



CD8⁺ T effector targeted elimination of regulatory tumor stroma cells for improved immunotherapy

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Mounting preclinical and clinical evidence over the past several decades implicated immune system in controlling malignancies. However, the translation of this knowledge into clinical benefit for cancer treatment has just recently been realized. A tumor-associated antigen (TAA) pulsed dendritic cell-based vaccine was the first immunotherapy product against cancer to be approved by FDA in the United States (1). This development not only overcame skepticisms about the potential of cancer immunotherapy, but most importantly galvanized the field for the development of various forms of immunotherapies. A major setback for the cancer immunotherapy field has been the lack of comprehensive understanding of interactions between tumors and the immune system and how such interactions could be exploited for the development of effective immune therapies. The discovery that tumor uses a complex set of extrinsic and intrinsic mechanisms to evade the immune system paved the way for the design of effective immunotherapies with significant positive impact recently. For example, the discovery that tumors utilize the immune checkpoint receptors, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathway, to effectively evade T cell responses resulted in FDA-approved therapies against various cancer types using blocking antibodies to these molecules (2,3). The checkpoint blockers, however, are only effective for certain tumor types and the efficacy is limited to a fraction (~30%) of treated patient population with the responsive tumors. Combined therapy with both checkpoint blockers in advanced melanoma was recently reported to reach an objective response rate of 61% with drug-related adverse events of grade 3-4 in 54% of patients (4). The question is if complementary approaches, particularly TAA-based vaccine could further improve the efficacy of immune

checkpoint blockers, reduce drug-related adverse effects, and broaden their application to unresponsive tumor types.

In addition to intrinsic mechanisms, tumors have also evolved to employ various extrinsic mechanisms to evade the immune system. Nonmalignant tumor stroma and the regulatory arm of the immune system represent such extrinsic mechanisms. Tumor stroma not only serves as a regulated physical barrier to intratumoral infiltration of immune effector cells, but also actively downregulates effector immune responses while promoting immune suppressive regulatory cells. For example, endothelial cells in tumor stroma were shown to upregulate FasL expression in response to prostaglandins and vascular endothelial growth factors and preferentially induce apoptosis in tumor infiltrating CD8⁺ T effector cells, but not CD4 + CD25 + FoxP3 + T regulatory (Treg) cells (5). Another regulatory cell population that has been specifically recruited into the tumor by stroma is myeloid derived suppressor cells (MDSC). Both Treg cells and MDSC represent major obstacles for the efficacy of various immunotherapies and in particular cancer vaccines. Systemic depletion of these regulatory cells may have unwanted consequences due to their roles in immune homeostasis. Therefore, targeted approaches to functionally and/or physically eliminate these cells within tumor microenvironment will have a significant clinical benefit.

A recent paper by Wu *et al.* published in *Clinical Cancer Research* has demonstrated that radiotherapy combined with intratumorally delivered TAAs as vaccine provides an effective means of priming CD8⁺ T effector cells not only against tumor, but also stromal cells and MDSC within the tumor microenvironment (6). Intratumoral injection of a peptide representing a dominant CD8⁺ T cell epitope for human papilloma virus E7 following radiotherapy was shown to mobilize DCs within tumor draining LNs for antigen

cross-presentation, activation of CD8⁺ T cells, and effective elimination of E7 expressing TC-1 tumor in mice. The therapeutic efficacy of this approach was associated with CD8⁺ T effector cells killing not only the tumor, but also MDSC cross-presenting TAA. Sensitivity to killing by CD8⁺ T cells was limited to MDSCs as intratumoral macrophages cross-presenting TAA were not killed. Importantly, the elimination of MDSC by CD8⁺ T cells did not require antigens expressed by the tumor. Mice treated with intratumoral injection of tumor-unrelated antigens, such as OVA and influenza NS1, following radiotherapy had decreased intratumoral MDSC and showed therapeutic efficacy. This effect was limited to intratumoral, but not a distant site, injection of the peptides and required signaling via type I IFN receptor and Toll-like receptor 4. Mice deficient in one of these receptors did not show therapeutic efficacy, implicating these innate immune pathways in effector immune responses against tumor, and suggesting that the radiotherapy-induced death of a tumor has immune adjuvant effect.

Specific functional and/or physical intratumoral depletion of MDSC or Treg cells has important implications for cancer immunotherapy. First, local elimination of regulatory cells will prevent significant adverse effects associated with systemic depletion of such cells and, in particular, avoids the risk of autoimmunity. Second, this approach may provide better efficacy as it occurs at the target, where a balance favorable to immune effectors is paramount for the destruction of the tumor. It remains to be seen if the therapeutic efficacy observed with this treatment modality applies to other tumor types, particularly using a bona fide endogenous TAA as vaccine. More importantly, if effective approaches for targeted delivery of antigens can be developed for tumors that are not amenable to intratumoral injection, and if such delivery approaches will achieve a similar therapeutic efficacy to that generated by intratumoral injection of TAA. Exploiting the adjuvanticity of danger molecules released by dying tumors may have significant implications for cancer immunotherapy. Such adjuvants are expected to have localized effects, thereby lacking adverse effects associated with systemic use of exogenous adjuvants. In this context, it will be important to test if the endogenous adjuvant activity seen with radiotherapy is also a common feature of any nonimmune therapy that target tumors for physical destruction.

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Conflicts of Interest: H Shirwan is the CEO and CSO of FasCure Therapeutics which develops adjuvant system for vaccines.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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