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.

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,4 as well as the data published in Circulation Research showing a 52±6% clearance of PCSK9 from plasma during LDL apheresis.5 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,6 but 48% of the bound PCSK9 as a result of adsorption of LDL via apolipoprotein B 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,7 and others have shown that >40% of total PCSK9 was associated with LDL in human plasma.8,9 In addition, the efficacy of LDL apheresis in clearance of PCSK9 requires verification, so we sought to corroborate these findings in a subgroup of 4 patients with severe heterozygous familial hypercholesterolemia treated with maximal tolerable LDL-lowering pharmacotherapy who were undergoing LDL apheresis using the Liposorber system (Kaneka Pharma America).6

PCSK9 in plasma was quantified by an ELISA using a rabbit polyclonal antibody against truncated (amino acids 31–454) recombinant human PCSK9 conjugated to horseradish peroxidase in combination with a luminol-enhanced horseradish peroxidase substrate for chemiluminescence detection, as previously described.1

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 LDL1 and is less well cleared during LDL apheresis. In 3 subjects who received a full LDL apheresis treatment, the plasma PCSK9 concentration decreased a mean of 52±9% (from 161±98 to 76±50 mg/mL; P=0.01) in parallel with a 74±5% reduction in plasma LDL cholesterol (from 200±38 to 53±15 mg/dL; P=0.01). These results are comparable with the findings reported by Tavori et al.2 The fourth subject received only a partial LDL apheresis treatment, lowering the plasma LDL cholesterol concentration by only 15% (from 212 to 181 mg/dL), but the PCSK9 concentration decreased by 37% (from 155 to 98). The 2-fold greater reduction of PCSK9 compared with LDL cholesterol during the partial apheresis treatment raises the possibility that PCSK9-containing LDL particles might be preferentially bound by the apheresis column. 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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