GAMMA DELTA T CELLS AND NODAL IN THE BREAST TUMOUR MICROENVIRONMENT

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Gamma delta T cells (GDTc) kill transformed cells, and increased circulating GDTc levels correlate with improved outcome in cancer patients. However, among a panel of various tumor infiltrating lymphocytes (TIL), GDTc were deemed the most significant independent factor predicting negative clinical outcome in human breast cancer. We hypothesize that GDTc become functionally altered by Nodal, an embryonic morphogen secreted by breast tumour cells in the hypoxic tumour microenvironment and implicated in aggressive disease. We have identified GDTc TIL in serial sections of breast cancer tissue in which Nodal is also expressed. Under hypoxic compared to normoxic conditions, GDTc viability and cell density increase, as does expression of activating receptor CD56, the gamma delta TCR, HLA-I and CD95; conversely, the inhibitory receptor CD94 is down-regulated. Thus GDTc can survive and proliferate in a hypoxic environment, and are armed with increased activating receptors implicated in cytotoxicity. Blood-derived *in vitro* expanded primary human GDTc kill breast cancer cell lines; however, Nodal-expressing breast cancer cells (231shC) resist GDTc killing compared to those in which Nodal has been silenced (231shN). Thus, Nodal expressed by breast tumour cells appears to suppress GDTc cytotoxicity. Preliminary results from chick chorioallantoic membrane assays suggest greater infiltration of GDTc into 231shN compared to 231shC tumours. Surprisingly, GDTc themselves appear to express Nodal and this expression is induced by hypoxia. Stimulation with recombinant human Nodal results in the tyrosine phosphorylation of a ~50 kDa protein that we aim to identify. We now plan to employ additional cell lines as well as examine GDTc therapy and TIL in xenograft mouse models of breast cancer. Understanding the dynamic interplay between Nodal and GDTc infiltration in breast cancer lesions will be of utmost importance to develop safe and effective GDTc immunotherapies.