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Complement System in Cancer: Dual Roles and Therapeutic Implications

Abstract – The complement system, traditionally recognized for its role in innate immunity, has emerged as a critical regulator in cancer biology. Complement proteins exhibit paradoxical functions in tumor microenvironments, simultaneously contributing to anti-tumor immunity through mechanisms including membrane attack complex formation, opsonization, and inflammatory responses, while also promoting tumor progression via angiogenesis, metastasis, and immunosuppression. This dual nature presents unique challenges and opportunities for cancer immunotherapy. Recent advances have identified strategies to harness complement activation against tumors or inhibit complement-mediated tumor promotion, depending on cancer type and stage. This review synthesizes current understanding of complement's contradictory roles in oncology and discusses emerging therapeutic approaches, including complement activation enhancement through monoclonal antibodies and complement inhibition strategies targeting regulatory proteins. Understanding these complex interactions is essential for developing effective complement-targeted cancer therapies.

Keywords – Complement system; cancer immunotherapy; tumor microenvironment; complement regulatory proteins; membrane attack complex

1 INTRODUCTION

Cancer remains a leading cause of mortality worldwide, with approximately 20 million new cancer cases and 9.7 million deaths reported globally in 2022 [1]. The disease is characterized by uncontrolled proliferation of abnormal cells, forming neoplasms that can metastasize to distant organs [2]. Despite advances in conventional treatments including surgery, chemotherapy, and radiation, the complexity of tumor biology necessitates innovative therapeutic strategies.

The complement system, comprising over 50 plasma and membrane-bound proteins, represents a crucial component of innate immunity [3]. Originally identified for its bactericidal properties, complement proteins are now recognized for broader physiological functions, including bridging innate and adaptive immunity, clearing immune complexes, and regulating inflammatory responses [4]. These proteins, primarily synthesized by hepatocytes and locally by macrophages, fibroblasts, and endothelial cells, exist as inactive precursors, effectors, receptors, or regulatory molecules.

Recent investigations have revealed the complement system's complex involvement in cancer biology [5,6]. While complement proteins can recognize and eliminate malignant cells through classical immune mechanisms, accumulating evidence demonstrates that tumors can manipulate complement pathways to promote their survival and progression [7,8]. This review examines the dual roles of complement in cancer and explores therapeutic strategies to modulate these pathways for clinical benefit (Figure 1).

2 DUAL ROLES OF COMPLEMENT IN CANCER

2.1 Anti-tumor Functions of Complement

The complement system contributes to anti-tumor immunity through multiple mechanisms that parallel its defense against pathogens [5]. Complement proteins recognize cancer cells as foreign entities due to altered membrane compositions, triggering activation cascades that lead to tumor cell destruction.

Classical pathway activation has been demonstrated in various malignancies. C1q directly binds to tumor cell surfaces in lung cancer, initiating complement cascades [9]. Studies have shown C5 deposition and subsequent C5a release in lung cancer cell lines, confirming complement's capacity to recognize malignant cells. Similarly, in glioblastoma multiforme, increased C1q levels with subsequent C3 and membrane attack complex (MAC) deposition indicate local complement activation [10]. Ovarian cancer research has revealed C1q and C3 product deposition on malignant cells isolated from ascitic

fluid, demonstrating in vivo complement activation [11].

The anti-tumor mechanisms include the formation of MAC on tumor cell membranes, which directly induces cell lysis, representing a potent cytotoxic mechanism [12]. Additionally, opsonization occurs when C3b-coated tumor cells are recognized by complement receptors on phagocytes, facilitating their elimination, while anaphylatoxins C3a and C5a recruit and activate immune cells, promoting inflammatory responses that can eliminate cancer cells [5].

Furthermore, complement proteins enhance adaptive immunity by promoting B-cell activation, differentiation, and antibody production, while also augmenting T-cell responses [4]. These immunomodulatory functions position complement as a critical bridge between innate and adaptive anti-tumor immunity.

2.2 Pro-tumor Functions of Complement

Paradoxically, complement activation can promote tumor progression through several mechanisms. Cancer cells have evolved sophisticated strategies to evade complement-mediated destruction while exploiting complement products for growth and metastasis [8,13].

