IN THE SPOTLIGHT

Complementing T-cell Function: An Inhibitory Role of the Complement System in T-cell–Mediated Antitumor Immunity

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Summary: New data from Wang and colleagues show that complement C3 suppresses the function of $CD8^+$ tumor-infiltrating T cells by inhibiting IL10 production, and targeting the complement receptors C3aR and C5aR enhances the antitumor activity of immune checkpoint blockade. Their results not only define a new role of complement receptors as T-cell coinhibitory receptors, but also are useful in the development of novel strategies to improve the effectiveness of cancer immunotherapy. *Cancer Discov; 6(9); 953–5. ©2016 AACR.*

See related article by Wang et al., p. 1022 (4).

A plethora of cosignaling pathways play a pivotal role in T-cell biology. Although T-cell activation is initiated by the binding of the T-cell receptor (TCR) and antigenic peptides presented by MHC molecules, the amplitude and quality of T-cell–mediated immune responses are determined by a balance between costimulatory and coinhibitory signaling pathways. These modulatory signals are transduced into T cells mainly through the receptors expressed on the surface of T cells, which are defined as T-cell cosignaling receptors. Most of the T-cell cosignaling receptors belong to either the immunoglobulin superfamily (IgSF) or the tumor necrosis factor receptor superfamily (TNFRSF). As of 2013, 29 IgSF cosignaling receptors and 26 TNFRSF cosignaling receptors have been identified (1). These receptors play essential roles in delivering optimized activation signal to T cells in responding to pathogenic infection and protecting normal tissues from T-cell attack. In the tumor microenvironment, tumor cells also utilize these cosignaling receptors, especially coinhibitory receptors, to evade immune surveillance (2). Among them, two IgSF cosignaling receptors, CTLA4 and PD-1, have been most actively studied in the tumor setting. Upon interaction with their ligands, both CTLA4 and PD-1 deliver inhibitory signals to T cells and impair their effector function; thereby, they are also named as immune checkpoints. The CTLA4 and PD-1 signaling pathways in tumor-infiltrating T cells (TIL) are often found to be activated and responsible for an exhausted phenotype of TILs. Antibody blockade of CTLA4 and PD-1 can induce tumor regression and improve survival in patients with advanced melanoma (3). Since the approval of anti-CTLA4 and anti–PD-1 biologics by the FDA, more clinical results have demonstrated that these treatments can lead to durable antitumor immunity in a broad spectrum of cancer types. However, a large portion of patients with cancer still fail to respond to anti-CTLA4 and/or anti–PD-1 therapy. This highlights the importance of studies to better understand the role of T-cell cosignaling pathways in the T-cell–mediated antitumor immune response and to identify novel T-cell cosignaling receptors. Defining additional T-cell cosignaling pathways will provide valuable information to design the next generation of cancer immunotherapy.

In this issue of *Cancer Discovery*, Wang and colleagues have unraveled an intriguing role of the complement system in modulating the effector function of $CD8^+$ TILs and identified the complement receptors C3aR and C5aR as a new type of coinhibitory receptor (4). By performing pathway analysis of differentially expressed genes in $IL10^+CD8^+$ T cells, a subset of $CD8^+$ T cells with enhanced effector function as shown in a viral infection model (5), the authors discovered that the complement pathway is highly enriched. This result inspired them to explore how the complement system regulates T-cell–mediated immune response, particularly in the setting of tumor. Their study using complement C3-deficient mice elegantly maps out the steps by which complement C3 inhibits the T-cell–mediated antitumor immune response. As shown in Fig. 1, the inhibitory role of the complement system requires at least four steps: (i) $CD8^+$ TILs secrete C3; (ii) the product from secreted C3 interacts with the receptors, C3aR and C5aR; (iii) the signals from C3aR and C5aR inhibit IL10 expression; and (iv) reduced IL10 production impairs the effector function of $CD8^+$ TILs.

