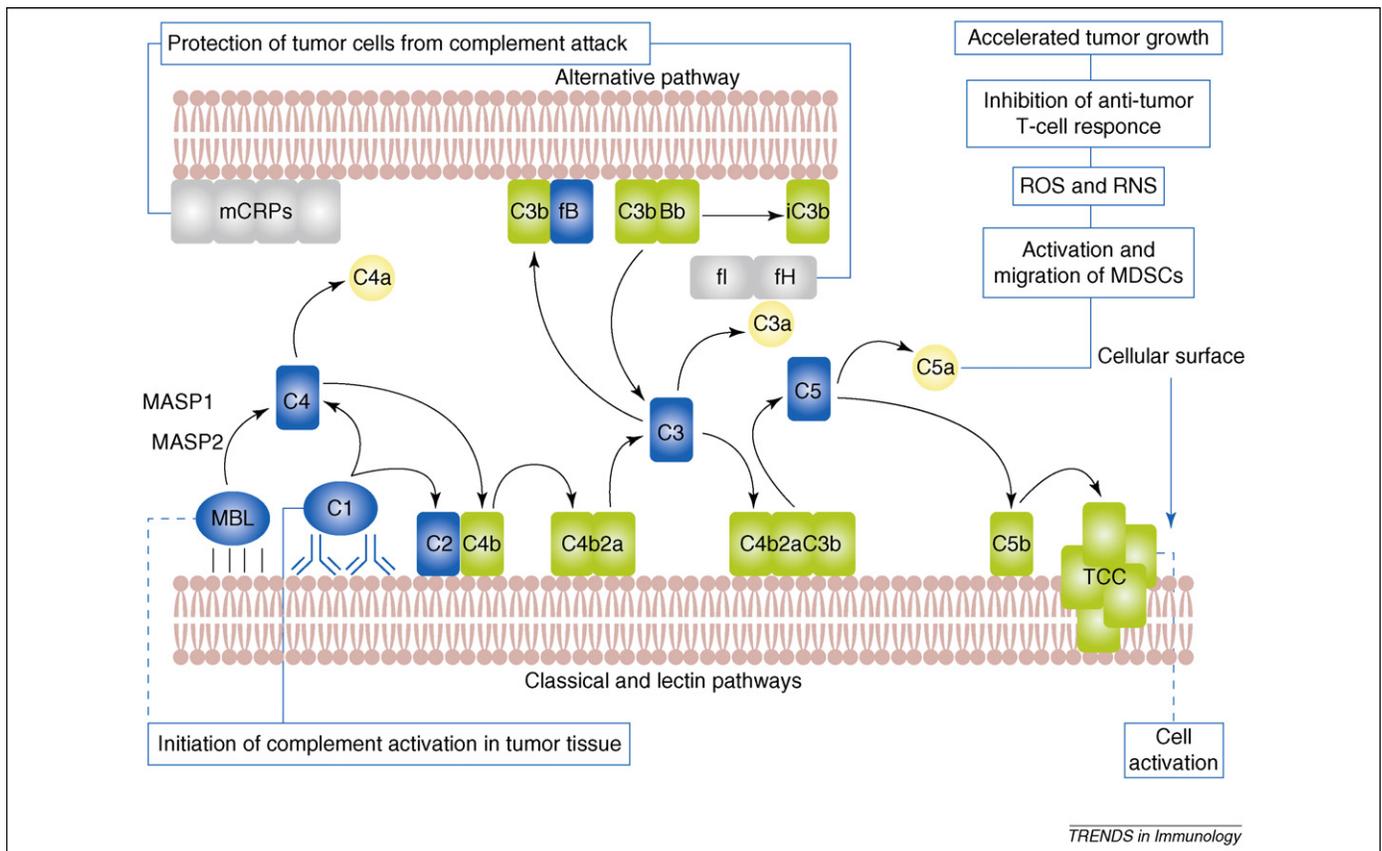

Figure 2. Some complement proteins can accelerate tumor growth. C5a, probably generated through the classical pathway, activates myeloid-derived suppressor cells (MDSCs). Activated MDSCs migrate to tumors and produce highly immunosuppressive reactive oxygen species (ROS) and reactive nitrogen species (RNS) that inhibit the anti-tumor T-cell response. In addition, tumor cells are protected from co attack by membrane complement regulatory proteins (mCRPs) and soluble complement inhibitors, secreted in the tumor microenvironment, such as factor H (fH) and factor I (fI). Factor H is a cofactor for fI-mediated cleavage of C3b to iC3b and accelerates the decay of the alternative pathway C3 convertase. The terminal complement complex (TCC) can be incorporated into cell membranes at sublytic doses and activate target cells. Unbroken lines connect complement proteins to their functions in tumor growth. Broken lines connect complement proteins to functions that currently can only be hypothetically linked to tumor growth.

