



## Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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## Literature references

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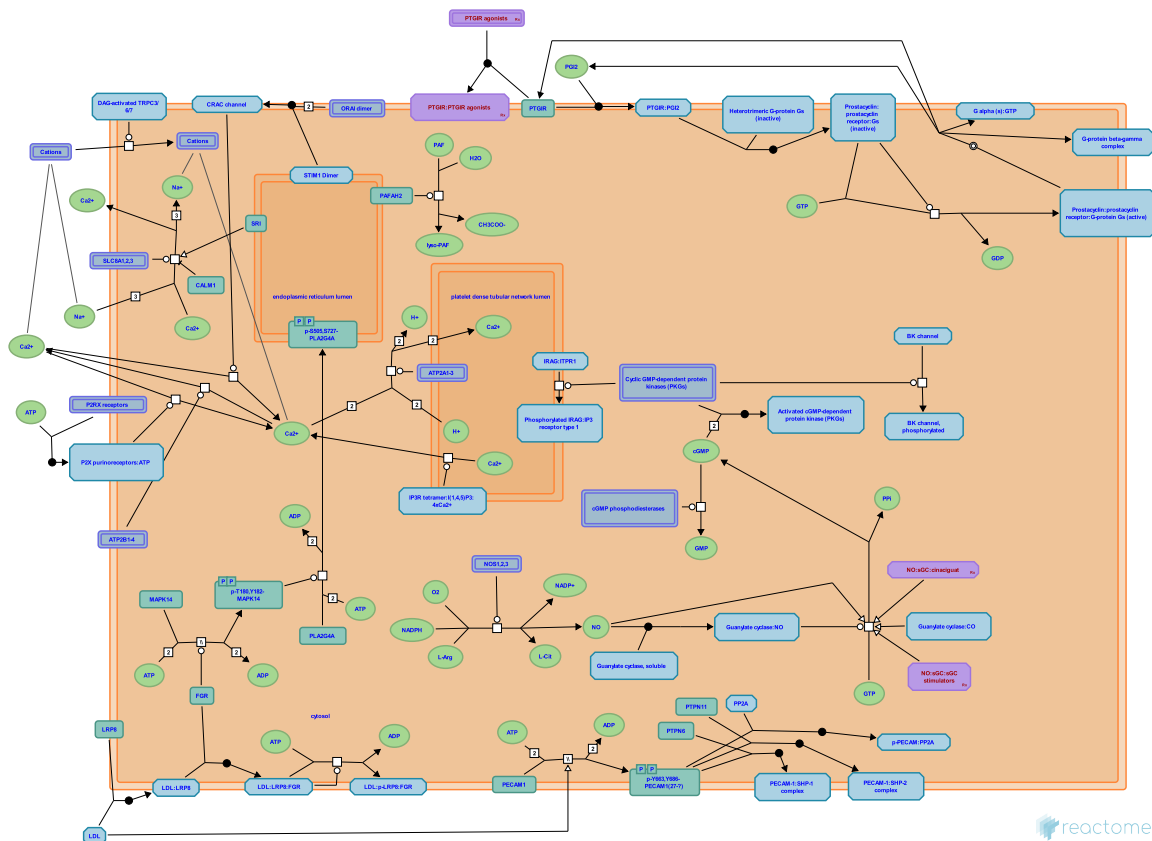
Reactome database release: 88

This document contains 5 pathways and 2 reactions ([see Table of Contents](#))

