Editorial

How complement activation via a C3a receptor pathway alters CD4+ T lymphocytes and mediates lung cancer progression? —future perspectives

Marcos Magalhães Filho[1], Pedro Nazareth Aguiar Junior[1,2], Jacob J. Adashek[3], Ramon Andrade De Mello[4,5,6]

[1]Faculdade de Medicina do ABC, Santo André, Brazil; [2]Américas Centro de Oncologia Integrado, São Paulo, Brazil; [3]Western University of Health Sciences, College of Osteopathic Medicine of the Pacific, Pomona, CA, USA; [4]Departament of Medical Oncology, State Hospital of Bauru, Bauru, São Paulo, Brazil; [5]Faculdade de Medicina, Universidade Nove de Julho, Bauru, São Paulo, Brazil; [6]Departamento de Ciências Biomédicas e Medicina, Universidade do Algarve, Faro, Portugal

Correspondence to: Ramon Andrade De Mello, MD, FACP, PhD. Division of Oncology, Faculdade de Medicina, Universidade Nove de Julho, Bauru, São Paulo, Brazil. Email: ramondemello@gmail.com.

Comment on: Kwak JW, Laskowski J, Li HY, *et al.* Complement Activation via a C3a Receptor Pathway Alters CD4$^+$ T Lymphocytes and Mediates Lung Cancer Progression. Cancer Res 2018;78:143-56.

Submitted Jan 23, 2019. Accepted for publication Jan 28, 2019.
doi: 10.21037/jtd.2019.02.21
View this article at: http://dx.doi.org/10.21037/jtd.2019.02.21

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).

Acknowledgements

Funding: Research grant from Brazilian National Development Council for Science and Technology (CNPQ) number 402621/2016-6.

Footnote

Conflicts of Interest: Dr. M Magalhães Filho has no disclosures. Dr. PN Aguiar Junior reports speaker fees from MERCK CO, outside the submitted work. Mr. JJ Adashek has no disclosures. RA De Mello: advisory board consultant for Zodiac, MSD, Pfizer. Speaker fee from Astrazenenca, Novartis. Honoraria from National Medical Research Council, Singapure, and National Science Centre, Krakow, Poland.

References

1. Walport MJ. Complement. N Engl J Med 2001;344:1058-66.
2. Wen L, Atkinson JP, Giclas PC. Clinical and laboratory evaluation of complement deficiency. J Allergy Clin Immunol 2004;113:585-93; quiz 594.
3. Wallis R, Mitchell DA, Schmid R, et al. Paths reunited: Initiation of the classical and lectin pathways of complement activation. Immunobiology 2010;215:1-11.
4. Mathern DR, Heeger PS. Molecules Great and Small: The Complement System. Clin J Am Soc Nephrol 2015;10:1636-50.
5. Varela JC, Tomlinson S. Complement: an overview for the clinician. Hematol Oncol Clin North Am 2015;29:409-27.
6. Holers VM. Complement and its receptors: new insights into human disease. Annu Rev Immunol 2014;32:433-59.
7. Ricklin D, Hajishengallis G, Yang K, et al. Complement: a key system for immune surveillance and homeostasis. Nat Immunol 2010;11:785-97.
8. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses. Cell Res 2010;20:34-50.
9. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.
10. Carroll MC, Isenman DE. Regulation of humoral immunity by complement. Immunity 2012;37:199-207.
11. Li K, Anderson KJ, Peng Q, et al. Cyclic AMP plays a critical role in C3a-receptor-mediated regulation of dendritic cells in antigen uptake and T-cell stimulation. Blood 2008;112:5084-94.
12. Corrales L, Ajona D, Rafail S, et al. Anaphylatoxin C5a creates a favorable microenvironment for lung cancer progression. J Immunol 2012;189:4674-83.
13. Nunez-Cruz S, Gimotty PA, Guerra MW, et al. Genetic and pharmacologic inhibition of complement impairs endothelial cell function and ablates ovarian cancer neovascularization. Neoplasia 2012;14:994-1004.
14. Markiewski MM, DeAngelis RA, Benencia F, et al. Modulation of the antitumor .immune response by complement. Nat Immunol 2008;9:1225-35.
15. Kwak JW, Laskowski J, Li HY, et al. Complement Activation via a C3a Receptor Pathway Alters CD4+ T Lymphocytes and Mediates Lung Cancer Progression. Cancer Res 2018;78:143-56.
16. Lin K, He S, He L, et al. Complement component 3 is a prognostic factor of non small cell lung cancer. Mol Med Rep 2014;10:811-7.

Cite this article as: Magalhães Filho M, Aguiar Junior PN, Adashek JJ, De Mello RA. How complement activation via a C3a receptor pathway alters CD4+ T lymphocytes and mediates lung cancer progression?—future perspectives. J Thorac Dis 2019;11(Suppl 3):S210-S211. doi: 10.21037/jtd.2019.02.21

