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Short Communication
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Proteins Interacting with PCSK9: A Potential for Personalized Medicine

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Short Communication

Hypercholesterolemia is still a major issue in the United States with 73.5 million adults suffering from this illness (https://www.cdc.gov/cholesterol/facts.htm; accessed: May 9, 2017). The proprotein convertase subtilisin/kexin 9 (PCSK9) is one of the genes identified as causative of familial hypercholesterolemia (FH) in an autosomal dominant manner [1-3]. Serum levels of PCSK9 are associated positively with LDL concentration in FH patients and appear to contribute to the phenotypic severity of the FH disorder [4].

This disease improves with a proper diet, an exercise program, and in many cases, with the use of cholesterol-lowering treatments, such as statins [5,6]. Unfortunately, many hypercholesterolemic patients are unable to achieve the recommended target levels of low density lipoprotein (LDL)-cholesterol usually due to resistance to statin [7,8]. Interestingly, PCSK9 has been identified as one of the genes responsible for statin resistance [9]. Other patients (10-25%) suffer from statin intolerance limiting the use of these drugs in these patients [7,8]. Other side effects of statins that concern many physicians and patients are diabetes [10,11], reduced mental performance [12], cataracts development [13]. However, these effects usually happen in a small number of patients.

Both gain-of-function (GOF) and loss-of-function (LOF) mutations in the PCSK9 gene have been identified. The GOF mutations of PCSK9 lead to hypercholesterolemia and a higher risk of atherosclerotic-related diseases [3,14-16]. The LOF mutations, on the other hand, are associated with hypocholesterolemia and a significant protection against cardiovascular diseases [17-20]. Many LOF mutations are more prevalent in African-Americans than in other ethnic populations [18,19].

Although secreted by many tissues, the majority of the PCSK9 present in the serum come from the liver, small intestines, and kidneys [21]. PCSK9 is also found in cerebrospinal fluid and atherosclerotic plaques (CSF) [22,23]. Plasma PCSK9 levels in humans range from 30 ng/mL up to 4 μg/mL [24,25]. The levels of wild-type PCSK9 are positively correlated with the levels of atherogenic lipoproteins such as large very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), the smallest LDL, the smallest high density lipoprotein (HDL), and all remnant lipoproteins in a patient specific manner [25,26].

PCSK9 controls serum LDL levels by influencing the expression of the LDL receptor at the plasma membrane, especially inhepatic cells [27-29]. PCSK9 also stimulates degradation of the VLDL receptor, the apolipoprotein (Apo) E receptors 1 and 2 (ApoER and ApoER2), the cluster of differentiation 36 and 81, beta-secretase 1, and the epithelial (NA+) channel [30-33]. Based on the extent of PCSK9's targets, it is expected that this convertase controls multiple pathways. In fact, high PCSK9 levels appear to lead to, or the consequence of, the accumulation of ApoB-containing lipoproteins in the circulation, including lipoprotein (a) [34-36], obesity [25,37,38] diabetes [38-40], inflammation [41-43], atherosclerotic plaque development [44,45], thrombosis [46-49], hypertension [25,50], and apoptosis in different organs [51-54]. Upregulation of PCSK9 is seen during cerebral ischemia [55], myocardial infarction [48,56], kidney disease [57,58], and hepatic cancer [59]. Thus, watching plasma PCSK9 levels is recommended to determine disease severity in patients [60,61]. Having PCSK9 is also beneficial since this protein is involved in brain development, especially the cerebellum [62], liver regeneration [63,64], and preventing infections [65,66]. Therefore, the identification of protein partners of the PCSK9 function is critical to personalize treatment for hypercholesterolemic patients.

Thus far, several proteins have been identified that interact with PCSK9. Annexin A2 (AnxA2), for example, plays a fundamental role in fibrinolysis, regulation of the LDL receptor and cellular redox regulation [67]. AnxA2 regulates the LDL receptor by directly controlling the PCSK9-

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dependent degradation of the receptor [68-70]. This protein works by directly binding to PCSK9, and this binding prevents the interaction of PCSK9 with the receptor [70]. AnxA2 also inhibits the translation of the PCSK9 mRNA resulting in a reduction in PCSK9 protein expression [68].

Matrix metalloproteinase-2 (MMP-2) is another protein shown to interact with PCSK9 [71]. MMP-2 works mainly be cleaving PCSK9 preventing the LDL receptor degradation [71]. Precursor protein-like protein-2 (APLP2) is another factor that interacts with PCSK9 and mediates the delivery of PCSK9 to lysosomes via a mechanism that does not require internalization of PCSK9 via the LDL receptor [72,73]. Interestingly, another study reported that APLP2 does not affect the PCSK9-mediated degradation of the LDL receptor despite its interaction with PCSK9 [74].

E3 ubiquitin ligase cellular inhibitor of apoptosis protein 1(c-IAP1) binds PCSK9 and enhances the autocatalytic activity of PCSK9 [75]. Also, c-IAP1 promotes the ubiquitination of PCSK9 targeting this convertase to the lysosome [75]. Other proteins that interact with PCSK9 and modulate PCSK9's expression/function are Sar1B [76], amyloid precursor protein (APP) [72], sortilin [74], and GRP94 [77]. Sar1B reduces the expression of intestinal PCSK9 [76]. Sortilin is involved in secretion of PCSK9 [74]. GRP94 has been shown to inhibit the PCSK9-dependent degradation of the LDL receptor [77]. Other ways to reduce the levels of PCSK9 in plasma are by activating the deacetylases sirtuin 1/6 (Sirt1/6) [78,79] and by upregulating tribbles pseudokinase 1 (TRIB1) [80]. Although many proteins that interact with PCSK9 have been identified, none of these proteins is specific for one of the effects of PCSK9 described above.

The use of monoclonal antibody therapy to inhibit PCSK9 and treat hypercholesterolemia has some promise. This type of treatment can reduce serum LDL levels up to 81% [81-84]. The levels of total cholesterol, triglycerides, Apo B, and Apo (a) Are also reduced with this treatment [81,83,85]. Unfortunately, neurocognitive events, which are a growing concern and new-onset diabetes, have been reported in patients receiving this type of treatment [81-83]. Other side-effects reported are gastrointestinal disturbances, infections, ophthalmologic events, and neutralizing antibodies [81-84].

In addition to the side effects, one major consideration when using PCSK9 inhibitors is how low LDL-cholesterol can go. There are concerns that very low levels of LDL-cholesterol may cause hemorrhagic stroke, cancer, hypertension, diabetes, reproductive problems, and neurocognitive dysfunction [86,87]. However, no association between low LDL-cholesterol levels and conditions such as hemorrhagic stroke or cancer has been found [88,89]. Related to the brain, statins, even if they cannot cross the blood-brain barrier, have the ability to alter the lipid composition of this organ [90]. Thus, there is a question of whether the inhibitors of PCSK9 can do the same. The association between low LDL-cholesterol and diabetes has been confirmed using clinical trials [91,92]. On the positive side, for the first time, there is a possibility of curing atherosclerosis [93].

At this point, it is critical if we know more about the different functions of PCSK9 and which proteins can modulate PCSK9's function. Patients on statins could develop drug resistance or intolerance, or they may just develop side effects that might be too unbearable to continuing the treatment. PCSK9 inhibitors appear to be a solution, but their cost and possibility of developing that patients could develop more serious side effects than when using statins have prevented broadening the utilization of these biologicals. More research is needed to identify additional regulators of PCSK9 function. These regulators could later become therapeutic targets that could be used to develop personalized treatment options for hypercholesterolemic patients considering the patient-specificmetabolic state.

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