PCSK9 association with lipoprotein(a)

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Background

Lipoprotein(a) Structure

Lipoprotein (a) Structure

Plasminogen

Unlike plasminogen, Lp(a) is only present in Humans, Apes, Old World Monkeys and the Hedgehog.

Size heterogeneity (~187- >1000 KDa)
Background

Lipoprotein(a) and Familial Hypercholesterolemia

- Independent, causal, genetically controlled risk factor for cardiovascular disease (CVD).

- Lp(a) confers CVD risk both through the atherogenic LDL and the thrombogenic apolipoprotein(a).

- Lp(a) levels in patients with FH are generally 2-fold higher compared to non-affected relatives, despite the fact that the LDL receptor is likely not involved in its clearance.

- Current pharmacological lipid lowering therapies are ineffective in treating elevated Lp(a) levels.
Background

Therapeutic Approaches for Elevated Lipoprotein (a) levels

• Apheresis - Most effective therapy. Average of ~70% acute reduction (not FDA approved for elevated Lp(a) levels).
• Nicotinic acid - Most effective drug therapy. 20-30% significant reduction.
• Statins, Ezetimibe, Bile acid-binding resins, Fibrates – no effect.
• Mipomersen - ~25% significant reduction.
• CETP inhibitors – no effects; in phase III testing
• PCSK9 inhibitors – 20% -30% significant reduction; in phase III in testing.
Background

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9)

Furin-Cleaved (55+13kDa)
Mature (62+13kDa)

Aim and Methods

We aim to study whether PCSK9 associates with Lp(a) particles and whether this association depends on Lp(a) levels and/or apo(a) size.

• Nine subjects with FH and elevated Lp(a).

• Natural gradient ultracentrifugation separation of LDL and Lp(a).

• Measurements of apoB, apo(a) and PCSK9, and their interactions.

• Direct measurement of PCSK9 association with Lp(a) in plasma.
Results — PCSK9 is associated with Lp(a)

Isolation and characterization of LDL and Lp(a) using natural gradient ultracentrifugation.

LDL and Lp(a) isolation

Reducing gel WB

Native gel WB

![Image of LDL and Lp(a) isolation]

- LDL
- Lp(a)

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<th>VLDL</th>
<th>LDL</th>
<th>Lp(a)</th>
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<td>apoB100</td>
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<td>PCSK9</td>
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![Image of reducing gel WB]

- Coomassie
- apoB
- apo(a)
- PCSK9

![Image of native gel WB]
Results – PCSK9 prefers Lp(a) over LDL

Measurement of Lp(a)-bound PCSK9 and PCSK9/apoB

Levels of Lp(a)-bound PCSK9 do not correlate with total Lp(a) levels

Higher PCSK9/apoB ratio in Lp(a) suggests preferential association
**Results** — PCSK9 prefers larger apo(a) isoforms

PCSK9 association as a function of Lp(a) levels and apo(a) size.

Lp(a)-PCSK9/LDL-PCSK9 ratio is unexpectedly inversely correlated with Lp(a) levels.

PCSK9 associates with Lp(a) particles carrying the higher molecular weight apo(a).
Summary

• PCSK9 is physically associated with Lp(a) particles.

• An 18-fold higher PCSK9/apoB ratio for Lp(a) compared with LDL suggests a preferential distribution of PCSK9 with Lp(a).

• PCSK9 preferentially associates with the higher molecular weight of apo(a).
Conclusions

Our results suggest that Lp(a)-bound PCSK9 exists in plasma of patients with FH and high Lp(a) and that this association depends on the size of apo(a).
This provides a possible mechanism for the reduction in Lp(a) caused by PCSK9mAb.
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