

Prothrombotic Role of Platelet Tlr2 in Hyperlipidemia

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A prothrombotic state and increased platelet reactivity are common in hyperlipidemia and oxidative stress. Lipid peroxidation, a major consequence of oxidative stress, generates highly reactive products including hydroxy-w-oxoalkenoic acids that modify autologous proteins generating biologically active derivatives. Phosphatidylethanolamine, the second most abundant eukaryotic phospholipid can also be modified by hydroxy-w-oxoalkenoic acids. However, the conditions leading to accumulation of such derivatives in circulation and their biological activities remain poorly understood. We now show that carboxyalkylpyrrole-phosphatidylethanolamine derivatives (CAP-PE) accumulate in plasma of hyperlipidemic *ApoE*^{-/-} mice. CAP-PE directly bind to TLR2 and induce platelet integrin $\alpha_{2b}\beta_3$ activation and P-selectin expression in TLR2 dependent manner. Platelet activation by CAP-PE includes assembly of TLR2/TLR1 receptor complex, induction of downstream signaling via MyD88/TIRAP, phosphorylation of IRAK4, and subsequent activation of TRAF6. This in turn activates the Src family kinases, Syk and PLC gamma 2 and platelet integrins. By intravital thrombosis studies we have demonstrated that CAP-PE accelerate thrombosis in TLR2 dependent manner. Furthermore, we demonstrate that TLR2 deficient mice are protected from accelerated thrombosis induced by hyperlipidemia. Taken together, our studies demonstrate a cross-talk between innate immunity and integrin activation signaling pathways in platelets and reveal that TLR2 plays a key role in platelet hyperreactivity and prothrombotic state in hyperlipidemia.

Disclosure Block:

S. Biswas: None. **L. Xin:** None. **S. Panigrahi:** None. **A. Zimman:** None. **V. Yakubenko:** None. **T. Byzova:** None. **R. Salomon:** None. **E. Podrez:** None.