Proteinase-activated

Overview: Proteinase-activated receptors (PARs, nomenclature as agreed by NC-IUPHAR Subcommittee on Protease-activated Receptors, see Hollenberg and Compton, 2002) are activated by proteolytic cleavage of their amino terminal exodomains. Alternative endogenous proteinases or ligands to thrombin for PAR1, PAR3 or PAR4 have not been demonstrated. Activation of PAR2 by trypsin or tryptase release *in vivo* is yet to be demonstrated. Several proteases, including cathepsin G and chymotrypsin, have an inhibitory effect at the PAR1 receptor such that they cleave the exodomain of the receptor without inducing activation, thereby preventing activation by thrombin but not by agonist peptides. The role of such an action *in vivo* is unclear. Agonist protease-induced hydrolysis is thought to unmask a tethered ligand at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. Tethered ligand sequences at human PAR1–4 are SFLLRN, SLIGKV, TFRGAP and GYPGQV respectively. With the exception of PAR3, these synthetic peptide sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors.

Nomenclature	PAR1	PAR2	PAR3	PAR4
Other names	Thrombin receptor, PAR-1, PAR_1	PAR-2, PAR_2	Thrombin receptor, PAR-3, PAR_3	Thrombin receptor, PAR-4, PAR_4
Ensembl ID	ENSG00000181104	ENSG00000164251	ENSG00000164220	ENSG00000127533
Principal transduction	$G_{q/11}/G_{i/o}/G_{12/13}$	$G_{q/11}/G_{i/o}$	$G_{q/11}/G_{i/o}$	$G_{q/11}/G_{i/o}$
Agonist proteases	Thrombin, trypsin	Trypsin, tryptase	Thrombin, trypsin, factor Xa	Thrombin, trypsin
Selective agonists	TFLLR-NH_2	2-Furoyl-LIGRLO-amide (Gardell *et al.*, 2008; Hollenberg *et al.*, 2008), SLIGRL, SLIGKV	–	GYPGQV, GYPGKF
Selective antagonists	RWJ56110 (Andrade-Gordon *et al.*, 1999)	–	–	–
Probes	[^{3}H]-haTRAP (Ahn *et al.*, 1997)	*Trans*-cinnamoyl-LIGRLO [*N*-[^{3}H]-propionyl]-NH_2 (Al Ani *et al.*, 1999)	–	–

TFLLR-NH_2 is selective relative to the PAR_2 receptor (Blackhart *et al.*, 1996; Kawabata *et al.*, 1999). Thrombin is inactive at the PAR_2 receptor.

Abbreviations: **[^{3}H]-haTRAP**, Ala-*p*-fluoroPhe-Ala-Arg-cyclohexylAla-homoArg-[^{3}H]-Tyr-amide; **RWJ56110**, (*αS*)-*N*-([1*S*]-3-amino-1-[{(phenylmethyl)amino}propyl]-*α*-[{(1-[{2,6-dichlorophenyl}methyl]-3-[1-pyrrolidinylmethyl]-1*H*-indol-6-yl)amino}carbonyl]amino)-3,4-difluoro-benzenepropanamide

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