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SnapShot: Ca^{2+}-Calcineurin-NFAT Signaling

Gerald R. Crabtree[1] and **Stuart L. Schreiber**[2]

[1] Stanford University School of Medicine, Stanford, CA 94305, USA

[2] Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA

Ca^{2+}-calcineurin-NFAT signaling transmits signals to the nucleus from a wide variety of receptors and is required for developmental events as diverse as axon outgrowth, cardiac morphogenesis, lung morphogenesis, neural crest diversification, epithelial stem cell maintenance, and immune responses. The pathway appears to be particularly dedicated to vertebrate-specific morphogenic events, perhaps reflecting its first evolutionary appearance in vertebrates. Calcineurin-NFAT signaling is the target of the drugs cyclosporin A and FK506 and several viral immune modulators. In addition, its malfunction is implicated in Down's syndrome, diabetes, and cardiac hypertrophy.

Receptors that induce the entry of Ca^{2+} into the cell resulting in the activation of calcineurin phosphatase are shown in the lower left. Ca^{2+} binds to the regulatory subunit of calcineurin as well as to calmodulin to activate the phosphatase activity of calcineurin (Stemmer and Klee, 1994). The immunosuppressive drugs FK506 and cyclosporin A inhibit calcineurin by binding first to the abundant intracellular proteins, FKBP and cyclophilin, respectively. These protein complexes then bind to calcineurin, preventing substrate access (Liu et al., 1991). The specificity of these calcineurin inhibitors is due to the large composite surface arising from FKBP bound to FK506 (see inset structure) (Griffith et al., 1995) or cyclosporin A bound to cyclophilin. FK506 and cyclosporin A are highly specific probes of the NFAT signaling pathway in tissues where the concentration of calcineurin is less than the concentration of FKBP or cyclophilin (Graef et al., 2001). Calcineurin removes several phosphate residues from the N terminus of NFATc proteins, the Ca^{2+}-calcineurin-sensitive subunits of NFAT transcription complexes. Removal of the phosphates exposes nuclear localization sequences in NFATc proteins leading to their rapid entry into the nucleus (Beals et al., 1997a). Once in the nucleus, the NFATc proteins assemble on DNA with partner proteins generically termed NFATn (lower right) that are often the endpoints of other signaling pathways (Crabtree and Olson, 2002). In most cases, NFAT-dependent transcription requires that the Ca^{2+} signaling be coincident with MAP kinase signaling, providing a mechanism for signal integration and coincidence detection.

The targets of NFAT signaling (panel, upper right) are largely cytokines, growth factors and their receptors, proteins involved in cell-cell interactions, as well as many microRNAs. Of particular importance are positive feedback loops initiated by direct binding of NFATc1 and NFATc4 to their promoters as well as the regulation of Ca^{2+} channels, such as the IP3 receptor, responsible for the release of intracellular Ca^{2+} stores (Genazzani et al., 1999). This positive feedback loop appears to be important in committing cells to specific fates. A negative feedback loop mediated by the NFAT-dependent activation of *RCAN* (*DSCR1*) gene expression appears to constrain the pathway (Arron et al., 2006).

NFATc proteins are actively removed from the nucleus by first priming with Dyrk1a or protein kinase A (PKA) followed by phosphorylation by GSK3 (Arron et al., 2006; Beals et al., 1997b; Gwack et al., 2006). The inhibition of GSK3 by AKT and PI3 kinase (PI3K) signaling increases the level of NFATc proteins in the nucleus and hence provides a second means of coincidence detection and signal integration. Many of the phenotypes of Down's syndrome

are thought to be due to the duplication of the *DSCR* and *Dyrk1a* genes on chromosome 21. Increased gene dosage both reduces NFATc import into the nucleus and also facilitates export leading to a reduction in NFATc function and compromised positive feedback (Arron et al., 2006).

Abbreviations

AKT	the cellular homolog of the acute transforming oncogene v-AKT
BCR	B cell receptor
CRAC	Ca^{2+} release-activated Ca^{2+} channel
DSCR1/RCAN	Down's syndrome critical region 1, now called regulator of calcineurin
Dyrk1a	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A
FKBP	FK506-binding protein
GSK3	glycogen synthease kinase 3
IP3R1	inositol 1,4,5-triphosphate receptor 1
NFAT	nuclear factor of activated T cells
NMDA	N-methyl-D-aspartate receptor
NFATc	Ca^{2+}-calcineurin-dependent subunits of NFAT complexes, also cyclosporin-sensitive subunit of NFAT complexes
NFATn	generic name for nuclear subunits of NFAT-transcription complexes
NF-κB	nuclear factor binding to the immunoglobulin kappa locus in B cells
PI3K	phosphatidylinositol 3-kinase
IP3	inositol 1,4,5-triphosphate
PLCγ	phospholipase gamma
STIM	stromal interaction molecule
Sox2	sex determination-box containing gene
TRP	transient receptor potential channel
TCR	T cell receptor
VEGF	vascular endothelial growth factor

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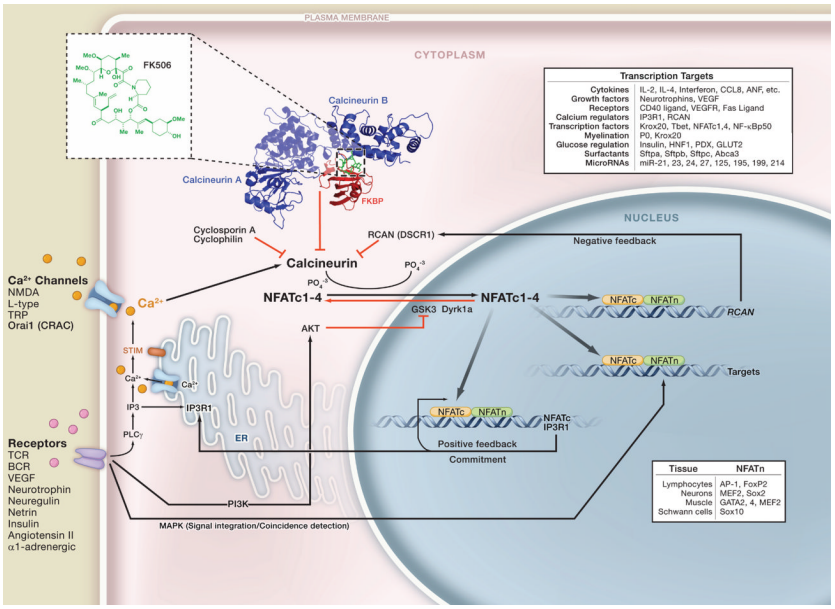

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