The calcineurin/NFAT pathway in lymphoid malignancies

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Calcineurin is a calcium-activated serine/threonine phosphatase critical to pre-TCR signaling during thymocyte development, to TCR-mediated positive selection of thymocytes into mature T cells and to many aspects of the immune response. The critical role of calcineurin in the immune response is underscored by the fact that calcineurin inhibitors, such as cyclosporine A (CsA) and FK506 are powerful immunosuppressants of wide clinical use. We have observed sustained calcineurin activation in human B- and T-cell lymphomas and in mouse models of lymphoid malignancies. In these models, inhibition of calcineurin activity by CsA or FK506 induced apoptosis of leukemic cells, rapid tumor clearance and significantly prolonged mouse survival. Conversely, ectopic expression of a constitutively activated mutant of calcineurin favored leukemia progression [1][2]. Ongoing loss- and gain-of-function genetic approaches aimed at dissecting the function of calcineurin in mouse models of T-ALL/lymphomas will be discussed.

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