Mechanisms of Platelet Activation in Cardio- and Cerebrovascular Disease: Impact of Phospholipase D

Platelet activation stimulates the enzymatic activity of PLD. PLD catalyses the hydrolysis of phosphatidylcholine into phosphatidic acid (PA) and choline. PA as well as its metabolites lysoPA and diacylglycerol (DAG) are important second messengers and are thought to regulate different cellular functions. Two isoforms of PLD have been identified: PLD1 has a low basal activity and is readily activated by PKC and small GTPases of the adenosine diphosphate (ADP)-ribosylation factor (ARF) and Rho family, while PLD2 shows a high basal activity and is only marginally induced by a variety of activators. Platelets contain both PLD isoforms that are activated by collagen, thrombin, and the TXA2-mimetic U46619.

First experiments using PLD1 deficient mice revealed that PLD1 is an important mediator of αIIbβ3 integrin activation. The absence of PLD1 affects glycoprotein (GP)Ib dependent platelet aggregate formation and stabilization under high shear flow conditions in vitro and in vivo. Beside PLD1 mediated integrin regulation, platelet mediated inflammation is modulated by PLD1 as well. PLD1 deficient platelets have a reduced capacity to adhere at inflamed endothelial cells under flow ex vivo and at the inflamed vessel wall in vivo confirming that PLD1 is important for platelet mediated inflammatory responses. Thus PLD1 is a critical regulator of platelet activity in the setting of ischemic cardio- and cerebrovascular events.

After myocardial infarction, PLD1 is highly up-regulated in the heart. Further PLD1 regulates the TNF-α triggered inflammatory response and has a pivotal role in the Extra Cellular Matrix (ECM) remodelling process and fibrosis of the remote myocardium after experimental myocardial infarction. The PLD1 mediated inflammatory response and collagen scar formation is crucial for cardiac left ventricle function after myocardial infarction.