EBioMedicine 41 (2019) 7–8

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Going -omics to identify novel therapeutic targets for cardiovascular disease

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Despite the use and success of cholesterol- and blood pressure-lowering agents, cardiovascular disease (CVD) remains a major cause of mortality worldwide, with about 1 in 4 deaths being related to this chronic inflammatory disease. Therefore, the field is in constant search for alternative treatment strategies. Since the development and progression of atherosclerosis is a highly complex process, studies aiming to discover new therapies and diagnostics should take this multifactorial aspect into account. High-throughput –omics approaches including metabolomics, lipidomics, genomics, (single cell) transcriptomics, cytomics and proteomics provide such a tool and have been applied in atherosclerosis studies [1–4]. Yet, their translation towards the clinic remains limited for various reasons.

In the current issue of *EBioMedicine*, Mokou et al. apply LC-MS/MS-based proteome analyses of vascular tissues from mice and patients with CVD to identify new proteins that can be pharmacologically targeted [1]. Where this initiative differs from previous studies is the application of distinct, well-established atherosclerotic animal models, including models in which diabetes is artificially induced with streptozotocin to accelerate the disease. As such, 177 common proteins were revealed that were associated with atherosclerosis development, regardless of the applied disease model or presence of diabetes. Mapping these differentially expressed proteins indicated that they participate in core metabolic pathways (including glycolysis, pentose phosphate pathway, Krebs cycle and fatty acid oxidation), as well as in NRF2-mediated oxidative stress responses and the immune system. Since rewiring of these metabolic pathways is a crucial regulator of immune cell function and disease outcome, it is tempting to speculate that (dys)regulation of these metabolic pathways in immune cells is a key driver of atherogenesis [5,6]. Supporting this hypothesis, a recent metabolomics approach highlighted that human high-risk plaques showed an altered metabolic signature in comparison to stable atherosclerotic lesions [4].

To further validate and translate their animal model observations to human disease, Mokou et al. compared the proteome in vascular tissues of CVD patients to vessels of healthy controls. Akin to the mouse models, at least a set of the regulated proteins mapped to pathways associated with metabolism. Despite this high similarity at the pathway level, only six individual proteins overlapped between mouse and human. This minor correspondence at the molecular level questions the effectiveness of this specific cross-species comparison, and maybe again raises the question how useful mouse models are for understanding human atherosclerosis [7]. Among these six common overlapping proteins, four (CTSD, HMGCS2, IGHM, ATLOs) were previously associated with atherosclerosis and two (ZFYVE1, KDM5D) had no earlier known implication in CVD. The authors didn't follow-up on zinc finger FYVE domain-containing protein 1 (ZFYVE1), leaving this open as an interesting study object. However, they focused on KDM5D as their new favourite therapeutic target. KDM5D is an epigenetic enzyme encoded on the Y chromosome that demethylates di- and tri-methylated lysine-4 on histone 3 (H3K4me2/3). Since KDM5D is male-specific, the question arises whether its increased expression in atherosclerotic tissue could contribute to the sex differences in the development of the disease. Along with the increased KDM5D expression in vessels of male CVD patients, the level of its substrate H3K4me3 is decreased. Yet, this new observation provides no insight into molecular mechanisms that drive atherogenesis. So far, a black box remains in which KDM5D is upregulated and its substrate is concomitantly decreased. A major follow-up question to be addressed is which cells are responsible for the increased KDM5D abundance and which genes in these cells are affected by the proposed dysregulated methylation status of H3K4. Noteworthy, H3K4me3 is an epigenetic modification that is generally associated with activated transcription of neighboring genes and thus, increased KDM5D levels will supposedly cause suppression of those genes. It would be interesting to identify the affected genes since they will potentially encode suppressors of atherogenesis. This is where other –omics approaches like (single cell) transcriptomics, cytomics (*e.g.* single cell RNA-sequencing, CyTOF mass cytometry), and chromatin immunoprecipitation sequencing (ChIP-Seq) will come into play [2,3]. Given the importance and high infiltration of immune cells in atherosclerotic lesions, it is likely that these cells account for the increased KDM5D expression and suppressed H3K4me3 levels in plaques. Indeed, histone modifications like H3K4 methylation are recognized as crucial regulators of inflammatory responses in macrophages [8,9].

Irrespective of the molecular mechanisms at play, the patient will only benefit from this new knowledge if the (dys)regulated processes can be pharmacologically targeted. Due to the lack of KDM5D inhibitors applicable for *in vivo* use, this is currently not possible and therefore it

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.02.040.
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https://doi.org/10.1016/j.ebiom.2019.03.005

remains difficult to estimate the value of KDM5D as a new therapeutic target for atherosclerosis. Nevertheless, the current study of Mokou et al. opens new avenues for cardiovascular research and the recent development of orally available inhibitors of other KDM5 family members gives hope for new future therapies [10].

Author disclosure

The authors disclose no conflicts of interest.

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