Tumor cells characteristically overexpress complement regulatory proteins (CRPs), including membrane-bound inhibitors CD46, CD55, and CD59, as well as soluble factor H [14,15]. These molecules prevent MAC formation and inhibit complement activation on tumor surfaces. Studies demonstrate that human carcinoma cell lines from mammary, ovarian, and prostate tissues express elevated levels of these CRPs, with CD59 being predominant [16]. Complement factor H (CFH) has emerged as a novel immune checkpoint in cancer, with tumor-secreted CFH preventing local complement activation and facilitating immune evasion [17].

Complement fragments, particularly C3a and C5a, promote angiogenesis by stimulating vascular endothelial growth factor (VEGF) production and endothelial cell proliferation [18]. These anaphylatoxins create a favorable microenvironment for tumor vascularization, essential for sustained tumor growth and metastasis. The complement system also regulates tumor-promoting activities mediated by myeloid-derived suppressor cells (MDSCs), contributing to immunosuppression [19].

In hepatocellular carcinoma (HCC), the complement system exhibits particularly complex roles, as the liver is the primary site of complement protein synthesis. Hepatic stellate cells, the main source of C3 in liver tissue, promote HCC tumor growth through C3-mediated immunosuppression [20]. The C3a/C3aR signaling axis enhances epithelial-mesenchymal transition, cell migration, and invasion in HCC cells [21].

Additionally, complement activation products contribute to immunosuppression within tumor microenvironments. C1q can act as a cancer-promoting factor independently of complement activation [22], promoting metastasis and colocalizing with immunosuppressive M2 macrophages [23]. These molecules modulate immune cell function, suppressing anti-tumor responses and creating an immunotolerant environment conducive to tumor progression.

Complement also facilitates tumor cell migration and metastasis through various mechanisms, including extracellular matrix remodeling and enhancement of tumor cell motility. Recent study demonstrates that complement regulators such as CD59 protect cancer stem cells from complement-dependent cytotoxicity, promoting chemoresistance and tumor recurrence [23].

The complement system exhibits dual roles in cancer, with both tumor-inhibiting and tumor-promoting functions are summarized in Figure 1.

3 THERAPEUTIC STRATEGIES TARGETING COMPLEMENT

The dual nature of complement in cancer presents opportunities for therapeutic intervention through either activation or inhibition strategies, depending on clinical context [24].

3.1 Complement Activation Strategies

Enhancing complement-mediated tumor destruction represents a promising therapeutic approach [25]. Monoclonal antibodies (mAbs) constitute the primary strategy for amplifying complement activation against cancer cells (Figure 2). These therapeutic antibodies bind tumor-associated antigens, triggering classical complement pathway activation through Fc region-C1q interactions, leading to complement-dependent cytotoxicity (CDC) [26].

Anti-CD20 monoclonal antibodies, including rituximab and ofatumumab, have demonstrated significant efficacy in B-cell malignancies through CDC mechanisms [27,28]. Recent 2024 studies have shown that obinutuzumab, a type II anti-CD20 antibody, can acquire complement-dependent cytotoxicity when combined with

hyperactive complement components, expanding therapeutic options for patients with lymphoid malignancies [29]. Novel approaches include linking complement factor H-derived short consensus repeats to CD20 antibodies to enhance CDC activity, showing promising results in chronic lymphocytic leukemia [30].

Emerging strategies include bispecific complement engagers that simultaneously target tumor antigens and complement proteins to potentiate CDC. Engineering antibodies with optimized Fc regions for improved C1q binding represents another avenue for enhancing therapeutic efficacy [31].

Regulation of antibody-mediated CDC can be modulated by adjusting the intrinsic affinity and binding valency of IgG for target antigens, with monovalent derivatives showing enhanced efficacy in previously resistant tumor cell lines [32]. These innovative approaches demonstrate the potential for next-generation mAbs with substantially improved CDC activity.

3.2 Complement Inhibition Strategies

When complement promotes tumor progression, inhibition becomes therapeutically advantageous [33]. Targeting CRPs overexpressed on tumor cells can restore complement-mediated cytotoxicity. Small interfering RNA (siRNA) approaches have successfully downregulated CD46, CD55, and CD59 expression, sensitizing tumor cells to complement attack and antibody-dependent cellular cytotoxicity (ADCC) [34].

