84th Congress of the European Atherosclerosis Society, 29 May -1 June, Innsbruck, Austria

Key Note Lecture: Not how low but <u>how long</u> to lower LDL cholesterol

That was the proposal by **Professor Michael S. Brown, Paul J. Thomas Professor of Molecular Genetics and Director of the Jonsson Center for Molecular Genetics (University of Texas Southwestern, Dallas, USA),** during his Key Note Lecture '*How genes control cholesterol*'. The lecture not only provided a look back at the low-density lipoprotein (LDL) receptor story, but also an overview of the role of sterol regulatory element-binding protein (SREBP) in regulation of cholesterol homeostasis in the cell, including discussion of SREBP cleavage-activating protein (SCAP), a regulatory protein that is required for the proteolytic cleavage of SREBP. As Professor Brown noted, SCAP has eight transmembrane helices and two large luminal loops. Loop1-Loop7 binding is a central event in cholesterol homeostasis, as it allows SCAP to bind COPII proteins for transport in coated vesicles; in contrast, when cholesterol in the endoplasmic reticulum rises, it binds to Loop1, resulting in dissociation from Loop7, and thus preventing COPII binding. SCAP therefore has a dual role, not only in mediating increased LDL cholesterol as on high fat diets and but also lowering LDL cholesterol with statins.[1] This last discovery represents the culmination of understanding of cholesterol homeostasis, a project which started over 40 years ago.

For the second half of his lecture, Professor Brown turned his attention to the question which has driven recent clinical research: *How low should LDL cholesterol be lowered.* Instead, Professor Brown questioned whether the preferred focus should be: *How **long** should LDL cholesterol be lowered*. In support, he cited the key paper by the Dallas group,[2] in which carriers of a PCSK9 variant associated with lower plasma LDL cholesterol levels had substantial reduction in the incidence of myocardial infarction at age 60 years. In Caucasian individuals, carriage of a PCSK9 variant responsible for lowering LDL cholesterol levels by 15% resulted in 47% reduction in coronary heart disease incidence; however, for African Americans, a nonsense PCSK9 variant resulted in 28% lowering of LDL cholesterol levels and 88% reduction in CHD incidence. Moreover, for comparable LDL cholesterol lowering achieved with a statin, the reduction in CHD risk associated with carriage of this variant was 3-fold higher. Thus, lifelong exposure to lower plasma LDL cholesterol levels was associated with substantial reductions in the incidence of coronary events, even in populations with a high prevalence of non-lipid-related cardiovascular risk factors.

Clearly this thinking is very much consistent with recent consensus for the management of familial hypercholesterolaemia (FH). By identifying the individual with FH early, ideally in childhood and initiating statin therapy early, it is possible to change the natural history of the condition, as highlighted by a recent EAS Consensus Panel paper.[3] Of course, the effects may be less dramatic in normal individuals, given that their risk is also influenced by other genetic variants that modify risk, together with other risk factors. Perhaps future research efforts need to be directed to identifying the threshold at which to intervene earlier, recognizing that this will not be the same in all individuals. As Professor Brown concluded: *'If we intervene earlier in life we may not need the drastic reductions in LDL cholesterol as with current therapeutic strategies. The challenge will be identifying the individual threshold, as well as the most appropriate timing for intervention.'*

The last step in this therapeutic puzzle will undoubtedly involve improved understanding at the molecular level.

References

1. Zhang Y1, Lee KM1, Kinch LN et al. Direct demonstration that Loop1 of Scap binds to Loop7, a crucial event in cholesterol homeostasis. J Biol Chem 2016 Apr 11. [Epub ahead of print].

2. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264-72.

3. Wiegman A, Gidding SS, Watts GF et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J 2015;36:2425-37.