# Platelet homeostasis ↗

Stable identifier: R-HSA-418346

Compartments: plasma membrane



Under normal conditions the vascular endothelium supports vasodilation, inhibits platelet adhesion and activation, suppresses coagulation, enhances fibrin cleavage and is anti-inflammatory in character. Under acute vascular trauma, vasoconstrictor mechanisms predominate and the endothelium becomes prothrombotic, procoagulatory and proinflammatory in nature. This is achieved by a reduction of endothelial dilating agents: adenosine, NO and prostacyclin; and by the direct action of ADP, serotonin and thromboxane on vascular smooth muscle cells to elicit their contraction (Becker et al. 2000). Cyclooxygenase-2 (COX-2) and endothelial nitric oxide synthase (eNOS) are primarily expressed in endothelial cells. Both are important regulators of vascular function. Under normal conditions, laminar flow induces vascular endothelial COX-2 expression and synthesis of Prostacyclin (PGI2) which in turn stimulates endothelial Nitric Oxide Synthase (eNOS) activity. PGI2 and NO both oppose platelet activation and aggregation, as does the CD39 ecto-ADPase, which decreases platelet activation and recruitment by metabolizing platelet-released ADP.

## Literature references

Heindl, B., Becker, BF., Kupatt, C., Zahler, S. (2000). Endothelial function and hemostasis. *Z Kardiol*, 89, 160-7. ↗

Page, CP., Vermynen, J., Gresele, P., Fuster, V. (2002). Platelets in thrombotic and non-thrombotic disorders. *Cambridge University Press*, 435-437.

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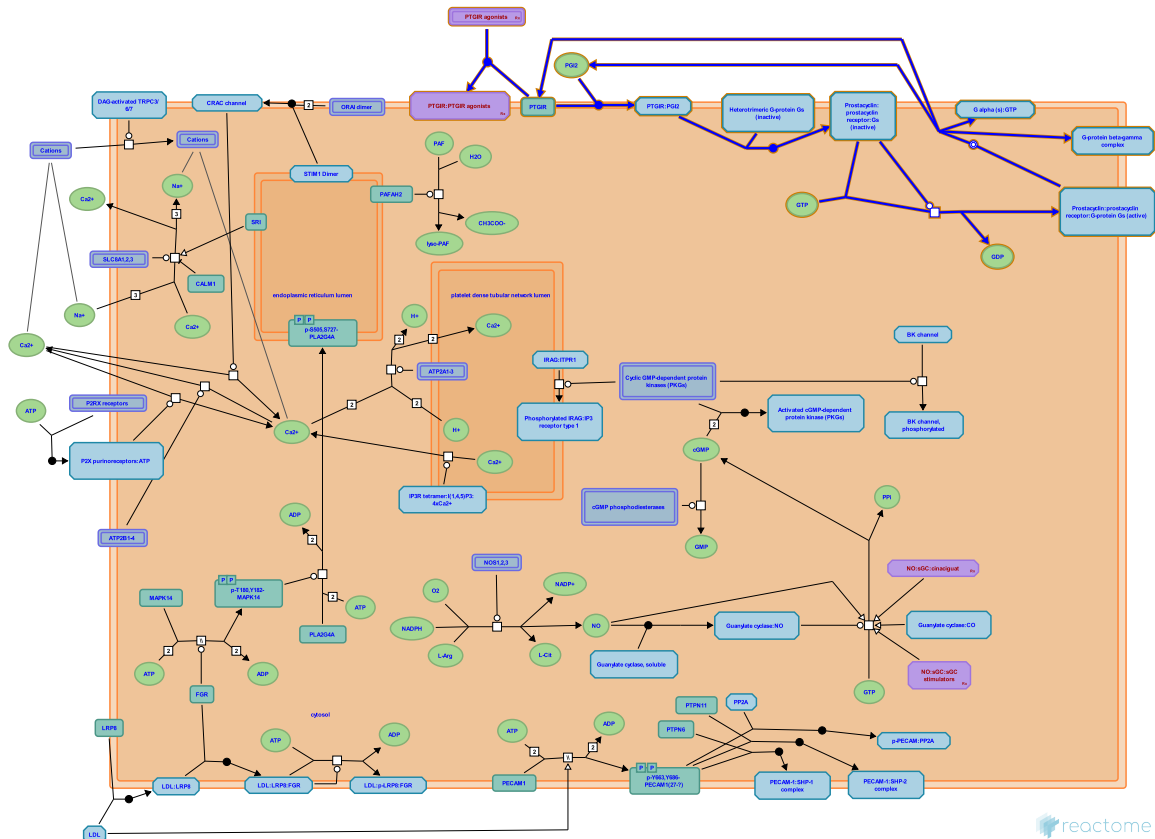
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| 2009-06-03 | Authored | Akkerman, JW. |
| 2010-06-07 | Edited   | Jupe, S.      |
| 2010-06-07 | Reviewed | Kunapuli, SP. |