Recent clinical developments include the evaluation of C5aR1 inhibitors in cancer therapy. The anti-C5aR1 antibody avdoralimab is currently being tested in combination with anti-PD-L1 therapy (durvalumab) in advanced solid tumors, representing a novel approach to modulate the immunosuppressive tumor microenvironment [35,36]. Additionally, targeting the C5a-C5aR1 axis shows promise in reducing MDSC accumulation and enhancing anti-tumor immunity [19].

Complement factor H, recognized as a novel innate immune checkpoint, has emerged as an attractive therapeutic target. Naturally occurring FH autoantibodies found in early-stage lung cancer patients correlate with favorable prognosis, suggesting that disrupting CFH function may enhance anti-tumor immunity [17,37]. Combination strategies integrating complement inhibition with immune checkpoint blockade show synergistic effects, with anti-CD55/CD59 combined with anti-PD1 increasing intratumoral infiltration of CD8+ T cells and M1 macrophages [23].

A study reported that C1r is markedly upregulated in esophageal squamous cell carcinoma (ESCC) and associated with unfavorable patient outcomes. Functionally, C1r promotes tumor cell proliferation, migration, invasion, and adhesion, while inhibiting apoptosis, potentially via upregulation of matrix metalloproteinase, MMP-1 and MMP-10 [38]. Given its protumorigenic role, inhibition of C1r or complement signaling may offer a viable therapeutic approach for controlling ESCC progression, warranting further mechanistic and preclinical evaluation.

The field of complement-targeted therapeutics is rapidly expanding, with numerous agents in clinical development for both rare diseases and cancer [39]. Optimizing the balance between complement activation for tumor cell killing and complement inhibition to prevent tumor promotion remains a critical challenge requiring personalized approaches based on tumor type, stage, and complement expression profiles.

4 CONCLUSION AND FUTURE PERSPECTIVES

The complement system occupies a unique position in cancer biology, exhibiting both protective and detrimental functions depending on tumor type, stage, and microenvironmental context. This duality necessitates careful consideration when developing complement-targeted therapies. While complement activation can eliminate tumor cells through CDC and enhance adaptive immunity, chronic complement activity may inadvertently promote angiogenesis, immunosuppression, and metastasis.

Current therapeutic strategies reflect this complexity, employing either activation approaches through engineered monoclonal antibodies and bispecific complement engagers, or inhibition strategies targeting CRPs and anaphylatoxin receptors [24,40]. The success of these approaches depends on precise patient selection, biomarker identification, and understanding tumor-specific complement dynamics.

Future research should focus on identifying biomarkers that predict complement's predominant role in individual tumors, enabling personalized therapeutic approaches. Advances in 2024-2025 have highlighted the potential of

complement as a platform technology applicable across diverse oncological contexts [41]. Additionally, investigating combination strategies that integrate complement modulation with existing immunotherapies, such as checkpoint inhibitors or CAR-T cells, may yield synergistic anti-tumor effects. Advanced understanding of complement's temporal dynamics during tumor evolution will be crucial for optimal therapeutic timing.

Ultimately, harnessing complement's anti-tumor potential while mitigating its pro-tumorigenic effects represents a promising frontier in cancer immunotherapy. Continued investigation into complement biology within tumor microenvironments, combined with innovative drug development approaches, will refine our ability to exploit this ancient immune system for modern oncological applications [41].

