

PAF Receptor

Key References

- Bazan, H.E.P., Cellular and molecular events in corneal wound healing: significance of lipid signaling., *Exp. Eye Res.*, **80**, 453-463 (2005).
- Chao, W. and Olson, M.S., Platelet-activating factor: Receptors and signal transduction., *Biochem. J.*, **292**, 617-629 (1993).
- Curtin, M.L., Current status of platelet-activating factor antagonists., *Exp. Opin. Ther. Patents*, **8**, 703-711 (1998).
- Hikiji, H., et al., Absence of platelet-activating factor receptor protects mice from osteoporosis following ovariectomy., *J. Clin. Invest.*, **114**, 85-93 (2004).
- Ishii, S., et al., Impaired anaphylactic responses with intact sensitivity to endotoxin in mice lacking a platelet-activating factor receptor., *J. Exp. Med.*, **187**, 1779-1788 (1998).
- Ishii, S., et al., Platelet-activating factor receptor., *Prostaglandins Other Lipid Mediat.*, **68-69**, 599-609 (2002).
- Ishii, S. and Shimizu, T., Platelet-activating factor (PAF) receptor and genetically engineered PAF receptor mutant mice., *Prog. Lipid Res.*, **39**, 41-82 (2000).
- Marrache, A.M., et al., Proinflammatory gene induction by platelet-activating factor mediated via its cognate nuclear receptor., *J. Immunol.*, **169**, 6474-6481 (2002).
- Peplow, P.W., Regulation of platelet-activating factor (PAF) activity in human diseases by phospholipase A(2) inhibitors, PAF acetylhydrolases, PAF receptor antagonists and free radical scavengers., *Prostaglandins Leukot. Essent. Fatty Acids*, **61**, 65-82 (2000).
- Seo, K.H., et al., Estrogen enhances angiogenesis through a pathway involving platelet-activating factor-mediates nuclear factor-kappaB activation., *Cancer Res.*, **64**, 6482-6488 (2004).
- Stafforini, D.M., et al., Platelet-activating factor, a pleiotropic mediator of physiological and pathological processes., *Crit. Rev. Clin. Lab. Sci.*, **40**, 643-672 (2003).
- Summers, J.B., et al., Platelet activating factor antagonists., *Curr. Pharm., Des.*, **1**, 161-190 (1995).

Overview

Following the identification of Platelet-Activating Factor (PAF) in 1972, and structural confirmation in 1979, there was intense interest in the biology of this phospholipid. These early studies demonstrated that PAF is released directly from cell membranes and mediates a wide range of potent and specific biological effects on target cells including the aggregation of platelets (hence the term platelet-activating factor).

The PAF receptor was first cloned in 1991 and sequence analysis indicates that the receptor belongs to Class A (rhodopsin like) of the superfamily of G protein-coupled receptors. There is 83% homology between the guinea pig lung and human leukocyte PAF receptors. There is no evidence of receptor subtypes from low stringency homology screening for the receptor in different cell types even though functional studies have suggested the existence of PAF receptor subtypes. The presence of functional PAF receptors at the cell nucleus has been recently confirmed. The PAF receptor may couple with G_i, G_s or G_q proteins depending on cell type.

Two metabolic pathways are involved in the biosynthesis of PAF, the *de novo* pathway and the remodeling pathway. The latter appears to be the principal or only pathway in neutrophils, endothelial cells and monocytes and operates when these cells are activated. It involves the action of phospholipase A₂ on membrane phospholipids to yield arachidonic acid and lyso-PAF. PAF is then synthesized from lyso-PAF by the action of an acetyltransferase. Once formed, PAF can be rapidly hydrolyzed back to lyso-PAF by the action of a specific PAF acetylhydrolase (PAF-AH). Both the

membrane ether phospholipids and lyso-PAF do not interact with the PAF receptor, but it has been found that oxidation of the arachidonyl side chain of membrane phospholipids produces compounds which are specific PAF receptor agonists (albeit with potencies approximately ten-fold less than PAF) that are also substrates for PAF-AH. The agonist action of PAF and oxidized phospholipids is blocked by PAF receptor antagonists.

The structures of compounds that possess PAF receptor antagonist activity are surprisingly diverse and include; i) quaternary nitrogen compounds; ii) heterocyclic sp² nitrogen compounds; iii) diaryl compounds; iv) miscellaneous compounds. Potent PAF antagonists that have been used as pharmacological tools and have been investigated in the clinic include apafant, lexipafant, SR 27417 and ABT-491.

The early enthusiasm within the literature suggesting a key role of PAF in inflammation and related pathological disorders has been tempered by the failure of clinical trials of PAF receptor antagonists to demonstrate efficacy in diseases such as septic shock, asthma, and pancreatitis. Recently, studies of mice in which the PAF receptor is either over expressed or deficient have provided new insights on the possible role of PAF in human disease. In PAF receptor deficient mice, it has been found that PAF is a dominant anaphylactic mediator, but is not required for reproduction, neural development or endotoxin shock. It has also been shown that the absence of PAF receptor protects mice from osteoporosis following ovariectomy leading to the suggestion that PAF antagonists could be used to prevent postmenopausal bone loss. PAF has also recently been implicated

in estrogen-induced angiogenesis via nuclear factor-kappaB (NFκB) activation and in delaying corneal wound healing via upregulation of certain genes including VEGF.

A lack of plasma PAF acetylhydrolase (PAF-AH) activity, caused by a missense mutation (V279F), is observed in approximately 4% of the Japanese population. This deficiency in PAF-AH has been identified as a severity factor in asthma, stroke and atherosclerosis. It has been previously proposed that the use of recombinant PAF acetylhydrolase could provide an alternative approach to the treatment of PAF mediated diseases, and recently it has been found that up-regulation of PAF-AH may be achieved by PPAR_γ ligands.

PAF Receptor

CURRENTLY ACCEPTED NAME	PAF receptor
ALTERNATE NAME	AGEPC receptor, Paf-acether receptor
STRUCTURAL INFORMATION	342 aa (human)
RECEPTOR SELECTIVE AGONISTS	PAF (P7568), C-PAF (H4648), Oxidized phospholipids
RECEPTOR SELECTIVE ANTAGONISTS	Apafant, Lexipafant, SR 27417, ABT-491 (A9227)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[³ H]-C18-PAF, [³ H]-C16-PAF, [³ H]-Apafant
TISSUE EXPRESSION	Blood, brain, cornea, endometrium, endosalpinx, heart, intestine, kidney, liver, lung, muscle, spleen
PHYSIOLOGICAL FUNCTION	Proinflammatory mediator
DISEASE RELEVANCE	AIDS related cognitive impairment, allergic conjunctivitis, anaphylactic shock, asthma, osteoporosis, pancreatitis, septic shock, ulcerative colitis

Abbreviations

ABT-491: 1-(N,N-Dimethylcarbamoyl)-4-ethynyl-3-(3-fluoro-4-[(1H-2-methylimidazo[4,5-c]pyrid-1-yl)methyl]benzoyl)indole HCl

PAF: 1-O-Hexadecyl/octadecyl-2-acetyl-sn-glycerol-3-phosphoryl choline

C-PAF: 1-O-Hexadecyl-2-N-methylcarbamoyl-sn-glycerol-3-phosphoryl choline

SR 27417: N-(2-Dimethylaminoethyl)-N-(3-pyridinylmethyl)(4-[2,4,6-triisopropylphenyl]thiazol-2-yl)amine

FOOTNOTES