# Prostacyclin signalling through prostacyclin receptor ↗

**Location:** Platelet homeostasis

**Stable identifier:** R-HSA-392851

**Compartments:** plasma membrane



Prostacyclin (PGI<sub>2</sub>) is continuously produced by healthy vascular endothelial cells. It inhibits platelet activation through interaction with the G<sub>s</sub>-coupled receptor PTGIR, leading to increased cAMP, a consequent increase in cAMP-dependent protein kinase activity which prevents increases of cytoplasmic [Ca<sup>2+</sup>] necessary for activation (Woulfe et al. 2001). PGI<sub>2</sub> is also an effective vasodilator. These effects oppose the effects of thromboxane (TXA<sub>2</sub>), another eicosanoid, creating a balance of blood circulation and platelet activation.

## Literature references

Douville, KL., Stitham, J., Arehart, EJ., Hwa, J., Gleim, SR. (2007). Human prostacyclin receptor structure and function from naturally-occurring and synthetic mutations. *Prostaglandins Other Lipid Mediat*, 82, 95-108. ↗

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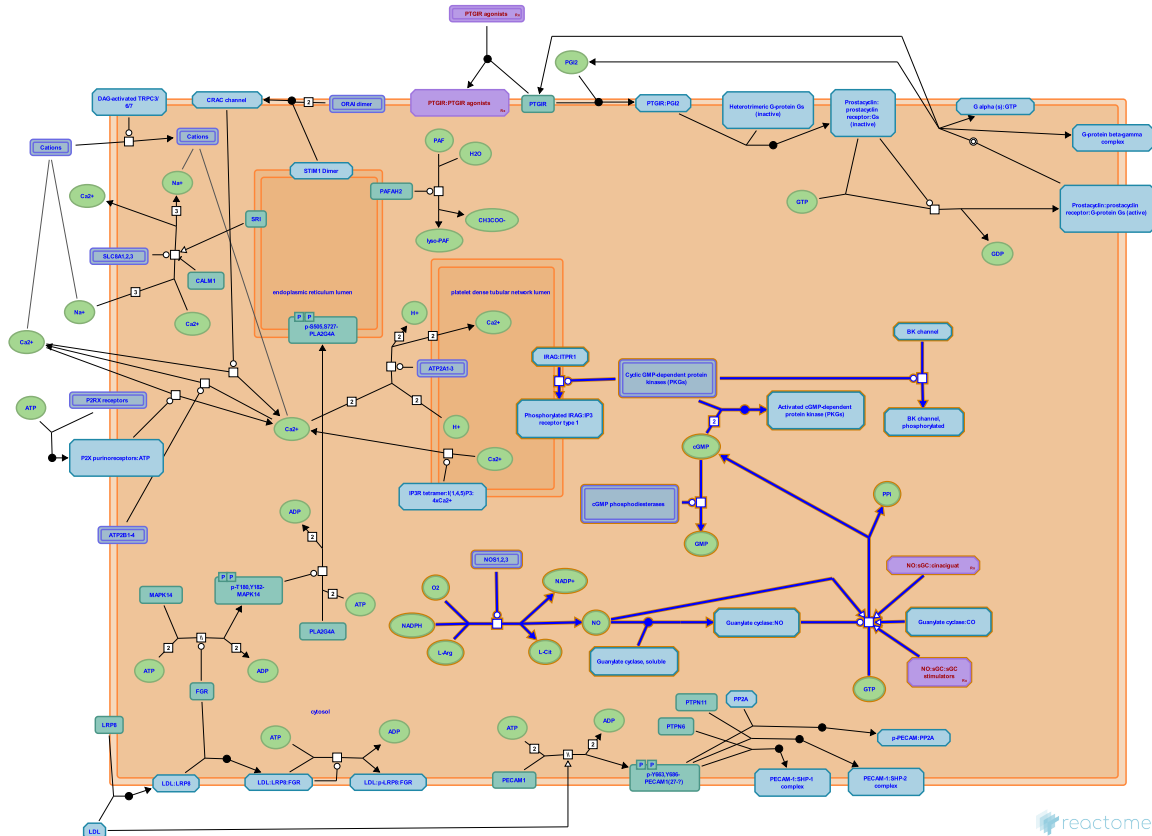
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| 2010-06-07 | Reviewed | Kunapuli, SP. |