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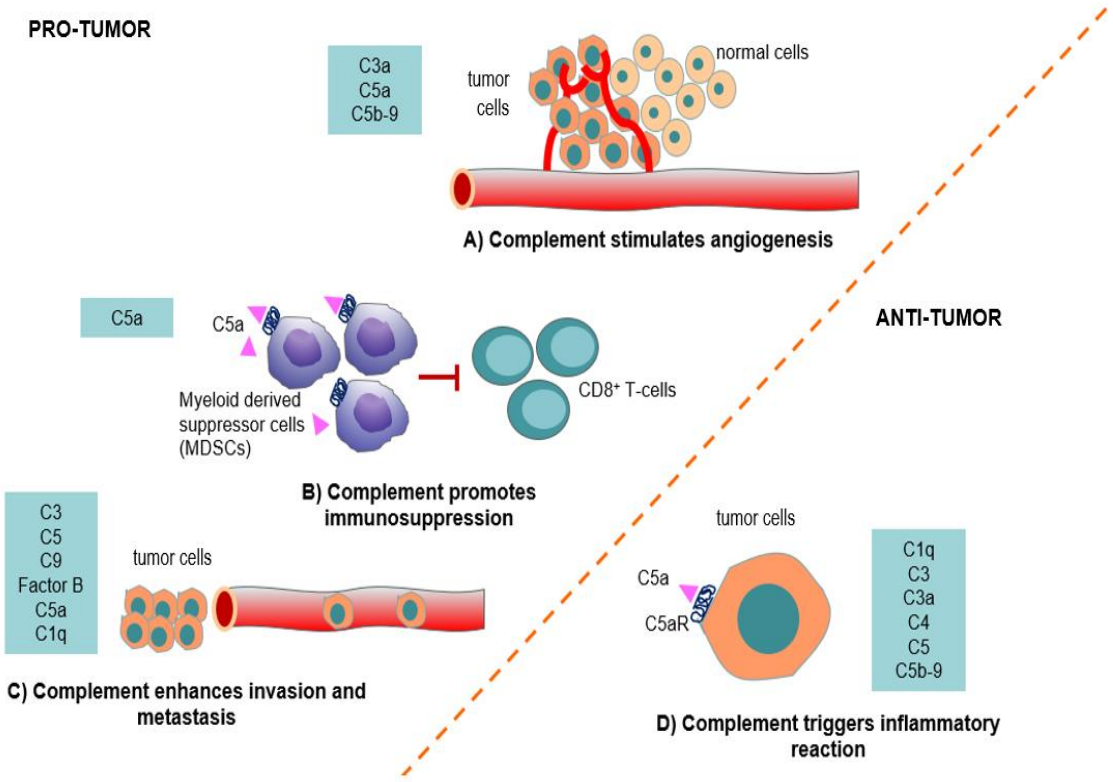

Figure 1. Dual roles of complement in cancer progression**.** The complement system exhibits paradoxical functions in tumor microenvironments. Left panel - Complement promotes tumor progression through: (A) Angiogenesis stimulation via C3a, C5a, and C5b-9 (MAC) production, (B) Immunosuppression by C5a-mediated activation of myeloid-derived suppressor cells (MDSCs) that inhibit CD8+ T-cells, and (C) Enhanced invasion and metastasis through complement components (C3, C5, C9, Factor B, C5a, C1q). Right panel - Complement inhibits tumor progression through: (D) Inflammatory reactions triggered by complement activation (C1q, C3, C3a, C4, C5, C5b-9) via C5a receptor (C5aR) signaling in tumor cells.

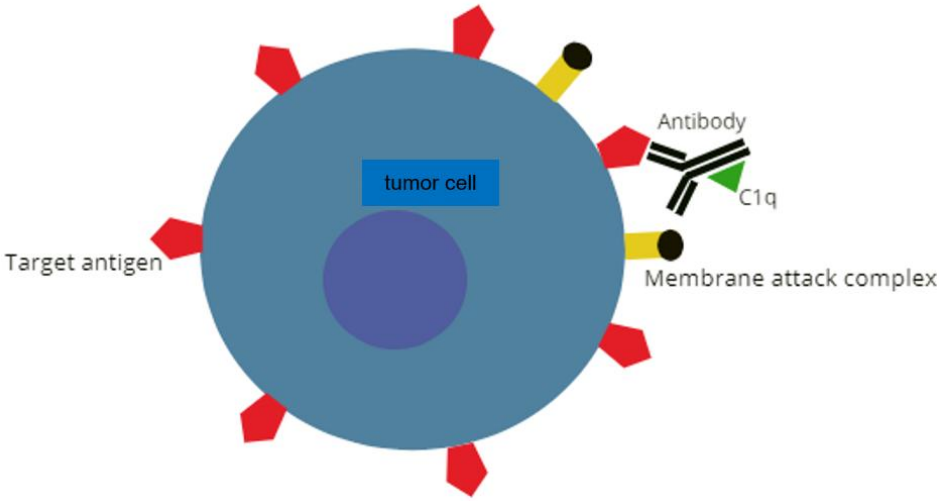

Figure 2. Antibody-mediated complement activation leading to membrane attack complex (MAC) formation. Monoclonal antibodies bind to tumor-associated target antigens on the tumor cell surface, triggering classical complement pathway activation through C1q recruitment. This initiates the complement cascade, culminating in the formation of the membrane attack complex (MAC) that directly lyses tumor cells through complement-dependent cytotoxicity (CDC).