

The complement system and cardiovascular disease

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Valorisation addendum

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Valorisation is the “process of value-creation out of knowledge, by making this knowledge suitable and available for economic or societal utilisation” [1]. Economic utilisation involves for example commercialisation of knowledge by generating patents and license contracts [2]. Societal utilisation means making knowledge available to individuals and public organizations who might apply research findings.

The studies included in the current thesis investigated the associations between plasma complement factors and development of cardiovascular disease (CVD) in a cohort of middle-aged to elderly individuals. We showed that circulating complement factors are associated with CVD and processes contributing to CVD. These findings are relevant to healthcare providers and to individuals at risk for CVD. However, this research project did not explore hypotheses that could directly lead to patent applications. Hence, this chapter describes how the current findings may be applied in order to decrease cardiovascular burden and provides an outlook on the steps to be taken in order to translate the current findings into prevention and treatment strategies of CVD.

The investigation of novel risk factors for CVD can create value at different levels. First, it can result in finding novel risk *markers* in order to assess the cardiovascular risk of an individual. Quantifying an individual’s cardiovascular risk can be utilized in clinical decision making, and can decrease cardiovascular burden by delivering medical interventions earlier and by providing personalized treatment. Identification of novel risk markers can also yield economic utilization, for example when the measurement method can be patented and is applicable on a large scale in clinical practice. Second, novel risk factors for CVD may pose potential targets for novel medical treatments or healthy behaviours and thereby decrease overall CVD risk at the population level. Third, elucidating the pathophysiology of CVD creates valuable knowledge by itself as it advances the understanding of a highly prevalent and harmful disease and provides the basis for further investigations.

Complement factors as potential novel risk markers

Our investigations suggested that properdin and C1q may potentially be suitable as risk markers of CVD. Plasma properdin and C1q provided independent information on cardiovascular risk, while other complement factors were associated with early processes of vascular damage but not with future disease. The American Heart Association recommends several steps in the identification of novel markers of cardiovascular risk [3]. Accordingly, an “initial proof of concept”, and subsequently a “prospective validation in independent populations” are the first steps to identify risk markers of CVD. The data on properdin can be considered as first proof of concept, because this is the first investigation of properdin in human CVD. Regarding C1q, our study provided the first prospective evaluation, as previous studies on C1q in human CVD were cross-sectional. This thesis thus provides the first steps in the investigation of properdin and C1q as potential novel markers of CVD risk. To confirm their suitability as risk markers, replication of our findings in prospective evaluations in other, larger populations is needed for both properdin and C1q. Importantly, in order to be used

for risk prediction in practice, the laboratory measurements of risk markers must be reliable, accurate and cost-effective [4]. In the present investigation, the laboratory measurement of C1q was only moderately accurate (inter-assay coefficient of variation 18.5%), and for properdin, two-to-three-fold higher concentrations were reported in previous studies [5, 6]. Thereby our study also points up the need to optimize and standardize the laboratory methods prior to a potential routine use in the clinic.

Complement activation pathways as potential targets

Factors that are associated with CVD and processes contributing to CVD may serve as potential targets of future treatment and prevention strategies, provided that they also play a causal role in CVD. The current findings suggest a role for all complement activation pathways in CVD, as factors from each pathway were associated with pathophysiological processes, i.e. inflammation, endothelial dysfunction and/or atherosclerosis. Notably, our investigations suggested that the alternative pathway may be most relevant in development of CVD. Therefore, the alternative pathway may be the most promising target for potential treatment and prevention strategies. First, relevance of the alternative pathway should be confirmed at the tissue-level, given that our findings are based on observations on systemic complement concentrations. If confirmed, the alternative pathway may be a particularly interesting target because it can be activated spontaneously. Understanding in which circumstances the alternative pathway is activated could result in novel treatment strategies and optimization of current treatment approaches. For example, current strategies to develop antioxidant therapies for CVD could take potential effects on alternative pathway activation into account, as the alternative pathway can be activated by oxidative stress [7, 8]. Furthermore, alternative pathway activation may be partly modifiable by lifestyle factors, as lipid-rich meals and smoking were reported to affect the alternative pathway [9-11]. A better understanding of the interplay between lifestyle and alternative pathway activation may provide further rationale to support the promotion of healthy behaviours at the population level.

Novel insights into the pathophysiology of CVD

This comprehensive evaluation of complement factors provided several novel insights that enrich the understanding of CVD. A better understanding of the complexity of CVD is valuable by itself and, in addition, provides the basis for further research. For example, our studies suggested that MASP-3 and MAp44 may play a role in endothelial dysfunction independently of lectin pathway activation. Although this finding cannot directly be translated into an application to recognize or intervene on cardiovascular risk, it may stimulate further research and potentially result in the discovery of novel pathways in endothelial (dys)function. Endothelial dysfunction is not only involved in CVD, but also in development of other chronic diseases such as type 2 diabetes mellitus [12, 13]. Identification of novel pathophysiological interplays in endothelial dysfunction may in the long-term perspective yield novel targets to decrease chronic diseases such as CVD or type 2 diabetes.

In conclusion, there is a clear potential to apply the current findings in the development of clinical risk markers and in the development of treatment and prevention strategies. For this, confirmation of our findings in other studies and optimisation of the laboratory measurements are needed in advance. Furthermore, it should be kept in mind that treatment and prevention strategies must be very cost-effective in order to be applicable on a large scale. Screening of individuals based on risk markers, personalized interventions and (development of) novel pharmacological treatments are highly costly. Viewed realistically, societal utilization of the present findings may thus be feasible in the more distant future, and potentially only in high-income countries. Nevertheless, each and every small contribution to advance the understanding of CVD is one step forward to combat a major health issue.

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