# Nitric oxide stimulates guanylate cyclase ↗

**Location:** Platelet homeostasis

**Stable identifier:** R-HSA-392154

**Compartments:** cytosol



Nitric Oxide (NO) inhibits smooth muscle cell proliferation and migration, oxidation of low-density lipoproteins, and platelet aggregation and adhesion. It can stimulate vasodilatation of the endothelium, disaggregation of preformed platelet aggregates and inhibits activated platelet recruitment to the aggregate. NO is synthesized from L-arginine by a family of isoformic enzymes known as nitric oxide synthase (NOS). Three isoforms, namely endothelial, neuronal, and inducible NOS (eNOS, nNOS, and iNOS, respectively), have been identified. The eNOS isoform is found in the endothelium and platelets. NO regulation of cyclic guanosine-3,5-monophosphate (cGMP), via activation of soluble guanylate cyclase, is the principal mechanism of negative control over platelet activity. Defects in this control mechanism have been associated with platelet hyperaggregability and associated thrombosis.

## Literature references

Koesling, D., Friebe, A. (2003). Regulation of nitric oxide-sensitive guanylyl cyclase. *Circ Res*, 93, 96-105. ↗

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| 2010-06-07 | Reviewed | Kunapuli, SP. |

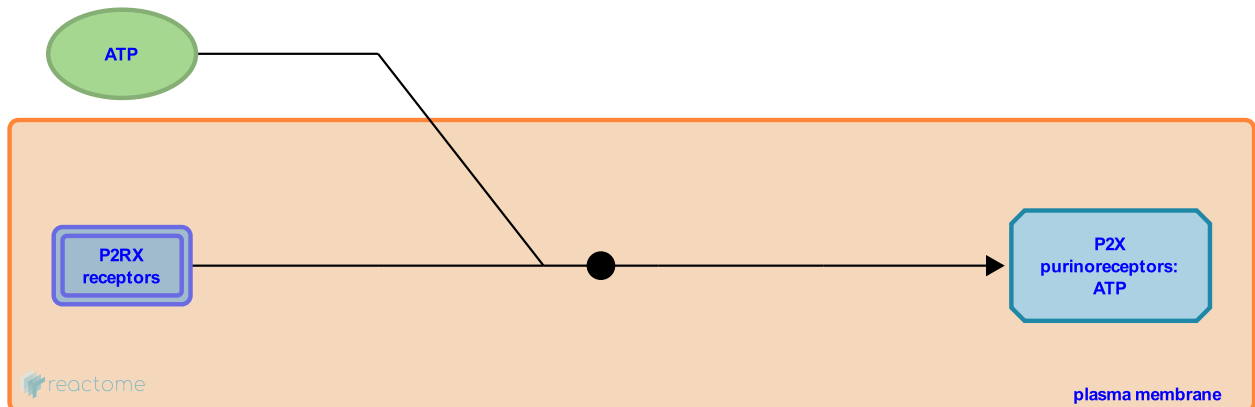
## Binding of ATP to P2X receptors ↗

**Location:** [Platelet homeostasis](#)

**Stable identifier:** R-HSA-419490

**Type:** binding

**Compartments:** plasma membrane, extracellular region



P2X receptors are a family of cation-permeable ligand gated ion channels that open in response to the binding of extracellular adenosine triphosphate (ATP) (Gicquel et al. 2015). All members of the family are thought to be functionally trimeric.

