An Abundant Dysfunctional Apolipoprotein A1 in Human Atheroma


High density lipoproteins (HDL) are a heterogeneous group of particles formed predominantly around the major structural protein, apolipoprotein A1 (apoA1). Contemporary findings suggest functional measures of HDL/apoA1 may provide improved clinical relevance. Moreover, recent studies indicate apoA1 in human atheroma is dysfunctional, extensively oxidized by myeloperoxidase (MPO)-generated oxidants, and that in vitro oxidation of apoA1 by MPO impairs its cholesterol acceptor function. Using phage-display affinity maturation and recombinant immunoglobulin engineering we developed a high affinity monoclonal antibody (mAb) that specifically recognizes apoA1/HDL modified by the MPO/H2O2/halide system. An oxindolyl alanine (2-OH-Trp) moiety at tryptophan 72 of apoA1 serves as the mAb recognition site. Mutagenesis studies confirm a critical role for apoA1 Trp72 in MPO-dependent inhibition of ABCA1-dependent cholesterol acceptor activity of apoA1 in vitro and in vivo. While apoA1 containing a 2-OH-Trp72 group (oxTrp72apoA1) is in low abundance within the circulation, it is remarkably abundant within human atherosclerotic plaque, accounting for 20% of apoA1 in aortic lesions. Functional characterization of immune-purified oxTrp72apoA1 from human atherosclerotic plaque and plasma reveals a lipid-poor lipoprotein virtually devoid of cholesterol acceptor activity. Recovered oxTrp72apoA1 demonstrated impaired capacity to promote HDL biogenesis in vivo, and potent pro-inflammatory activities including NF-κB activation and VCAM-1 surface expression on endothelial cells. Elevated oxTrp72apoA1 levels among sequential subjects presenting to a preventive cardiology clinic (n=627) were associated with increased cardiovascular disease risk, including after adjustments for traditional risk factors, apoA1 and MPO [Odds ratio (95%confidence interval), 4.2(1.5-13.0)]. Circulating oxTrp72apoA1 levels provide a window into monitoring the generation of an abundant pro-atherogenic apoA1 form within the artery wall.

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