Universität Basel

Research Project

Correlates of protective immunity to SArs -Coronavirus 2

Third-party funded project

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Correlates of protective immunity to SARS-Coronavirus 2Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus responsible for the acute illness termed coronavirus disease 2019 (COVID-19). In light of the recent pandemic, a critical question relates to whether a primary SARS-CoV-2 infection leads to immunological memory able to confer long-term immunity to re-infection.Hypothesis. We hypothesize that protective immunity can form following SARS-CoV-2 infection, but its generation is influenced by disease severity (and thus antigen load) during primary infection. COVID-19 ranges from asymptomatic infection to patients developing severe pneumonia and acute respiratory distress syndrome. In our COVID-19 cohort (n = 181 as of 22 May 2020, recruitment ongoing), we recently found that SARS-CoV-2-specific IgA and IgG antibody responses correlated significantly with disease severity (Cervia et al. bioRxiv 2020). We submit that mild versus severe SARS-CoV-2 infection exerts quantitative and tissue-specific differences in T and B cell stimulation during primary infection, which in turn lead to significant qualitative differences in terms of protective long-term immunity.Specific aims. This hypothesis shall be tackled within the following two aims:Aim 1 - Primary SARS-CoV-2 infection: In our well-characterized COVID-19 cohort, we will assess the immune response to primary SARS-CoV-2 infection in mild versus severe COVID-19 cases. Using 80-parameter mass cytometry, we will characterize the ex vivo innate and adaptive immune response. 30-40-color spectral flow cytometry will enable us to study phenotypic and functional properties of SARS-CoV-2 peptide pentamer-specific CD8+ T cells, which will be complemented by single cell RNA sequencing and proteogenomic approaches. SARS-CoV-2-specific B cells will be assessed using enzyme-linked immunospot assays and flow cytometry. We will also determine SARS-CoV-2-specific IgM, IgA and IgG titers in sera and mucosal fluids and conduct SARS-CoV-2 neutralization assays to functionally assess these antibodies. Using SARS-CoV-2 peptides, we will stimulate antigen-specific T cells to assess their cytokine production, proliferation and cytotoxicity.Aim 2 - Immunity: We will determine the above-mentioned properties of SARS-CoV-2-specific T and B cells at 6 and 12 months after primary SARS-CoV-2 infection in our entire cohort. Moreover, we will monitor our cohort for clinical signs of upper respiratory tract infection and, if suspected, perform sampling of respiratory mucosa to assess SARS-CoV-2 by quantitative reverse-transcriptase polymerase chain reaction. In subjects with proven SARS-CoV-2 re-infection, we aim to sequence the viral genome for signs of immune escape and perform the aforementioned tests to elucidate the status of SARS-CoV-2-specific T and B cells. Lastly, by using computing-intensive mathematical algorithms, we will identify the kinetics and determinants of protective SARS-CoV-2 immunity.Expected results and impact. Our project will provide insights into the phenotypic and functional properties of SARS-CoV-2-specific T and B cells during the primary immune response and the memory phase in mild versus severe COVID-19 cases. By comparing these data with clinical correlates of mild versus severe COVID-19 disease as well as protection from a secondary infection with SARS-CoV-2, we will gener-

ate crucial knowledge on determinants of protective immunity, knowledge that will be instrumental for informing clinical diagnosis and care, vaccine development, and policy makers.

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