### Literature references

Sachs, F., Ding, S. (1999). Single channel properties of P2X2 purinoreceptors. *J. Gen. Physiol.*, 113, 695-720. ↗

Evans, RJ., Vial, C., Rolf, MG., Roberts, J., Mahaut-Smith, MP., Pitt, SJ. (2003). Lack of evidence for functional ADP-activated human P2X1 receptors supports a role for ATP during hemostasis and thrombosis. *Blood*, 102, 3646-51. ↗

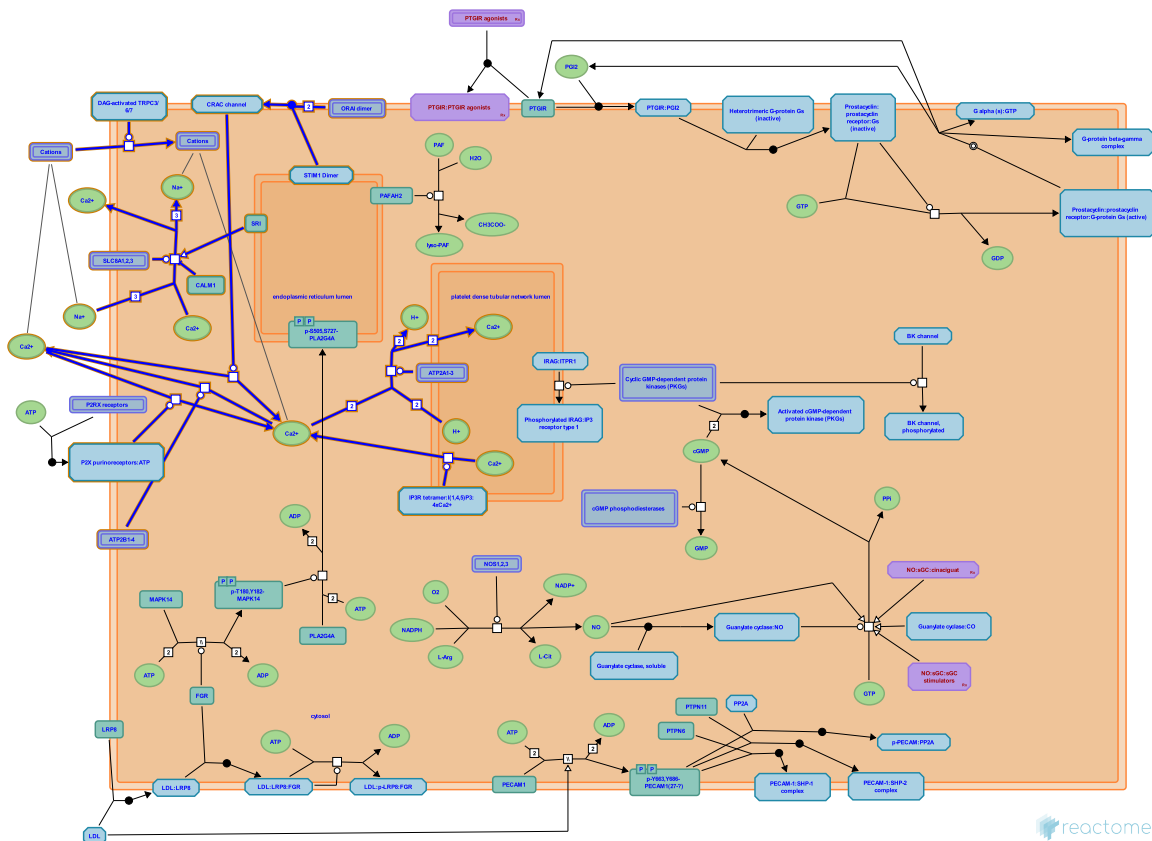
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# Platelet calcium homeostasis ↗

