Structure-function characterization of the extreme C-terminus of apolipoprotein A-V

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Abstracts

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circulating CD34+ cells is assumed to be indicative for the potential of these cells to support vascular maintenance and repair. However, in BM or in granulocyte-colony-stimulating factor-mobilized peripheral blood, very low numbers of CD34+ cells express KDR (<1%). Using an ex vivo injury model, we show that upon rolling and adhesion of isolated CD34+ cells on injured, platelet- and fibrin-rich endothelial cell surface, KDR was translocated from an early endosomal compartment and subsequently expressed on the surface. In summary, we have developed apoA-I mimetic peptides that have the potential to increase RCT and thus reduce atherosclerosis. However, optimal administration route, dose, and therapeutic window are yet to be determined.

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**Evidence for a Highly Cooperative Interaction Between Apolipoprotein A-I and ATP-Binding Cassette Transporter A1/Phospholipid Microdomain Binding Sites System: Implications for Nascent High-Density Lipoprotein Speciation and Biogenesis**

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Recent studies on the lipolysis of apoA-I have proposed a two-binding site model involving ABCA1 and a putative phosphatidylcholine (PC)-rich plasma membrane high-capacity binding site (HCBS). However, the specifics of apoA-I interaction with this domain and its relationship to HDL genesis remain poorly understood. To explore this issue, the dynamics of apoA-I and dissociation of apoA-I and the HCBS were investigated. Fibroblasts or BHK cells expressing ABCA1 were incubated with 125I-apoA-I, crosslinked, and the ABCA1-complex was immunoprecipitated. The amount of 125I-apoA-I associated with ABCA1 or with the HCBS was quantitatively determined. The dissociation rate of 125I-apoA-I from ABCA1 was extremely rapid (t1/2 0.9 min), whereas the dissociation rate from the HCBS was 10-fold slower (t1/2 30 min). During the first hour of dissociation from the HCBS, apoA-I was released as beta, alpha-migrating, phospholipid-containing complexes without detectable cholesterol. In contrast, particles generated after one-hour were 9.5–20nm and enriched in cholesterol and phospholipids. ApoA-II exhibited similar kinetics as apoA-I for binding to both ABCA1 and the HCBS, 125I-apoA-I, 125I-apoA-II, ABCA1, and the HCBS were localized within non-raff domains. LpA-I particles dissociated from the HCBS were enriched in PC and sphingomyelin, while LpA-II particles were enriched in PC and phosphatidylethanolamine. These results support that during lipolysis, apolipoproteins initially contact the apoA-I G1 domain of ABCA1. Subsequently, ABCA1 mediates the transfer of apolipoproteins to the HCBS, thereby allowing first phospholipid and then cholesterol extraction and dissociation of the lipoprotein product. The differences in particle size and lipid content of nascent LpA-I and LpA-II may reflect heterogeneity in lipid composition of different membrane environments within the HCBS. Overall, the cooperative interaction between apolipoproteins and the ABCA1/HCBS system is consistent with a tandem two-binding site model for nascent HDL genesis.