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Immunophilins and Immunosuppression by Cyclosporins and Macrolide Structures

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The immunosuppressive drug Cyclosporin A has long been used in the prevention and treatment of transplant rejection and a variety of autoimmune diseases, before a basic understanding of its mode of action emerged. Its powerful selective immunosuppressive effect rests on the inhibition of lymphokine gene transcription. In the absence of IL-2, clonal proliferation of antigen-activated T cells cannot occur and therefore the immune system is reversibly inhibited.

A breakthrough in our understanding of the molecular mechanism involved in Cyclosporin-mediated immunosuppression came from the discovery of a highly specific binding protein for Cyclosporins, called Cyclophilin. Since then four different Cyclophilins have been characterized and cloned: Cyclophilins A, B, C and D, which occur in virtually all cell types and are highly conserved in evolution. They are peptidyl-prolyl isomerases (rotamases) which are inhibited by Cyclosporin-binding.

Studies on the molecular mode of action of Cyclosporin were strongly stimulated when the structurally unrelated macrolide FK 506 was found to have effects strikingly similar to those of Cyclosporin A. Like Cyclosporin, FK 506 inhibits T cell proliferation by preventing IL-2 gene-transcription, binds to a family of specific binding proteins called FKBPs, which are also peptidyl-prolyl isomerases (rotamases) and are inhibited by ligand binding.

The lack of correlation between immunophilin binding and immunosuppressive effects of a large variety of Cyclosporins and different macrolides showed unambiguously that binding of Cyclosporins or macrolides to their respective binding proteins (immunophilins) is required, but is not sufficient for immunosuppression. The immunophilin-ligand complexes (Cyclosporin–Cyclophilin or FK 506 FKBP) bind to the calmodulin-dependent serine/threonine phosphatase, calcineurin, thereby inhibiting its phosphatase activity for phospho-peptide substrates.

The molecular targets of the serine/threonine phosphatase calcineurin are most likely cytosolic components of the transcription complex which has to be assembled or activated to make possible coordinated expression of the early T cell activation genes, particularly the IL-2 gene.

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