Tumor Microenvironmental Signatures Associated With Low DARC/ACKR1 Expression in Solid Tumors, and Potential Mechanistic Insights

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Atypical Chemokine Receptor 1 (ACKR1/DARC) is a non-signaling chemokine receptor expressed on erythrocytes and endothelial cells. In tumors, ACKR1 modulates inflammation, chemokine gradients, and immune trafficking in the tumor microenvironment (TME). ACKR1 underexpression is associated with poor prognosis in breast cancer (BC), possibly contributing to the 40% higher mortality rate in Black women with BC compared to White women. This study aimed to (a) identify factors regulating ACKR1 intratumoral expression, (b) examine TME features of low-ACKR1 tumors to elucidate their biology, and (c) understand how ACKR1 downregulation impacts development of tumor-supportive vasculature and aggressive phenotypes. muTarget analyses revealed that ACKR1 expression was TP53-responsive in BC; thus, loss of p53 function may contribute to ACKR1 downregulation in BCs. Pairwise correlation analyses between ACKR1, its upstream regulators, and established proliferation and tumor aggressiveness markers (including epigenetic regulators) showed low-ACKR1 breast tumors to be highly proliferative despite poor angiogenic support. TIMER2.0 was used to estimate enrichment scores of TME cell types in 7 selected cancer types, and showed conspicuous depletion of endothelial cells, hematopoietic stem cells, and cancer-associated fibroblasts across all 7 cancer types. In KM Plotter, a novel prognostic signature that leveraged the aforementioned features of low-ACKR1 tumors was developed. Tumors expressing above cutpoint levels of this gene signature showed poorer overall survival across 5 cancer types. Collectively, this study translates novel mechanistic insights and pan-cancer low-ACKR1 TME phenotypes into a potential tool for identifying high-risk hypovascularized tumors for personalized treatment.

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