Universität Basel

Research Project

Understanding the PROtectiVe Inflammation in DiabEtes

Third-party funded project

Project title Understanding the PROtectiVe Inflammation in DiabEtes
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Type-2 diabetes (T2D) is promoted by multiple mechanisms that underlie a defect in insulin secretion and reduced response to insulin-stimulated glucose uptake in liver, muscle and adipose tissues, known as insulin resistance. These mechanisms include glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress and alterations of the gut microbiota. Interestingly, all of these mechanisms are associated with inflammatory response. Clinical studies have demonstrated that anti-inflammatory treatments including IL-1- antagonism, salsalate and probably TNF-antagonism improve glucose metabolism. Some anti-inflammatory treatments may be more effective at improving insulin secretion, while others primarily enhance insulinsensitivity. Furthermore, there are different mechanisms that engage different branches of immune response during the course of diabetes. Given the heterogeneity of the disease and the complexity of the inflammatory response, optimal anti-inflammatory strategies are a challenge and studies in humans have yielded variable results. However, inflammation is not in itself a disease but a manifestation of a disease. It may have beneficial effects allowing for adaptation to the metabolic stress. Increasing evidence suggests physiological and beneficial effects of the inflammation (called protective immune response) in the adaptive process of increased insulin secretion and reduced insulin resistance. A metabolic inflammatory response consists of four components: inflammatory inducers (such as nutrients), cell sensors (such as macrophages, dendritic cells), inflammatory mediators (such as T cells) and the target tissues (adipose tissue, liver and pancreas) that are affected by inflammatory mediators. The time line of events and the molecular mechanisms that integrate the inflammatory response with metabolic homeostasis at the tissue and systemic levels are still to be characterized in T2D. Recently, we discovered that inflammatory pathways controlled by Interferon Regulatory Factor 5 (IRF5) in macrophages (the sensor cells) orchestrate the immune response towards a pro-diabetogenic program (Dalmas et al. Nature Medicine in press). Interfering with IRF5 pathways (IRF5 macrophage specific KO mice) lead to modification of the innate and adaptive response leading to a healthier metabolic status. Extensive characterisation of the IRF5-dependent immune response is required for a better understanding of physiological (protective) versus pathological immune programs involved in T2D (mouse studies). These immune programs will also be validated in different clinical situations (human studies) ie: weight loss, exercise and immune-therapy (IL-6 modulation) known to improve diabetes and reduce inflammation. The overall objective of the proposed project is to reveal the physiologic role of inflammation dependent of IRF5 pathways in the adaptation to metabolic stress linked to T2D. Understanding the physiological and the pathological role of the immune system may allow designing personalized treatments promoting a beneficial immune status in patients with T2D.

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