

Innate Immunity: From Innate Sensing to Adaptive Responses (D2)
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Hs-CRP was increased in both T1D and T2D but higher in T2D. A number of 41 circulating inflammatory markers were higher in T1D compared to healthy controls (FDR<0.05), 64 inflammatory markers were higher in T2D compared to healthy controls (FDR<0.05). The increased markers were mostly overlapping between T1D and T2D. 14 markers were positively associated with chronic glycemic level (HbA1c) in both type 1 and type 2 diabetes (FDR<0.05). A strong positive association was found between BMI and inflammation in T2D, not in T1D. The presence of nephropathy was positively associated with several inflammatory markers in both type 1 and type 2 diabetes including IL-10RB, IL15-RA and TNFRSF9 (FDR<0.05). These markers are all important in initiating responses from the innate and adaptive immune system. Using the follow up data, we found that MCP-1, GDNF, CDCP1, LAP TGF-beta-1 and TRAIL were associated with an increased risk of developing cardiovascular complications in type 2 diabetes (p-value<0.05), whereas FIT3L, CCL11, CCL19, IL8 and TRANCE were associated with a reduced risk of developing cardiovascular complications (p-value<0.05).

Conclusions

Although inflammatory markers are higher in type 2 diabetes, both type 1 and type 2 diabetes are associated with increased levels of inflammation. Chronic low-grade inflammation in type 1 diabetes seems mainly associated with glycaemic control, whereas BMI may be an additional factor associated with inflammation in type 2 diabetes. Interestingly, the inflammatory markers that associate with long-term complications are similar in type 1 and type 2 diabetes. These results suggest that the drivers of inflammation might be different in type 1 and type 2 diabetes, while similar pathways may be involved in the development of diabetes associated complications.

Innate and adaptive immune responses after primary COVID-19 mRNA vaccination: in the search for surrogates of vaccine-induced protection

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Despite the effective vaccine strategies to combat COVID-19, new SARS-CoV-2 strains emerge and vaccine-induced immunity wanes with consequential breakthrough infections. Therefore, a better understanding of the mechanisms that determine the quality and quantity of underlying immune protection by the COVID-19 vaccines is crucial. The vaccine induced innate immune response, that shape the protective adaptive responses, could be used as surrogate of vaccine-induced protective responses and help to identify individuals with supra- or sub-optimal responses. Here we characterized the innate immune responses of adults, 1 to 3 days after receiving a primary COVID-19 mRNA vaccination, which will be correlated with adaptive outcome.

In the IIVAC study, individuals were vaccinated as part of the National COVID-19 immunization program. To evaluate innate immune responses, blood samples were collected from individuals (20-51 years of age, 15 male, 33 female) before (n=32) and at 1, 2, or 3 days after (n=48) COVID-19 (BNT162b2) vaccination. To monitor the antibody, B and T cell responses blood samples were collected at 28 days after primary and booster vaccination. The innate immune response was characterized by measuring cytokines and chemokines in serum using legendplex, FACS analysis, and RNAseq of peripheral mononuclear cells (PBMCs).

Innate immune response early after primary COVID-19 vaccination was characterized by increased serum cytokines/chemokines IFN γ , TNF α , CXCL9, CXCL10, CXCL11 and CCL20. RNA-seq analysis from PBMCs collected before and at 1, 2 or 3 days after vaccination revealed a distinct expression profile associated with inflammatory and interferon-gamma response pathways. Cellular analysis showed slightly lower percentage of CD19 $^{+}$ (B cells), CD3 $^{+}$ CD4 $^{+}$ (T cells), and CD56 $^{+}$ (NK cells), whereas CD14 $^{+}$ cells (monocytes) were significantly increased in PBMCs shortly after vaccination compared to pre-vaccination samples. Within the monocyte population a significant higher proportion of intermediate monocyte (CD14 $^{+}$ CD16 $^{+}$) subset was present. All monocyte subsets showed an activated phenotype with increased expression of co-stimulatory molecules CD80 and/or CD86 after vaccination. The expression of CD80 and CD86 on intermediate monocytes positively associated with SARS-CoV-2 spike-RBD specific antibody levels, measured at day 28 after primary vaccination. Notably, the day of blood sampling proved to be an important confounding factor for the innate responses. The peak of TNF α , IFN γ , CXCL10 and CCL20 was observed on day 1, whereas CXCL11 was most prominent on day 2, and distinct changes in monocyte subpopulations on day 2 post vaccination.

Altogether we show that COVID-19 mRNA vaccination induced an innate immune profile characterized by increased serum cytokines/chemokines, distinct PBMCs transcriptional profile, and changes in the proportion of circulating monocyte

subpopulations, some of which correlated with specific antibodies. Although correlation analysis with the T cell responses still need to be completed, we propose using innate immune responses as surrogate of protection which can help in predicting an individual's (in)ability to mount a proper immune response.

Innate immune sensing of viral protease activity by the CARD8 inflammasome

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Self versus non-self discrimination allows host cells to induce appropriate and protective innate immune responses upon pathogen recognition. In vertebrates, germline-encoded pattern recognition receptors (PRRs) detect microbes by binding to pathogen-associated molecular patterns (PAMPs) – essential and thus highly conserved features of microbial life. In addition to PAMP-based strategies of innate immune detection, we and others have recently shown that the inflammasome-forming sensors NLRP1 and CARD8 sense and respond to 'patterns of pathogenesis' including the enzymatic function of viral proteases encoded by positive-sense RNA viruses.

Inflammasomes are intracellular immune complexes that initiate inflammatory signaling and pyroptotic cell death following pathogen recognition by inflammasome-forming sensors. Both NLRP1 and CARD8 function as bipartite 'molecular tripwires' comprised of non-covalently associated N-terminal 'sensing' and C-terminal 'signaling' domains. Viral protease cleavage of NLRP1 and CARD8 trips the tripwire, resulting in proteasome-mediated degradation of their N-terminal domains and the release and assembly of the bioactive C-terminus, which is sufficient for inflammasome activation. NLRP1 has been characterized as an innate immune sensor with the capacity to detect a diversity of pathogens. However, the extent of CARD8's antiviral breadth, and the impact of host and viral diversity on CARD8 function, has not been established.

Using an evolution-guided approach, we find that human CARD8, in addition to its previously reported role in sensing the human immunodeficiency virus (HIV)-1 protease (HIV-1pro), can also sense viral proteases from human pathogenic coronaviruses and picornaviruses. CARD8 recognition and response to these viruses is dependent on viral