The complement system is characterized by proteins, which participate both in the innate immune response, opsonizing pathogens, and also in the adaptive immune response, inducing a cascade of inflammatory reactions. Produced by the liver, the highest concentration of complement proteins is found in the plasma and are sparsely in the intracellular spaces and in another body tissues (1-5). The origin of its name comes directly from its function as a “complement” to the antibodies’ antimicrobial reactions, activated by three basic pathways: classic, lectin, and alternative. Independent of one another, C3 and C5 are common points of activation of each pathway in the complement system (6-8).

Another important mechanism of the inflammatory response is the liberation of C3a and C5a, also known as anaphylatoxins. Several mechanisms have been described as to how these anaphylatoxins promote tumor growth. First, these anaphylatoxins aid in the evasion of both the innate and adaptive immune systems, as well as promote the proliferation and migration of tumor cells. Furthermore, they promote angiogenesis and specifically the inactivation of the adaptive immune system leads to increased resistance via stimulation of the myeloid derived suppressor cells and regulatory T cells (Tregs). Additionally, these anaphylatoxins increase the production of IL-10 and inhibit the expression of tumor necrosis factor-alpha (TNF-α), IL-12, and interferon gamma (IFNγ) in the tumor microenvironment (9-11).

In lung cancer, recent studies have demonstrated higher concentrations and expression of C3a and of C5a by tumor cells in comparison to nonmalignant cells (12). This newfound relationship between the complement system and cancer development offers novel insights for therapeutic use. Animal model studies have shown that blocking C3a causes a decrease in tumor growth and this finding was additionally found with C5a antagonism (13,14).

In another animal study by Kwak et al., the authors reported increased levels of C3 after engraftment of tumor cells in the lungs. This study compared C3-deficient and wild-type mice and found that the C3-deficient cohort had fewer metastases to other lung areas and greater amounts of CD3+, CD4+, and CD8+ T cell tumor infiltration. The authors reported that the complement proteins were produced solely by the host and not by the tumor. Additionally, the authors found that only the classic pathway of complement system activation was related to tumoral immunology (15).

Studies evaluating the complement system as a future target for therapies are promising. However, the available analyses were all done in animal models designed with optimal tumor microenvironments.

Interestingly, Lin et al. reported a correlation of longer overall survival and higher tumor infiltration by CD4+ and
CD8+ T cells in patients with higher levels of C3a, contrary to the findings previously described (16).

Additional studies are necessary to better identify the relationship between the inactivation of the complement system and CD4+ and CD8+ T cell production. Likewise, future studies could potentially shed light on how complement induces Tregs to generate a more immune-resistant tumor microenvironment.

Another concern regarding complement system inactivation in clinical practice is the potential for adverse reactions. There is an intrinsic relationship between the complement system and immune system; where inhibiting complement could potentially hinder the body’s immunologic response, ability to regenerate tissue, and perform angiogenesis (7).

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Footnote

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