LS18-090 - Beyond lipid lowering - defining residual risk of cardiovascular events

Abstract

Cardiovascular disease is the leading cause of death worldwide and severely impacts life quality. Heart attacks represent an acute exacerbation of an often undiagnosed disease of the coronary arteries. Many factors influence development and progression of coronary artery disease such as high blood cholesterol, high blood pressure, and diabetes. It is not yet understood why some patients experience aggravation of their disease despite optimization of these risk factors. Our project focused on the interplay between protective and harmful factors influencing immune cells in myocardial infarction.

We have confirmed previous studies showing the enhanced release of small vesicles from activated cells into the circulation. They can serve as intercellular messengers and represent the activity of their parental cell. We found that specifically vesicles from immune cells carried oxidized moieties. In our experiments, we showed that these vesicles were able to activate so-called neutrophil granulocytes. Activation of these cells can result in 1) the release of mediators promoting inflammation, 2) the generation of reactive oxygen species, or 3) the formation of neutrophil extracellular traps (NETs), which are webs of DNA. The ability of NETs to entangle other blood components such as red blood cells or platelets can lead to the blockage of coronary vessels and a heart attack. Our results indicate that this mutual activation nurtures a vicious cycle effecting reduced heart function.

In light of these results, we have also measured protective factors with the potential to disrupt such an inflammatory cycle. There is a type of natural antibody (IgM), which belongs to the innate immune system and neutralizes harmful molecules i.e. oxidized lipids as they might occur on oxidized lipoproteins, dying cells or vesicles from dying cells. The addition of these antibodies to our experiments protected neutrophil granulocytes and reduced the release of NETs. In line, in patients with higher levels of endogenous IgM we could detect fewer NETs. At the same time, the balance introduced by high IgM levels improved heart function after myocardial infarction.

In conclusion, an increase of pro-inflammatory factors might be compensated by the presence of protective IgM. This concept emphasizes the importance of protective factors for patient outcome apart from the effects of an acute adverse event.

Scientific disciplines:
Internal medicine (50%) | Cardiology (25%) | Immunology (25%)

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Further links to the persons involved and to the project can be found under
https://www.gmbh.wwtf.at/funding/programmes/ls/LS18-090/