Complementing the tumor-specific immunity in tumor radiotherapy

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The role of immune system and inflammation in tumor development has recently rekindled the attention of researchers and Douglas Hanahan and Robert A. Weinberg have listed them to one of the ten cancer hallmarks (1). Though the protective function of immune system to fight against infection was widely recognized (2), its role in tumorigenesis has been a controversial topic because while adaptive and innate immunity convincingly demonstrate anti-cancer function, certain clinical observations and animal experiments showed that the immune system could also promote the spontaneous and chemically-induced cancer development (3). Recent researches demonstrated that immune system could be manipulated as an auxiliary tool for therapeutic strategies of chemotherapy and radiotherapy to destroy cancer (4-6).

Radiotherapy is a standard treatment for cancer that triggers massive and irreversible damage to DNA. While radiotherapy was reckoned as a classical immunosuppressive treatment, accumulating evidence illustrates that it also serves a local tumor-specific immunity supporting role. This type of classical treatment strategy could induce increased presence or function of tumor-infiltrating CD8+ T cells, type I interferon (IFN) resulting in enhanced antigen cross-presentation (7), increased expression of major histocompatibility complex (MHC) class I glycoproteins and tumor-associated antigens (8), and maturation of tumor-associated dendritic cells (DCs) (9). These immunological events could further enhance the tumor-destroying effects. However, the possible upstream events that initiate these alterations remain to be elucidated.

To identify the upstream events that might be responsible for these immunological alterations of the tumor-specific immunity in tumor radiotherapy, Laura *et al.* conducted an unbiased analysis of immune response-related transcripts after radiotherapy in a preclinical model of melanoma and found that the local production of pro-inflammatory anaphylatoxins C3a and C5a was essential to the tumor response to radiotherapy. More interestingly, the authors identified that the microenvironmental complement was produced by local immune cells like DCs and CD8+ T cells. The complement system has been traditionally considered only to "complement" the action of the immune system in the antibody-mediated defense against pathogens. The role of complement in other pathological and physiological processes like as transplant rejection, autoimmunity, neurodegeneration, cell malignant transformation or the therapeutic process of these conditions is still a realm remained to be mined. In particular, the functions of the complement system in cancer is still controversial as the production of complement-inhibiting proteins by tumor cells or stroma has been suggested to promote tumor growth (10), whereas it is also proposed that complement in the context of chronic inflammation promotes tumor growth, migration and angiogenesis (11). Interestingly, this research coheres to a previous publication showing increased efficacy of fractionated radiotherapy when C3 was blocked (12), which further gives support to the notion that in certain context; complement system could exert tumor-killing effects. These results indicate that anaphylatoxins are critical players in radiotherapy-induced tumor-specific

immunity and subsequent clinical responses, which could be manipulated in future clinical practice for reinforcing the therapeutic efficacy of cancer treatment.

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Footnote

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References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
2. Janeway CA Jr. How the immune system works to protect the host from infection: a personal view. Proc Natl Acad Sci U S A 2001;98:7461-8.
3. de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. Nat Rev Cancer 2006;6:24-37.
4. Bhattacharyya T, Purushothaman K, Puthiyottil SS, et al. Immunological interactions in radiotherapy-opening a new window of opportunity. Ann Transl Med 2016;4:51.
5. Weir GM, Liwski RS, Mansour M. Immune modulation by chemotherapy or immunotherapy to enhance cancer vaccines. Cancers (Basel) 2011;3:3114-42.
6. Bracci L, Schiavoni G, Sistigu A, et al. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ 2014;21:15-25.
7. Takeshima T, Chamoto K, Wakita D, et al. Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy. Cancer Res 2010;70:2697-706.
8. Burnette BC, Liang H, Lee Y, et al. The efficacy of radiotherapy relies upon induction of type i interferon-dependent innate and adaptive immunity. Cancer Res 2011;71:2488-96.
9. Gupta A, Probst HC, Vuong V, et al. Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation. J Immunol 2012;189:558-66.
10. Kolev M, Towner L, Donev R. Complement in cancer and cancer immunotherapy. Arch Immunol Ther Exp (Warsz) 2011;59:407-19.
11. Pio R, Corrales L, Lambris JD. The role of complement in tumor growth. Adv Exp Med Biol 2014;772:229-62.
12. Elvington M, Scheiber M, Yang X, et al. Complement-dependent modulation of antitumor immunity following radiation therapy. Cell Rep 2014;8:818-30.

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