Mechanism of action of cyclosporine or tacrolimus (FK506)

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Figure 2. Mechanism of action of cyclosporine or tacrolimus (FK506). In the cytoplasm, cyclosporine (CsA) binds to its immunophilin, cyclophylin (CpN), forming a complex between cyclosporine and CpN. The cyclosporine–CpN complex binds and blocks the function of the enzyme calcineurin (CaN), which has a serine/threonine phosphatase activity. As a result, CaN fails to dephosphorylate the cytoplasmic component of the nuclear factor of activated T cells (NF-ATc), and thereby the transport of NF-ATc to the nucleus and the binding of NF-ATc to the nuclear component of the nuclear factor of activated T cells (NF-ATn). The NF-ATc–NF-ATn complex binds to the promoter of the interleukin 2 (IL-2) gene and initiates IL-2 production. Consequently, T cells do not produce IL-2, which is necessary for full T-cell activation. Tacrolimus (FK506) binds to FK506-binding protein (FKBP), forming a FK506–FKBP complex, which binds to and blocks CaN. The FK506–FKBP–CaN complex inhibits the activation of NF-ATc, thus preventing its entrance into the nucleus. Although the pre-drugs cyclosporine and FK506 bind to different target molecules, both drugs inhibit T-cell activation in the same fashion (fig002ssh).