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Commentary

Non-lipogenic ABCA1 inducers: The holy grail in cardio-metabolic diseases?

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Since the characterization of mutations in the *ABCA1* gene in Tangier disease patients, this cholesterol transporter has become an attractive yet elusive therapeutic target in cardio-metabolic disorders with potential applications in diabetes and cardiovascular diseases. Beyond modulation of HDL cholesterol levels, mouse models with selective or constitutive *Abca1* deficiency uncovered a beneficial role for ABCA1 in improving insulin-response, glycemia and limiting atherosclerosis development [1,2]. In patients, loss-of-function mutations in *ABCA1* gene are associated with impaired insulin secretion, increased atherosclerosis and plaque inflammation [3,4]. Very recently, two genome-wide association studies in East-Asian populations demonstrated an association between polymorphisms in the *ABCA1* gene with type 2 diabetes and the risk of coronary heart disease [5,6].

For the last decades, the development of liver X receptors (LXR) agonists has constituted the main strategy to target ABCA1. Indeed, ABCA1 is dynamically regulated by LXRs and the beneficial effects of LXR agonists on inflammation and cholesterol metabolism appear to be related in large part to ABCA1 and its ability to stimulate cholesterol efflux and to control membrane cholesterol content. However, the clinical development of LXR agonists has proven to be particularly challenging, mainly due to an uncontrolled activation of hepatic lipogenesis mediated by the LXRα-SREBP1c axis. Different strategies have been proposed to overcome this adverse effect including tissue-specific LXR activation, development of nano-vectors carrying LXR agonists to target macrophages and, mainly, the development of LXRβ selective agonists with several molecules that have reached phase 1 clinical studies [7].

In this study published in EBioMedicine [8], Lewandowski et al. used an unconventional phenotypic screening approach in cell models to identify molecules capable of inducing ABCA1 without activating SREBP1c before the retrospective identification of their molecular targets. They identified a family of molecules able to induce ABCA1 with the expected beneficial impacts, i.e. stimulation of cholesterol efflux and anti-inflammatory action, but with significantly attenuated lipogenic effects. Target deconvolution revealed that the lead molecule was an LXR agonist, with a partial selectivity for LXRβ over LXRα, as well as a relatively weak antagonist for RXRγ, PPARδ/β, and PPARγ.

In mice challenged with high fat diet, the lead compound, CL2-57 spectacularly improved glycemia along with increased insulin sensitivity in the liver and skeletal muscles, reduced fat mass and decreased plasma and liver triglycerides. Metabolic profiling revealed that gluconeogenesis and fatty acid metabolism were the major pathways affected in CL2-57-treated mice. It also uncovered a reduction in pro-inflammatory lipid mediators following CL2-57 administration.

While these results are promising, several points need to be addressed in future studies. In the first place, the impact of CL2-57 on cholesterol metabolism is intriguing with: (1) no effect on HDL cholesterol despite upregulation of ABCA1, (2) an increase in liver cholesterol concentration under high fat diet (3) a reduction of two well-known LXR target genes: the biliary cholesterol transporter *Abcg5* and the rate-limiting enzyme of bile acid synthesis *Cyp7a1*. Thus, in depth characterization of the impact of CL2-57 on lipoprotein profile and on the dynamics of reverse cholesterol transport in different metabolic contexts will be welcome.

In the second place, the mechanism of action also remains to be clarified and in particular the relative contribution of LXR agonism and RXR/PPAR antagonism to the depicted phenotype. Indeed, partial antagonists of RXR/PPARγ or non-agonist PPARγ ligands blocking Cdk5-mediated phosphorylation also induced protection against obesity or diabetes [9,10]. Murine models with selective Lxrβ or Abca1 deficiency could be valuable in answering this question.

Finally, the translatability of these results to the human context will be the biggest challenge. LXR agonists have very different

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impacts on metabolism and inflammatory responses in humans versus rodent models. A recent study showed that BMS-852927, an LXR agonist exhibiting a good specificity for LXRβ and showing no effects on liver or circulating triglycerides in non-human primates, induced a significant hepatic steatosis in a phase I trial. This suggests that conventional preclinical models may underestimate the human lipogenic response [7].

Despite all these caveats, this work demonstrates the value of the phenotypic approach chosen by the authors, which led to the characterization of molecules with undeniable potential in a field as difficult as that of ABCA1 and LXR based therapeutics. A more detailed characterization of the mechanism of action and studies in different experimental models and metabolic contexts (cholesterol-enriched diet, atherosclerosis) are required for a better assessment of the potential of these compounds to move to clinical development.

Declaration of Competing Interest

The authors have no competing interest to disclose.

Authors contribution

D.M. writing original draft; C.T. writing-review and editing; T.G. writing-review and editing.

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