Clearance of Plasma Proprotein Convertase Subtilisin/Kexin 9 by Low-Density Lipoprotein Apheresis

To the Editor:

Proprotein convertase subtilisin/kexin 9 (PCSK9) is a secreted protein that modulates plasma low-density lipoprotein (LDL) concentrations in part by facilitating degradation of the LDL receptor. It also mediates degradation of the very-low density lipoprotein receptor and apolipoprotein E receptor 2. PCSK9 in plasma is primarily secreted by hepatocytes and is thought to have paracrine and exocrine effects, but the role of circulating PCSK9 in the modulation of LDL clearance from plasma remains unclear.1 Insights into the partitioning of PCSK9 in plasma were provided by recent studies published by Tavori, Fazio, and colleagues that demonstrated a high degree of binding of PCSK9 to LDL particles in plasma,2 as well as the data published in Circulation Research showing a 52±5% clearance of PCSK9 from plasma during LDL apheresis.3 The removal of PCSK9 during LDL apheresis seemed to be mediated predominantly by sequestration of 81% of LDL-bound PCSK9 as a result of adsorption of LDL via apolipoprotein B binding to the dextran sulfate apheresis column,3 but 48% of the non-LDL-bound PCSK9 was also cleared by apheresis.

Some uncertainty has remained about the partitioning of PCSK9 among plasma lipoproteins because some investigators have been unable to demonstrate binding of PCSK9 to LDL particles in plasma,2 as well as the data published in Circulation Research showing a 52±5% clearance of PCSK9 from plasma during LDL apheresis.3 The removal of PCSK9 during LDL apheresis seemed to be mediated predominantly by sequestration of 81% of LDL-bound PCSK9 as a result of adsorption of LDL via apolipoprotein B binding to the dextran sulfate apheresis column,3 but 48% of the non-LDL-bound PCSK9 was also cleared by apheresis.

PCSK9 in plasma was quantified by an ELISA using a rabbit polyclonal antibody against truncated (amino acids 31–454) recombining human PCSK9 conjugated to horseradish peroxidase in combination with a luminol-enhanced horseradish peroxidase subunit.4 This binding to the dextran sulfate apheresis column,3 but 48% of the non-LDL-bound PCSK9 was also cleared by apheresis. Some uncertainty has remained about the partitioning of PCSK9 among plasma lipoproteins because some investigators have been unable to demonstrate binding of PCSK9 to LDL particles in plasma,2 as well as the data published in Circulation Research showing a 52±5% clearance of PCSK9 from plasma during LDL apheresis.3 The removal of PCSK9 during LDL apheresis seemed to be mediated predominantly by sequestration of 81% of LDL-bound PCSK9 as a result of adsorption of LDL via apolipoprotein B binding to the dextran sulfate apheresis column,3 but 48% of the non-LDL-bound PCSK9 was also cleared by apheresis.

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PCSK9 in plasma was quantified by an ELISA using a rabbit polyclonal antibody against truncated (amino acids 31–454) recombining human PCSK9 conjugated to horseradish peroxidase in combination with a luminol-enhanced horseradish peroxidase subunit for chemiluminescence detection, as previously described.4 The preapheresis plasma PCSK9 and LDL cholesterol concentrations were significantly inversely correlated (r=−0.74; r²=0.55; P=0.017), but the postapheresis concentrations were unrelated (r=0.09; P=0.53), which may be a reflection of the pool of ≈60% of PCSK9 in plasma that is unbound to LDL and is less well cleared during LDL apheresis. In 3 subjects who received a full LDL apheresis treatment, the plasma PCSK9 concentration decreased by 37% (from 155 to 98). The pooled results from our 4 subjects demonstrated a 48±11% reduction in PCSK9 (P=0.038) in association with a 59±30% reduction in LDL cholesterol (P=0.03).

Our results are concordant with the findings of Tavori et al1 and provide further evidence in support of the notion that a large proportion (≈40%) of PCSK9 in plasma is bound to apolipoprotein B–containing lipoproteins (primarily LDL) and that the majority of LDL-bound PCSK9 can be removed from plasma during LDL apheresis with dextran sulfate adsorption. Additional studies are needed to elucidate the physiological and clinical implications of these observations.

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Disclosures

P.B. Duell served as a consultant to Kaneka for purposes unrelated to this study. The other authors report no conflicts.

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