Location: Platelet homeostasis

Stable identifier: R-HSA-418360



Ca<sup>2+</sup> homeostasis is controlled by processes that elevate or counter the elevation of cytosolic Ca<sup>2+</sup>. During steady state conditions, cytoplasmic Ca<sup>2+</sup> is reduced by the accumulation of Ca<sup>2+</sup> in intracellular stores and by Ca<sup>2+</sup> extrusion. The primary intracellular calcium store in platelets is the dense tubular system, the equivalent of the ER system in other cell types. Ca<sup>2+</sup> is extruded by Ca<sup>2+</sup>-ATPases including plasma membrane Ca<sup>2+</sup> ATPases (PMCA) and sarco/endoplasmic reticulum Ca<sup>2+</sup> -ATPase isoforms (SERCAs).

Activation of non- excitable cells involves the agonist-induced elevation of cytosolic Ca<sup>2+</sup>, an essential process for platelet activation. It occurs through Ca<sup>2+</sup> release from intracellular stores and Ca<sup>2+</sup> entry through the plasma membrane. Ca<sup>2+</sup> store release involves phospholipase C (PLC)-mediated production of inositol-1,4,5-trisphosphate (IP<sub>3</sub>), which in turn stimulates IP<sub>3</sub> receptor channels to release Ca<sup>2+</sup> from intracellular stores. This is followed by Ca<sup>2+</sup> entry into the cell through plasma membrane calcium channels, a process referred to as store-operated calcium entry (SOCE). Stromal interaction molecule 1 (STIM1), a Ca<sup>2+</sup> sensor molecule in intracellular stores, and the four transmembrane channel protein Orai1 are the key players in platelet SOCE. Other major Ca<sup>2+</sup> entry mechanisms are mediated by the direct receptor-operated calcium (ROC) channel, P2X1 and transient receptor potential channels (TRPCs).

## Literature references

Varga-Szabo, D., Braun, A., Nieswandt, B. (2009). Calcium signaling in platelets. *J Thromb Haemost*, 7, 1057-66. ↗

Jardin, I., López, JJ., Rosado, JA., Salido, GM., Pariente, JA. (2008). Intracellular calcium release from human platelets: different messengers for multiple stores. *Trends Cardiovasc Med*, 18, 57-61. ↗

