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Commentary

Role of Endogenous T-Cell Immunity and Response to Immune Checkpoint Inhibition

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DESCRIPTION

According to the immunoediting theory, the intratumoral immunity that targets tumor neoantigens primarily makes up the endogenous antitumor immunity that controls tumor evolution. The identification of Immune Checkpoint Inhibitors (ICI) (such CTLA-4 and PD-1), as well as the subsequent development of monoclonal antibodies that target these inhibitory receptors and their associated ligands, have significantly improved the modulation of endogenous antitumor immunity. Through ICI-based immunotherapy, the critical function of endogenous T-cell immunity in regulating tumor growth has been identified. A transition from a pre-existing antitumor immune response to a treatment-regulated immune response is caused by dynamic changes in the intratumor immune landscape. This is supported by enough clinical evidence to suggest that in order for anticancer treatments to be effective, they must induce *de novo* antitumor immunity or revive the endogenous antitumor response. Therefore, it can be argued that successful endogenous antitumor immunity requires immunological ($CD8^+$) T cell infiltration into inflammatory tumors.

Non-inflamed tumors, on the other hand, don't have immune lymphocyte infiltrates and don't respond to ICI. However, it's important to keep in mind that these non-inflamed tumors may still express neoantigens that T cells can detect and that there are still ways to make them more vulnerable to immune attack. For instance, the findings that CTLA-4 blockade induces intratumoral infiltration of tumor-reactive T cells and PD-1 inhibition activates intratumoral T cells support the use of these two antibodies in combination as the most effective method for inducing antitumor immunity in tumors that are not T-cell inflamed. The absence of T-cell attracting chemokines may also contribute to T-cell exclusion from the tumor. For instance, it has been discovered that constitutive activation of the -catenin pathway inhibits STING activation, which is followed by inadequate type I interferon production and inadequate recruitment of mature dendritic cells, both of which contribute to low levels of CXCL9 and CXCL10 and insufficient T-cell infiltration. Because T cells may be drawn into the tumors as a result of suppression of -catenin signaling, ICI may be used in combination with other therapies.

By inducing the response of vaccine-specific and neoantigen-targeting T cells, therapeutic cancer vaccines based on neoantigen targeting may also enable tumor infiltration; this represents an alternative therapeutic approach that aims to create a *de novo* T-cell-inflamed tumor and to combine vaccines with ICI. Based on these findings, the intratumoral environment and endogenous antitumor immunity may play a major role in dictating how therapeutic responses to ICI turn out. Therefore, to evaluate the topic of how much the neo-antigenic landscape influences intratumoral antitumor immunity, it is crucial to look at the differences between clonal *vs.* subclonal expression of neoantigens in tumors with high Tumor Mutational Burden (TMB) and their respective clinical responses to ICI. To this purpose, it is crucial to make reference to clinical studies in which the development of new tumor subclones and an increase in genetic modifications during chemotherapy imply that chemotherapy can enhance TMB and intratumor heterogeneity, leading to a reduction in clinical response.

As mentioned above, tumor cells can still use mechanisms of acquired immune resistance that may impede the development of antitumor immunity, such as those that affect the tumor antigen-presentation machinery, even though clonal expression of neoantigens is associated with clinical efficacy after ICI. Under the selective immunological pressure of T cells directed against immunogenic neoantigens, many forms of escape tumors may form during immunoediting. Therefore, it becomes sense to assume that immune selection affects neoantigen heterogeneity by removing the bulk of tumor cells and producing more clonal tumors. This suggests that tumor T-cell infiltration is necessary for tumor clonality and, in turn, for clinical success during ICI treatments.

Contrarily, tumors without endogenous antitumor immunity (i.e., lacking intratumoral T cells) may produce subclonal neo-antigenic heterogeneity, resulting in tumor heterogeneity that is linked to clinical failures during ICI. The question of whether the tumor's heterogeneity is shaped by the strength of the immune pressure or whether the degree of tumor heterogeneity

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determines the robustness of the antitumor immune response is raised and one could also argue that high levels of tumor neo-antigenic heterogeneity dampen antitumor immune reactivity even in T-cell-infiltrated tumors. These scenarios may lead to the variable intratumoral expression of neoantigens and the subsequent development of intratumoral TCR heterogeneity, which in turn reflects the variations in the capacity of various tumor compartments to produce antitumor immunity. The integration of neo-antigenic heterogeneity, which will confer positive clinical outcomes following ICI, and for enabling the formulation of more effective treatment methods will be made possible by further unraveling the process of tumor clonal evolution in response to selective immunological pressure.