CD35 [59–61]. The growing interest in the expression of mCRPs by cancer cells is a result of many attempts to use monoclonal antibodies (mAbs) that bind to tumor antigens for anti-cancer therapy [62]. In fact, some of these mAbs, including rituximab (an anti-CD20) and trastuzumab (also commonly known as Herceptin), have already been successfully tested in clinical settings [62]. Because the mechanisms through which mAbs kill tumor cells are thought to include antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (Figure 1), the presence of mCRPs on cancer cells could impair the therapeutic efficacy of these mAbs. Furthermore, *in vitro* sensitivity of lymphoma cells to CDC induced by rituximab treatment can predict a clinical response to this drug [63], and complement supplementation with the use of fresh frozen plasma dramatically increases the therapeutic efficacy of rituximab in patients with chronic lymphocytic leukemia [64,65]. Therefore, overcoming the inhibition of complement activation on tumor cells seems to be a promising approach for improving the effectiveness of mAbs in the treatment of cancer. Towards this end, several mAbs that neutralize mCRPs have been tested, as have small interfering RNAs and anti-sense oligonucleotides for mCRPs [66]. Studies performed *in vitro* have demonstrated the feasibility and efficiency of these approaches. However, the application of mCRP-neutralizing mAbs *in vivo* has raised several concerns because mCRPs are widely expressed on normal cells [66]. A solution to this problem could potentially be found in the use of bispecific antibodies that recognize both tumor specific antigens and mCRPs [62,67]. These antibodies are composed of an anti-tumor arm that mediates specific binding to tumor cells and an anti-mCRP arm that neutralizes the activity of complement inhibitors. The higher affinity of the anti-tumor arm, compared with the anti-mCRP region, guarantees preferential binding of these mAbs to tumor cells, thereby protecting host cells from ADCC and CDC. Thus, enhancing complement activation by blocking mCRP seems to improve the efficacy of therapeutic mAbs in killing tumor cells. However, a recent study which has demonstrated that NK cell activation and ADCC-induced by rituximab-coated target cells is inhibited by C3b [68], challenges this concept. It has been suggested that C3b deposition inhibits the interaction between the rituximab Fc region and the NK cell receptor CD16, limiting the ability of rituximab-coated target cells to induce NK cell activation and ADCC. Therefore, further studies are needed to define in more detail the impact of complement fixation on ADCC.

Unpredictable complement
Although the role of complement in the immune surveillance of malignant neoplasms has not yet been clarified, the successful use of mAbs to treat cancer has motivated researchers to attempt to increase the activation of complement, as a supplement to antibody immunotherapy [69–71]. In fact, several *in vitro* and animal studies have demonstrated that an approach of this kind can improve the effectiveness of mAbs in killing tumor cells. However, a recent and rather unexpected discovery has challenged the concept that increased complement

activation is potentially beneficial for cancer patients [72–74]: C5a generated through the activation of the classical complement pathway within tumor tissue (Figure 2) was shown to promote malignant growth [72]. The C5a activity is connected to the activation and recruitment of MDSCs into tumors (Figure 2). It is likely that C5a interacts with these cells directly because MDSCs, like their mature counterparts such as monocytes and neutrophils, express the C5a receptor [72].

MDSCs represent a heterogeneous population that is recruited by malignant tumors to shield cancer cells from T-cell-mediated immune attack. Although MDSCs have been found in animals and humans lacking malignancy, the number of these cells is drastically increased in tumor-bearing individuals. MDSCs can be found in the bone marrow, peripheral blood, lymphoid organs and in the tumor microenvironment itself [75]. The immune suppression mediated by MDSCs is considered to be the most important reason for the failure of cancer immunotherapies in clinical trials. The exact mechanism of MDSC-mediated immune suppression still requires further clarification; however, the large amounts of ROS and RNS produced by these cells have been shown to impair the ability of T cells to respond to tumor antigens [75].

C5a regulates the production of ROS and RNS by MDSCs (Figure 2). In doing so, it contributes to the regulation of activities essential for the immune suppression produced by MDSCs. The importance of the heterogeneity of this cellular population has been underscored by the observation that C5a attracts mainly neutrophil-like MDSCs to tumors, whereas monocyte-like MDSCs in tumors are activated by C5a to produce highly immunosuppressive ROS and RNS [72].

The possibility of using a therapeutic blockade of the complement system to reduce tumor growth has been explored by inhibiting the C5a receptor with a peptide antagonist. Remarkably, inhibition of the C5a receptor was found to be as efficient in reducing tumor growth as was treatment with the well-recognized anti-cancer chemotherapeutic paclitaxel. The significant increase in the number of CD8$^+$ T cells infiltrating tumors that occurs after treatment with C5a receptor antagonist has further confirmed that the impairment of tumor growth in mice treated with the complement inhibitor is a result of stimulation of the anti-tumor immune response [72]. The findings of this study could be viewed as unexpected because the antibody-dependent and complement-mediated destruction of tumor cells has traditionally been recognized as a mechanism of tumor-related immune surveillance. However, a tumor-promoting role for C5a is consistent with the currently accepted view of inflammation as exacerbating the growth of various cancers [73,74] because C5a is a key regulator of the inflammatory response [76].

Although the results of this study will need to be extended to other experimental models and translated into human research to confirm that the tumor-promoting role of C5a is a more general paradigm rather than an exception, the prospect of using a C5a receptor antagonist for cancer therapy is particularly exciting, considering the low toxicity of this compound compared with that of current

anti-tumor chemotherapeutic agents. In addition, the combination of complement inhibition and anti-cancer vaccines could become a key approach to improving the efficacy of these vaccines in patients with advanced malignancies.

Concluding remarks

Recent developments in complement research have demonstrated several interconnections between the complement system and cancer. Some of these complement-cancer associations are in accordance with our traditional understanding of complement function in immunity, whereas others are surprising. The supportive role of complement in the antibody-mediated killing of cancer cells obviously belongs to this first category, corresponding to the role of complement as an adjuvant of humoral immunity, whereas the discovery that C5a promotes tumor growth challenges the dogma that the enhancement of complement activation is uniformly beneficial for cancer patients. Thus, as might be expected, the question: 'Is complement good or bad for cancer patients?' remains open. In addition, given that other complement proteins are actively involved in regulating the activity of various immune cells, a role for these proteins in tumor growth can also be anticipated, although at present it is difficult to predict whether these proteins promote or inhibit the growth of malignant tissues.

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