Their results expand our thinking about two conventional facets in immunology and how they function and interplay. First, the complement system is traditionally considered to be a component of the innate immune response. Since 2002, several research groups unexpectedly observed that complement proteins, such as anaphylatoxins C3a and C5a, can be produced by T cells and other immune effector cells. The anaphylatoxins interact with their receptors, C3aR/C5aR, which are expressed on the surface of T cells. This interaction activates the

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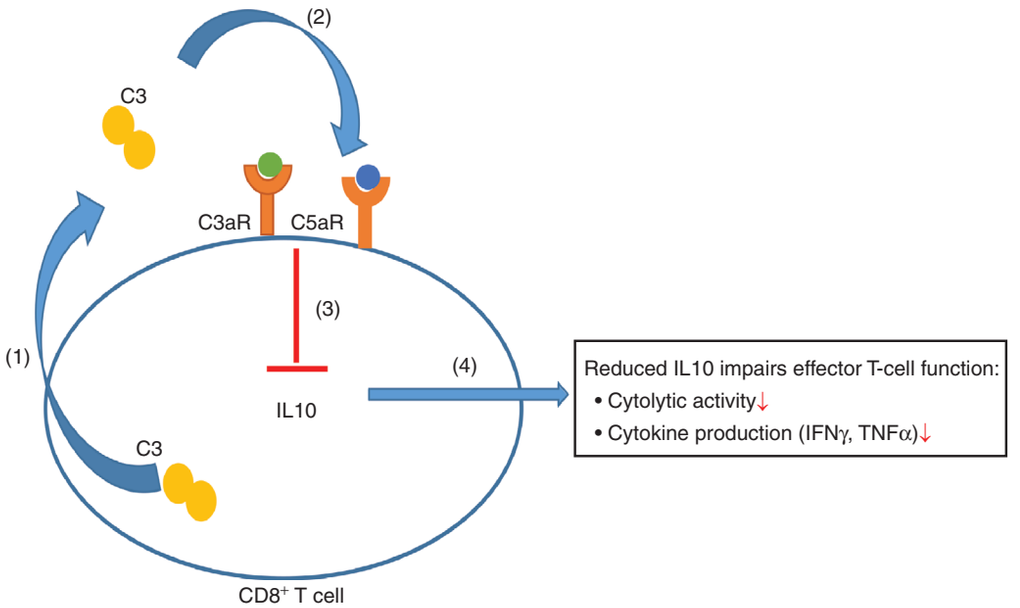

Figure 1. Schematic representation of complement-mediated immunosuppressive effects on the T-cell–mediated antitumor immune response. In the tumor microenvironment, the complement system can modulate the effector function of CD8+ T cells via four steps, as indicated in the figure. Briefly, complement C3 secreted by CD8+ T cells (1) activates C3aR/C5aR signaling on T cells (2). Consequently, the expression level of IL10 in CD8+ T cells is reduced (3). Reduced IL10 expression leads to impaired effector function of CD8+ T cells, including cytolytic activity and cytokine secretion (4).

AKT pathway and leads to an enhanced T-cell–mediated immune response by increasing IFNγ production, in addition to proliferation and survival of T cells (6). However, these studies were mainly performed in autoimmune disease models and focused on CD4+ T cells. The immunologic role of the complement system in TILs, especially CD8+ TILs, remains unknown. In contrast to the autoimmune disease setting, the authors show that the complement system displays an inhibitory role in the T-cell–mediated antitumor immune response, and this role is largely dependent on suppressing the effector function of CD8+ TILs. Second, IL10 is commonly defined as an immunosuppressive cytokine. However, IL10-deficient mice display an increased susceptibility to tumor development, and systemic administration of IL10 delays tumor growth in mice bearing sarcomas, melanoma, or colorectal carcinomas (7, 8). These results indicate that the biological role of IL10 is multifaceted and largely context dependent. Here, the study by Wang and colleagues provides additional evidence to support the antitumor effect of IL10. The establishment of an interplay between the complement system and IL10 gives the first reasonable theory to explain clinical observations from patients with cancer showing a positive correlation between increased complement level and poor clinical outcome (9). Given the complexity of the immune system, the success of this latest study once again emphasizes the importance of unbiased experimental design and an open mind in understanding sophisticated biological events in the T-cell–mediated antitumor immune response.

