Tangible heart, silicon brain

Chapter 10

Impact

SCIENTIFIC IMPACT

Systematic depiction of molecular processes in atherosclerosis

Atherosclerosis is a chronic inflammatory disease hallmarked by a series of complex biological processes including intravascular lipid accumulation, innate and adaptive immune responses, and angiogenesis and the dysfunction of vascular smooth muscle cells[1–3]. Even though tremendous efforts have been made to study the mechanisms of atherogenesis, a systematic depiction of the formation and progression of atherosclerosis at a molecular level is still lacking. These insights are required for better understanding the disease progression, and the identification of therapeutic targets and the design of new drugs.

Biological entities, such as genes, proteins and metabolites, function as a system. With the recent progress in systems biology and computational biology, as well as the wide application of biological big-data collection, constructing a systematic disease model for atherosclerosis is becoming realistic. In this thesis, we demonstrated the advantages and perspectives of a systems biology approach to the study of atherosclerosis, as compared to a single focus. Specifically, through gene co-expression clustering followed by directional, causal network analysis, in **chapter 2** we revealed the interaction of key atherogenic processes, and pinpointed the pivotal role of T cell activities in atherosclerosis. In **chapter 4**, we constructed a metabolic model of the atherosclerotic plaque based on the mRNA expression profile of this tissue. To our knowledge, this is the first metabolic atlas for human atherosclerosis. Further analysis revealed metabolic key changes in atherosclerotic disease progression, including in glutamate/glutamine metabolism, and was able to link this to compromised macrophage function. This pathway could serve as a novel therapeutic target for the disease. However, the established plaque metabolic atlas is more versatile and represents a referential metabolic map of atherosclerosis to the cardiovascular research field, facilitating further explorations of disease-associated metabolites and reactions by the other researchers.

Seeking innovations through interdisciplinary collaboration

Innovations often emerge at the intersection of multiple disciplines. As a PhD candidate with a background in computer science and bioinformatics, I have been working in this biomedical group and collaborating with biologists throughout my PhD career. I received substantial supports in biological content from the vascular pathology group, meanwhile, my colleagues and biologists in collaboration have been influenced by the opportunities and power of computational strategies to biomedical research. The close collaboration between biologists and computer scientists eventually led to the discovery of novel findings, which could not have been obtained on the basis of a single discipline.

The major part of this thesis aims at solving biological research questions using computational-driven biological data analysis, including machine learning, biological network modelling and multimodal data integration. These methods and analyses allow 1) extensive screening of valid targets from large data; 2) revealing hidden knowledge and associations underlying biological big-data; and 3) reconstruction of the whole biological system, to levels far beyond what conventional biomedical approaches could achieve. In this thesis, these computational-driven methods play essential roles in discovering new drug targets and providing novel insights into the disease mechanisms, creating unprecedented value (for example, by creating a metabolic map of human carotid plaque) across boundaries between computer science and biomedicine. Moreover, to address biomedical research questions, this thesis goes one step further, by harmonising and fusing data from biological experimentation, biological public databases, and omics analyses with help of advanced computer algorithms. Our studies inspire biologists to keep an open mind in tracking and deploying cutting-edge informatics and computational technology in biomedical research, and encourage more and more computer scientists to enter life science and develop algorithms for scientific and realistic biological questions.

SOCIAL IMPACT

Novel therapeutic targets and drugs for cardiovascular diseases

Cardiovascular diseases, which are mainly driven by atherosclerosis, remain one of the leading causes of death worldwide[4]. It is estimated the CVD-related public healthcare expenditures will continuously rising, appealing to the urgent requirement for the discovery of new therapeutic targets and strategies for CVDs.

This thesis brings forward several potential therapeutic targets and drugs, as discussed in **chapter 8**. Current antiatherosclerotic therapies focus on the control of cardiovascular risk factors, such as dyslipidaemia, hypertension, and diabetes. However, a growing number of studies raised interest in targeting disease-associated molecular dysfunctions in plaque key cell types including T cells, macrophages and smooth muscle cells[5]. The therapeutic targets that were identified in our studies all belong to the latter, and may hold promise for clinical application.

It should be noted that, in this thesis, we mainly relied on computational and network-based modelling of the atherosclerotic plaque and on machine learning algorithms for target discovery and drug screening. On the one hand, we made use of the publicly available omics data as well as biological pathway and drug target databases, which allowed establishing a comprehensive disease model while saving expenditures for unnecessary and redundant experiments. On the other hand, the extensive application of *in silico* analyses provided a more targeted approach to guide the subsequent biological exploration, which streamlines the following wet-lab experiments, reduces the costs of the experiments and, in the end, of novel target identification and drug design. Compared with the conventional time-consuming and costly design and development of new drugs, *in silico* screening and repurposing of "old" drugs that are approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) is much faster, as these drugs have already proved to be safe in clinical trials. This important feature of *in silico* data-driven drug screening and repurposing can help to significantly reduce the costs for drug development and shorten the developing timelines[6].

Based on network-guided *in silico* drug screening and repurposing, in **chapter 2** we identified epidermal growth factor receptor (EGFR) inhibitors as candidate drugs, targeting adverse T cell functions related to plaque stability. To translate our findings into clinical application, we will perform *ex vivo* experiments to test the effect of these drugs on the human plaque. Further *in vivo* experiments and clinical trials would need to verify the validity of the candidate drugs; however, the safety of these drugs has been tested, which may simplify the trial design and accelerate the landing on the ground. Moreover, in **chapter 4** we proposed the central role of

macrophage glutamate/glutamine metabolism in plaque inflammation. Future experiments have been planned to validate the Glu/Gln metabolic pathways *in vitro* by inhibiting key enzymes in this pathway, such as glutamine synthetase (GLUL), in human macrophage culture, and evaluating the functional changes of GLUL inhibition through the macrophage functionomics platform we have established (see **chapter 5**). These novel therapeutic solutions could add to the current lipid-lowing strategy, especially in cardiovascular patients that are insufficiently responding to the latter therapy.

CONCLUSIONS

In conclusion, this thesis attempts to explore atherosclerotic disease by systems-based computational approaches, in order to identify novel targets and drugs for therapeutic intervention. These findings may bring new conceptions for the pathogenesis, but also for the prevention or treatment of this disease, which could benefit the patients and reduce the socio-economic burden of CVD. But more importantly, it illustrates the merits of the employed systems-based methodology to study atherosclerosis, and may encourage further and more advanced applications of computational-driven big-data analysis in biomedicine research.

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