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Editorial

More on Cholesterol Trafficking in the Body!

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Proprotein convertases are secretary proteolytic enzymes that process multiple proteins such as proteases, growth factors and receptors. Some of these proteases have been linked to interruption of important biological processes leading to human disease.[1] New therapeutic strategies based on these proteases have shown the potential to widen treatment options in several disease areas. An example is the serine protease called Proprotein Convertase Subtilisin-like Kexin type 9 (PCSK-9), which influences low density lipoprotein cholesterol (LDL-C) homeostasis.[2] PCSK-9 is expressed in the liver, intestine, brain and kidney. The expression of PCSK-9 is regulated by cellular cholesterol levels as well as sterol regulatory element-binding proteins (SREBPs). PCSK-9 acts by binding to the LDL receptor (LDL-R) growth factor-like repeat A domain which promotes its lysosomal degradation.[3] In essence the PCSK-9 provides the function of a 'brake' in controlling cellular cholesterol accumulation.

A recently identified mutation involving gain of function (GOF) of PCSK-9 has been shown to cause an autosomal dominant hypercholesterolemia with a phenotype that is even more severe and less responsive to statin treatment than that caused by mutations involving LDL-R or apolipoprotein B (Apo B).[4] Up regulated liver PCSK-9 function degrades LDL-Rs, thus preventing its recycling. This increases the LDL-C concentration in the blood with an associated increase in risk for vascular disease.[5] In contrast, a loss of function (LOF) mutation found in African Americans is associated with low total cholesterol level and LDL-C level and an associated reduction in premature vascular disease by up to 80%.[6]

Plasma or serum PCSK-9 levels in subjects with the GOF mutation were shown to be high; whereas the levels were shown to be lower in those with LOF mutation.[7] Measuring PCSK-9 concentration in blood may reflect clinical benefit. For example, PCSK-9 levels increase with statin administration, speculating that the smaller than expected decrease in LDL-C level on doubling the dose of statin may be accounted for by up-regulation of PCSK-9 activity.[8] A further increase in PCSK-9 levels is also observed with combination therapy of statin and ezetimibe. However, monotherapy with ezetimibe does not elevate PCSK9 levels in blood.[9]

Patients with homozygous familial hypercholesterolemia (FH) or a severe form of heterozygous FH do not reach the optimum levels of LDL-C concentration, even when maximal tolerated doses of statin are administered combined with other drugs such as ezetimibe and/or bile acid sequestrants. These subjects often require a more drastic form of intervention such as intense LDL apheresis or even liver transplantation.[10]

More recently, novel therapies involving PCSK-9 inhibition have been developed and these are being supported by an extensive clinical trial program.[11] These therapies will raise the hopes of subjects with either homozygous FH or severe forms of heterozygous FH undergoing regular apheresis treatment. Although, subjects who are homozygous for LDL-R mutations are not expected to derive similar benefit as those who are heterozygous (as they work predominantly by blocking the degradation of LDL-Rs), a clinical trial is in progress investigating the use of PCSK-9 inhibition in homozygous FH.

A bi-weekly dosage regime of a human monoclonal antibody to PCSK-9, SAR2536553 (Regeneron), in patients with primary hypercholesterolemia treated with a statin produced a reduction in LDL-C concentration of 40, 64 and 72% with 50, 100 and 150 mg, respectively, and a 43 and 48% reduction with 200 and 300 mg with a 4 weekly dosing.[12] A dosage regime of 70-140 mg biweekly of a human monoclonal antibody to PCSK-9, AMG 145 (Amgen), another PCSK-9 inhibitor gave a reduction in LDL-C concentration of 41.8 and 66.1% and a 4 weekly dosage of 280-420 mg gave a 41.8 to 50.3% reduction in LDL-C concentration.[13] There is some controversy about the methodology for LDL-C measurement used in these trials.[12,13] A calculated LDL using the Friedewald formula may underestimate LDL-C levels at low levels in the SAR2536553 trial, but the more accurate ultracentrifugation-based LDL-C method used in the AMG145 trial may reflect a more accurate LDL-C value.[12,13]

These published studies show variable LDL-C response even with the same dose and agent in a patient population, although both drugs inhibit PCSK-9 by an antibody-mediated mechanism. Regulation of LDL-C concentration in blood may not be that simple a process and may involve further fine tuning at the molecular level. These molecular mechanisms still need unravelling.

In this issue of the journal, Al-Waili et al.[14] reported some of the difficulties in understanding the molecular basis of PCSK-9 activation or inhibition through gene variants. They reported the presence of a missense mutation 1474V in PCSK9 gene in two Omani Arabs with a severe form of autosomal dominant FH.[14] A similar mutation has failed to show an association with high LDL-C in other populations other than the Japanese population,[15]

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where such mutation with an intronic polymorphism lead to a higher LDL-C level. The presence of Apo B mutation in these two Omani patients is also under investigation. An interaction between these 2 genes controlling LDL-C concentration cannot be excluded. It has been reported that 2 individuals heterozygous for GOF mutation for PCSK-9 (S127R) had shown increased Apo B production rate as much as 3-fold compared with controls.[16] It is possible that PCSK-9 also regulates Apo B production as part of the machinery controlling intracellular cholesterol concentrations. However, no difference has been shown in LDL-C production rate between heterozygous FH subjects with PCSK-9 mutation and those without.

It is interesting to note that inactivation of PCSK-9 may have provided a positive selection as suggested from the African population who by their LOF mutation are able to affect the lifecycle of malaria or some viruses.[17] Increased LDL-R activity would be expected to reduce exposure of the peripheral tissues to organisms such as hepatitis C, as they have a propensity to associate with lipoprotein particles.[18]

The dynamics of evolution may provide some explanation for some of the variation in PCSK-9 levels or genotypes. Newer therapies which exhibit a wide difference in LDL-C response also require elucidation of ways to channel these expensive therapies to those who derive the maximum clinically relevant benefit or reduction in LDL-C concentration. Biochemical or genetic markers including functional and structural determination of gene variants as explained by Al-Waili et al.[14] and measures of gene to gene interactions related to cholesterol homeostasis are necessary in relation to response with these newer agents. Such developments may make these expensive therapies more economically viable.

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