11.1 Cyclophilin Distribution, Function and Inhibition by Cyclosporine A

11.1.1 Cyclophilins

11.1.1.1 Expression

The Cyp family of proteins share a common enzymatic activity, peptidylprolyl isomerase (PPIase), which serves to effect a *cis–trans* isomerization of amide bonds amino-terminal to proline residues, and thus play a regulatory role in protein folding.[4–6] Currently, 19 members of the Cyp family (Figure 11.1) have been identified in humans, with sizes ranging from small, single PPIase-domain Cyps (CypA, CypB, CypC, CypD, CypJ, PPIL1, PPIAL4 and USA-Cyp) to large multi-domain proteins in which a catalytic PPIase activity is linked to various additional activities.[7] CypA is the most abundantly expressed member of the family, representing the majority of the PPIase activity in a cell, with CypB being the only other Cyp being found above trace level. In addition to the Cyps, two other families of proteins with PPIase activity, FKBPs and parvulins (Figure 11.1), have been described.[8,9] Inhibition of the PPIase activity of FKBPs by either FK506 or rapamycin was shown to be required for the immunosuppressive activity of these compounds,[10] and one member of the parvulin family, Pin 1, interacts with phosphoproteins involved in the cell cycle of some cancer cells.[11] However, the lack of potent and selective inhibitors for parvulins has limited research in this area.[12]

The Cyps show widely differing expression profiles, with CypA being found predominantly in the cytoplasm whereas more restricted localization is

Structure	HCV (EC_{50}, uM)	IL-2 (EC_{50}, uM)	Structure	HCV (EC_{50}, uM)	IL-2 (EC_{50}, uM)
[O-Acetyl-MeBmt]^{1}CsA^{72}	**>10**	>2xCsA	[MeIle]^{4}CsA (NIM811)	**0.1**	>10
[Thr]^{2}[5′-HOMeLeu]^{9}CsA^{158}	**<3**	ND	[4′-AcOMeLeu]^{4}CsA (**13**)	**0.25**	0.03
[D-Sar-OMe]^{3}CsA^{136}	**0.06**	<0.1	[MeVal]^{5}CsA	**0.77**	0.05
[D-Sar-SMe]^{3}[4′-HOMeLeu]^{4}CsA	**0.04**	0.06	[BnVal]^{5}CsA	**0.5**	>10
[D-Sar-$SCH_2CH_2NMe_2$]^{3}[4′-HOMeLeu]^{4}CsA	**0.1**	>2	[Me-D-Ala]^{3}[EtVal]^{4}CsA (Alisporivir)	**0.03**	>2
[D-Sar-SCH_2(3-pyridyl)]^{3}[4′-HOMeLeu]^{4}CsA (**10**)	**0.06**	>10	[D-Lys]^{8}CsA	**2.0**	0.1
[D-Sar-SCH_2(4-thiazolyl)]^{3}[4′-HOMeLeu]^{4}CsA (**11**)	**0.1**	24	[3-CN-D-Ala]^{8}CsA	**0.04**	0.005
[D-Sar-$CH_2SCH_2CH_2NMe_2$]^{3}[4′-HOMeLeu]^{4}CsA (**12**)^{139}	**0.05**	ND	[N-ε-Me_2-D-Lys]^{8}CsA	**0.14**	0.4
[MeVal]^{4}CsA	**0.15**	>2	[MeAla]^{10}CsA^{72}	**8.48**	>15xCsA

Figure 11.1 Human peptide bond *cis–trans* isomerase enzyme class.