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Therapeutic potential of the TRIM21-Notch1 axis blockade in triple-negative breast cancer

Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype representing about 15% of diagnosed breast cancer patients. TNBC is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor 2 (HER2). Effective breast cancer treatments typically block the growth-simulating effects of ER, PR, and/or HER2. The lack of these therapeutic targets makes treating TNBC especially difficult resulting in a poor prognosis for TNBC patients. Therefore, the identification of alternative therapy targets is critical to the development of new and effective treatment options for TNBC. A core attribute of cancer cells is their capability to induce immunosuppression and circumvent the body's immune system. The Notch1 signaling pathway is a key component in T-cell activation and proliferation. In addition, this signaling pathway has been shown to modulate antitumor immune responses. Our previous studies established that activation of the Adenosine A2A receptor (A2AR) pathway, by tumor-induced immunosuppressive signals, downregulates Notch1 in T-cells thereby decreasing their anticancer response. Activation of A2AR positively regulates casitas B-lineage lymphoma b (Cbl-b), an E3 ubiquitin ligase that promotes Notch1 degradation. We also previously demonstrated that reactivation of Notch1 in T-cells overcomes immunosuppression when the A2AR pathway is inhibited using a Cbl-b inhibitor. Tripartite motif containing-21 (TRIM21) is another E3 ubiquitin ligase that may have a regulatory function in adenosine-mediated activation of the A2AR pathway, potentially influencing the immune response through inhibition of Cbl-b, thereby presenting a promising target for therapeutic intervention. In this study, we investigated multiple therapeutic strategies that may either activate or inhibit TRIM21 and/or Cbl-b. We tested dihydroartemisinin (DHA), an effective treatment for malaria, vilazodone (VZD), an antidepressant, NTX-801, a known Cbl-b inhibitor, and CGS-21680, a known A2AR agonist. Our findings indicated that DHA, VZD, and CGS-21680 promote tumor progression via an immunosuppressive mechanism while NTX-801 enhances the anticancer immune response. Specifically, we found that DHA, CGS-21680 and VZD reduce proliferation and activation of T-cells as well as Notch1 expression while NTX-801 displayed an opposite effect in primary cell cultures. Furthermore, *in vivo* and *ex-vivo* studies revealed increased tumor progression and reduced T-cell responses in a TNBC mouse model treated with DHA which was in contrast to the anticancer effect of NTX-801 observed in a previous study. These findings suggest that the TRIM21-Notch1 axis is a promising therapeutic target in the treatment of TNBC. Future studies will focus on identifying a viable anti-tumor drug agent targeting the TRIM21-Notch1 axis.