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Vascular Medicine

OXIDIZED PHOSPHOLIPIDS ON APOLIPOPROTEIN(A) ARE ONLY PRESENT ON HUMAN LP(A): IMPLICATIONS FOR UNDERSTANDING LP(A) ATHEROGENICITY

Moderated Poster Contributions

Poster Sessions, Expo North

Saturday, March 09, 2013, 10:00 a.m.-10:45 a.m.

Session Title: Vascular Medicine Basic: Atherogenesis

Abstract Category: 33. Vascular Medicine: Basic

Presentation Number: 1125M-172

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Background: Lp(a) is only present in humans and apes/monkeys but its physiological role is not known. Lp(a) is an independent, genetic and likely causal risk factor of cardiovascular disease (CVD), but the mechanisms through which it mediates clinical events are not well known. Apolipoprotein(a) [(apo(a))] contains multiple kringle (K) repeats. Oxidized phospholipids (OxPL) on apo(a)/Lp(a) may be a key mediator of the pro-inflammatory effects of Lp(a).

Methods: Our goal was to define the sites of OxPL binding to apo(a)/Lp(a) and assess species differences, which have subtle but important differences than human Lp(a). The presence of OxPL on apo(a)/Lp(a) was evaluated in healthy humans, apes/monkeys, mice (wild type, apoE^{-/-}, LDLR^{-/-}, apo(a)/Lp(a) transgenic mice, and mutant apo(a)/Lp(a) mice with Asp55/57 to Ala55/57 substitution in the lysine binding site (LBS) of kringle (K) IV-10 [termed LBS-/OxPL- apo(a)/Lp(a) mice]), and recombinant apo(a) [r-apo(a)] constructs containing 17K. The presence of OxPL on apo(a)/Lp(a) was documented by ELISA, immunoblotting with antibody E06 binding OxPL and by tandem liquid chromatography-mass spectrometry (LC-MS/MS).

Results: E06 immunoreactivity was present only when an intact LBS was present, such as in humans and apo(a)/Lp(a) mice with a human construct, but not if a modified LBS was present, as in apes/monkeys, LBS-/OxPL- apo(a)/Lp(a) mice or r-apo(a)s with modified LBS. Lipid extracts of purified human Lp(a) contained both E06- and non-E06-detectable OxPL.

Conclusions: E06 and non-E06 detectable OxPL are present in the lipid phase of Lp(a) and covalently bound to apo(a). The presence of OxPL on apo(a)/Lp(a) is strongly influenced by the KIV-10 LBS and is unique to human Lp(a). This unique human property of Lp(a) to bind OxPL may define its pro-atherogenic potential and explain its genetic influence on clinical events.