Determining the Role of Inflammatory Signaling on B7H3 Expression for Triple-Negative Breast Cancer

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Obesity is a major risk factor for breast cancer and its prevalence continues to rise in the United States. Obesity drives immunosuppression in multiple cancer types, including triple-negative breast cancer (TNBC). The underlying mechanisms of obesity-driven immunosuppression are only partially understood but likely involve inflammation. B7 Homology 3 (B7H3), an immunosuppressive protein highly expressed in TNBC, is associated with poor prognosis. Hence, identifying how B7H3 expression is regulated in TNBC is critical to understanding its role in tumor progression. Given that other members of the B7 family (such as programmed death-ligand 1 [PDL1]) are regulated by inflammatory cytokines, we hypothesized that the inflammatory cytokines interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα) would promote B7H3 expression in TNBC cells.

E0771 cells (murine TNBC) were treated alone or in combination with IFNγ (20 ng/ml), and/or TNFα (20 ng/ml) for 4 or 24 hours. Western blots and qPCR were used to determine PDL1 and B7H3 protein and gene expression levels, respectively. We confirmed activation of IFNγ and TNFα target pathways by western blot following 24 hours of the respective individual cytokine treatments. At 24-hour time points, individual treatment with IFNγ or TNFα significantly upregulated B7H3 expression in E0771 relative to untreated control. Combined cytokine treatment increased B7H3 expression by 80% compared to the untreated control.

Taken together our findings reveal previously unknown regulation of B7H3 expression by inflammatory cytokines. Inflammatory cytokine signaling promotes cancer proliferation and immunosuppression in part by upregulating other members of the B7 family, such as PDL1. Thus, our finding that B7H3 is also induced by inflammatory cytokine signaling may represent a novel axis through which inflammation, including that driven by obesity, may promote tumor progression.