Synergistic effects of OSM and TNFα on estrogen receptor expression in breast cancer

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Currently endocrine therapy of breast cancer is the most important systemic treatment available for estrogen-receptor alpha (ERα)-positive breast cancer. Unfortunately, up to 50% of these patients will fail ER-targeted therapies due to either de novo or acquired resistance. It has recently been shown that inflammation derived cytokines may be a player in the development of more aggressive, therapy-resistant ER-positive breast cancers. Previous studies have focused predominantly on cytokines such as IL-6, IL-1α, TNFα, and TGFβ. Oncostatin M (OSM) is an IL-6 family cytokine that is produced at high levels by macrophages and other immune cell types. We have recently shown that OSM suppresses ERα in breast tumor cell lines and we have found correlations between OSM and low ER and reduced levels of ER regulated genes in breast tumors, suggesting that this may be a functional and clinically important pathway in-vivo. Also we have found that while OSM is the most effective, some other cytokines (TNFα, TGFβ1, TGFβ2, IL-1β, IL-8) also influence ER expression, and synergistic effects between OSM and TNFα result in the most significant suppression. Additionally, our results suggest that these cytokine effects on ER are associated with parallel induction of the S100A7 gene in cell lines. S100A7 may serve as a biomarker of cytokine action. It also mediates some of the effects of OSM and promotes tumor progression through pro-survival and invasive pathways, and influences the pattern of inflammation through its chemotactic effects on inflammatory cells. Ongoing work seeks to confirm these observations in the in-vivo setting and establish a role for these effects in the resistance to endocrine therapy.