Effect of HDL on Platelet Apoptosis and Aggregation

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Recent clinical trials have again questioned the cardioprotective role of high-density lipoprotein cholesterol (HDL-C). Attention has now focused on high-density lipoprotein (HDL) function. As HDL is highly heterogeneous in composition, and based upon some exciting preliminary results, we suspect that composition of HDL may play differential roles in platelet regulation, thus explaining the variable clinical results.

Confirming a number of recent studies, we have found that HDL appears to inhibit platelet aggregation and activation in response to collagen in a time and dose response manner. This should be a clear beneficial effect of HDL, inhibiting thrombosis. However, in the same studies, we also observed that HDL induces substantial platelet mitochondrial membrane potential loss and damage, leading to platelet apoptosis (increased p53 phosphorylation, caspase 3 activation, and cytochrome c release), which has recently been shown to increase thrombosis. We were intrigued by how HDL can seemingly both inhibit and induce thrombosis. Based upon the literature and our further studies, we have developed a series of hypothesis to explain these seemingly opposing actions on platelets; 1) Apoptotic platelets do not aggregate and thus the inhibition of platelet aggregation, 2) With evidence that small dense HDL have more “platelet inhibitory effects“ and are more prevalent in atherogenic dyslipidemia and diabetic patient, we hypothesize that the proapoptosis effect of HDL on platelet apoptosis is from small dense HDL and 3) Platelet apoptosis promotes thrombosis. Composition of HDL may have important differential roles on platelets.

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