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Transforming growth factor-β globally and specifically inhibits Natural killer cells

Human natural killer (NK) cells are important in the innate immune response against viral infection and tumours. In the human tumour microenvironment resident and infiltrating lymphocytes are subjected to a multiple soluble factors that determine their activation status and cell fate. One such factor is Transforming Growth Factor (TGF)-beta a pleiotropic cytokine secreted by tumours but also by multiple cell types such as tumour associated stroma and immune cells such as macrophages.

We have previously shown that TGF-β can counteract NK cell activation, reducing the expression of multiple NK cell activation receptors and effector molecules, such as the cytotoxic apparatus and interferon-gamma. However the extent of this inhibition had not been examined.

Using gene expression profiling and a method for high-throughput multiplex flow cytometry, we have analysed the effect of cytokines and tumour cells on the human NK cell surface phenotype. Our results show that the composition of the NK cell surface is highly dynamic, with numerous cell surface molecules being co-ordinately regulated by activation and inhibition events and we identify a number of novel molecules associated with an inhibited NK cell phenotype. Furthermore, gene expression profiling has identified pathways by which NK cell activation and inhibition might be modulated. Such pathways represent potential targets for agents that might modify NK cell activation to improve the immunosurveillance function of these cells.