Kimberly D. McCarter, PhD
GeneBIORETS Summer 2025
Huntington High School
Shreveport, LA

Giulia Monticone, PhD
LSUHSC-New Orleans, Louisiana Cancer Research Center

Trim21 is a critical modulator of Notch1-dependent T-cell antitumor immunity in triple-negative breast cancer

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that accounts for approximately 15% of all breast cancer diagnoses. It is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), making many conventional targeted therapies ineffective. As a result, patients with TNBC often experience poor clinical outcomes, highlighting the urgent need to identify novel therapeutic targets capable of improving treatment efficacy. One of the defining features of TNBC is its ability to evade immune surveillance by establishing an immunosuppressive tumor microenvironment. The Notch1 signaling pathway plays a critical role in T-cell activation, proliferation, and antitumor immune responses. Our previous studies demonstrated that tumor-derived adenosine activates the Adenosine A2A receptor (A2AR) pathway, leading to suppression of Notch1 signaling and impaired T-cell function. We further showed that activation of A2AR increases expression of the E3 ubiquitin ligase casitas B-lineage lymphoma-b (Cbl-b), promoting Notch1 degradation, whereas pharmacologic inhibition of Cbl-b restores Notch1 signaling and enhances T-cell-mediated antitumor activity. Our recent findings have identified tripartite motif-containing protein 21 (TRIM21), another E3 ubiquitin ligase, as a potential upstream regulator of this signaling network. We hypothesize that TRIM21 modulates adenosine-mediated A2AR signaling through regulation of Cbl-b, thereby influencing Notch1 stability and downstream T-cell activation. These observations suggest that both TRIM21 and Cbl-b represent promising therapeutic targets for overcoming tumor-induced immunosuppression in TNBC. To investigate this signaling axis, we evaluated several pharmacologic agents predicted to modulate TRIM21 and/or Cbl-b activity, including quisinostat (QST), dihydroartemisinin (DHA), vilazodone (VZD), and NTX-801, a Cbl-b inhibitor. Mouse T cells were treated with each compound and analyzed using multiparameter flow cytometry to quantify changes in T-cell populations (CD3, CD4, and CD8), activation status (CD69), intracellular Notch1, TRIM21 and Cblb expression, and effector function through interferon-γ (IFN-γ) production. Selected compounds were then used to treat TNBC immunocompetent mouse models. In parallel, computational molecular docking studies were performed to evaluate predicted binding interactions between these therapeutic candidates and TRIM21, providing structural insight into potential mechanisms of action. Together, these complementary experimental and computational approaches seek to identify novel immunomodulatory strategies capable of restoring T-cell function and enhancing antitumor immunity in TNBC.