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Calcineurin-Nuclear factor of activated T cells axis in early stem cell commitment: a novel pathway in tissue regeneration

OTHER TOPICS

The Nuclear Factor of Activated T Cells (NFAT) is a family of transcription factors composed of five members, four of which (NFATc1-4) are regulated by calcineurin (CN), a calcium-dependent phosphatase. Our group has highlighted additional non-inflammatory roles of NFAT in dendritic cells (DCs).

To investigate the role of the CN-NFAT pathway in early DC differentiation, we transduced a growth factor-dependent splenic DC line with a CN inhibitor (CNi). Inhibiting CN-NFAT signaling increased DC proliferation and altered the cell cycle by prolonging the G2/M phase and shortening the G1 phase. Metabolically, CN-NFAT inhibition induced a pronounced Warburg effect, typical of rapidly proliferating cells and a highly immunosuppressive phenotype. Since this resembled a more “stem-like” state, we extended our focus to adult stem cell (SC) differentiation, studying two tissues with distinct regenerative capacities: the brain and the small intestine/colon.

In vitro, we infected neural stem cells (NSCs) with a lentivirus carrying iCN, while in vivo, we performed intracranial injections targeting the ventricular-subventricular zone. In the intestinal system, we used mice with inducible CN-NFAT inhibition in LGR5+ SCs, found in intestinal and colon crypts. We also employed two disease models: Parkinson’s disease (PD) and dextran sulfate sodium (DSS)-induced colitis. NFAT-CN inhibition led to NSC expansion both in vitro and in vivo under resting conditions and in the PD model. A similar expansion of LGR5+ cells in the intestine resulted in tissue elongation, mitigating DSS-induced colitis damage. Additionally, we identified NFAT as a regulator of an immune checkpoint phase.

We propose that NFAT plays a key role in early SC differentiation, directly or indirectly controlling this process and coordinating immune system surveillance on activated progenitor cells.