More importantly, in addition to these new insights into T-cell biology, the authors found that blocking the complement signaling by complement receptor antagonists synergizes with PD-1 pathway blockade to delay tumor progression in a murine melanoma model. It suggests that releasing the "complement" brake naturally present in CD8+ TILs can efficiently enhance T-cell–mediated antitumor immune activity. Their findings support the development of complement inhibitors in cancer treatment. However, tumor cells are largely heterogeneous. Tumors from different types of tissues or bearing different oncogenic mutations have been reported to display different sensitivities to T-cell–based immunotherapy. Therefore, it is possible that the inhibitory role of the complement system on the T-cell–mediated antitumor immune response will apply to certain types of cancers, such as melanoma, but may not be universally applicable.

To translate this preclinical study and de-risk the clinical development of complement inhibitors, further studies are required to evaluate the antitumor activity of complement receptor antagonists in additional types of tumors. Moreover, besides blockade of the CTLA4 and PD-1 pathways, additional promising approaches to activating tumor-reactive T cells are under clinical development. These approaches include but are not limited to: (i) targeting inhibitory molecules, such as LAG3 and indoleamine 2,3-dioxygenase; (ii) activating stimulatory molecules such as OX40, GITR, 4-1BB, CD40, and CD27; (iii) adoptively transferring tumor-reactive T cells; and (iv) tumor antigen–based vaccination. Defining the toxicity profile and therapeutic effect of complement inhibitors in combination with the above-listed approaches will help us to better fit complement inhibitors to the landscape of current cancer immunotherapy.

Overall, this report reshapes several conventional facets and recalls our attention to the complement system, which

may be underappreciated in the field of tumor immunology. This study highlights the T-cell coinhibitory role of complement receptors and shows the potential application of complement receptor inhibitors in cancer therapy. Although further studies are required to confirm their results in other types of cancer, their study opens a new avenue for us to modulate the T-cell–mediated antitumor immune response. Last but not least, given that this study focused only on complement C3 and its fragments, it will be beneficial for us to gain a comprehensive understanding of the immunologic role of the complement system in antitumor immunity by studying other key complement molecules, such as C1q and DAF, which have been reported to have an immunologic role on T cells in other pathogenic settings (10).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

1. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol 2013;13:227–42.
2. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol 2013;14:1014–22.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
4. Wang Y, Sun S-N, Liu Q, Yu Y-Y, Guo J, Wang K, et al. Autocrine complement inhibits IL10-dependent T-cell–mediated antitumor immunity to promote tumor progression. Cancer Discov 2016;6:1022–35.
5. Trandem K, Zhao J, Fleming E, Perlman S. Highly activated cytotoxic CD8 T cells express protective IL-10 at the peak of coronavirus-induced encephalitis. J Immunol 2011;186:3642–52.
6. Kwan WH, van der Touw W, Heeger PS. Complement regulation of T cell immunity. Immunol Res 2012;54:247–53.
7. Berman RM, Suzuki T, Tahara H, Robbins PD, Narula SK, Lotze MT. Systemic administration of cellular IL-10 induces an effective, specific, and long-lived immune response against established tumors in mice. J Immunol 1996;157:231–8.
8. Tanikawa T, Wilke CM, Kryczek I, Chen GY, Kao J, Nunez G, et al. Interleukin-10 ablation promotes tumor development, growth, and metastasis. Cancer Res 2012;72:420–9.
9. Pio R, Corrales L, Lambris JD. The role of complement in tumor growth. Adv Exp Med Biol 2014;772:229–62.
10. Clarke EV, Tenner AJ. Complement modulation of T cell immune responses during homeostasis and disease. J Leukoc Biol 2014;96:745–56.

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