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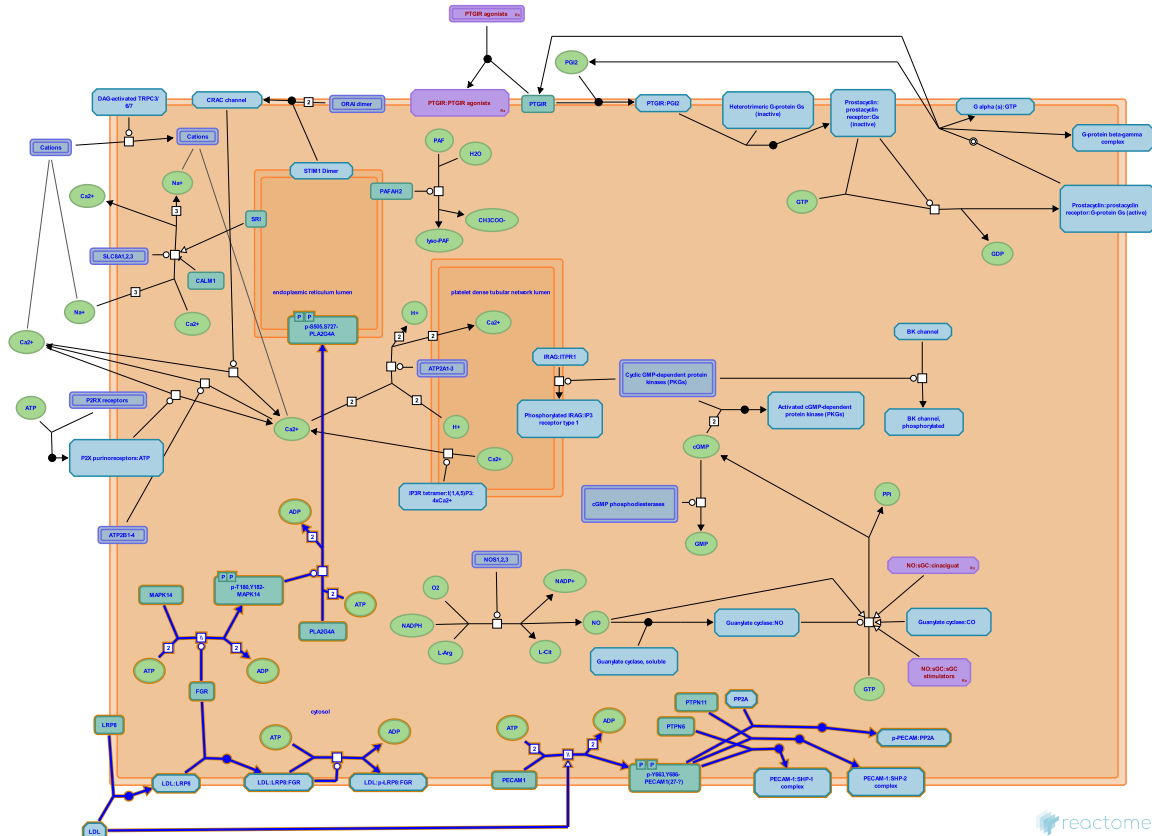
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# Platelet sensitization by LDL ↗

**Location:** Platelet homeostasis

**Stable identifier:** R-HSA-432142

**Compartments:** plasma membrane



Physiological concentrations (1g/L) of Low density lipoprotein (LDL) enhance platelet aggregation responses initiated by thrombin, collagen, and ADP. This enhancement involves the rapid phosphorylation of p38 mitogen-activated protein kinase (p38MAPK) at Thr180 and Tyr182. The receptor for LDL is ApoER2, a splice variant of the classical ApoE receptor. ApoER2 stimulation leads to association of the Src family kinase Fgr which is probably responsible for subsequent phosphorylation of p38MAPK. This stimulation is transient because LDL also increases the activity of PECAM-1, which stimulates phosphatases that dephosphorylate p38MAPK.

## Literature references

- Akkerman, JW., Gorter, G., Ferreira, IA., Relou, IA., van Rijn, HJ. (2003). Platelet endothelial cell adhesion molecule-1 (PECAM-1) inhibits low density lipoprotein-induced signaling in platelets. *J Biol Chem*, 278, 32638-44. ↗
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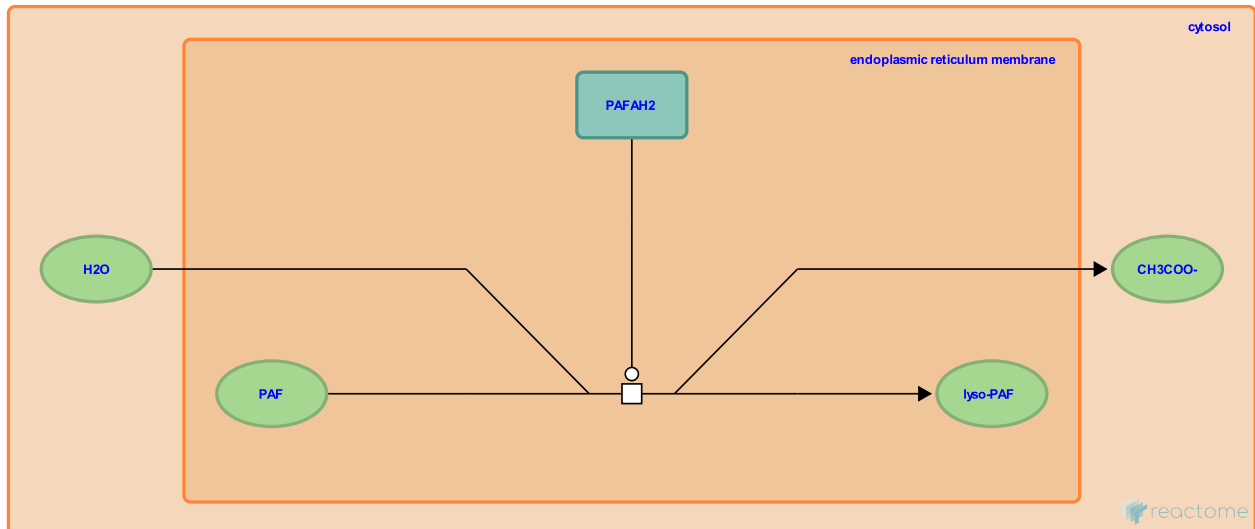
## PAFAH2 hydrolyses PAF to lyso-PAF and acetate ↗

**Location:** [Platelet homeostasis](#)

**Stable identifier:** R-HSA-8869206

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, cytosol



Platelet-activating factor acetylhydrolase 2 (PAFAH2) (Rice et al. 1998) is an intracellular phospholipase A2 enzyme that inactivates the potent phospholipid mediator platelet-activating factor (PAF) and other structurally similar bioactive lipids produced in response to oxidative stress. PAFAH2 hydrolyses PAF at the sn-2 position, producing lyso-PAF and acetate (CH<sub>3</sub>COO<sup>-</sup>). Following oxidative stress, cytoplasmic PAFAH2 (present in homodimeric form) trafficks to the membranes of both the endoplasmic reticulum and Golgi apparatus; membrane localisation is critical for substrate acquisition and effective oxidative stress protection (Thevenin et al. 2011, Monillas et al. 2015). The enzyme that performs the last step in PAF synthesis is located on the outer leaf of the ER membrane. PAFAH2 ER localisation would allow it to access newly synthesized PAF, potentially serving as a control mechanism for PAF levels.

### Literature references

- Bahnson, BJ., Czymmek, K., Thévenin, AF., Winget, JM., Monillas, ES. (2011). Trafficking of platelet-activating factor acetylhydrolase type II in response to oxidative stress. *Biochemistry*, 50, 8417-26. ↗
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- Boyd, HF., Rice, SQ., MacPhee, CH., Tew, DG., Gloger, IS., Terrett, JA. et al. (1998). Expression, purification and characterization of a human serine-dependent phospholipase A2 with high specificity for oxidized phospholipids and platelet activating factor. *Biochem. J.*, 330, 1309-15. ↗

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# Table of Contents

|   |   |
|---|---|
| Introduction  | 1 |
| ❖ Platelet homeostasis                                  | 2 |
| ❖ Prostacyclin signalling through prostacyclin receptor | 3 |
| ❖ Nitric oxide stimulates guanylate cyclase             | 4 |
| ⤵ Binding of ATP to P2X receptors                       | 5 |
| ❖ Platelet calcium homeostasis                          | 6 |
| ❖ Platelet sensitization by LDL                         | 7 |
| ⤵ PAFAH2 hydrolyses PAF to lyso-PAF and acetate         | 8 |
| Table of Contents                                       | 9 |