Translational Immunology

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Balancing immunity: Autoimmunity, immunosuppression, Infection and Vaccination

The translational immunology lab focuses on human immunology. We are interest-
ed in antigen-specific immune responses in the context vaccinations and autoim-
mune disease.

Evolution of the humoral immune response following repeated seasonal influenza vaccination

Viruses mutate and thereby evade the host immunity. If this happens at a high rate, as in influenza, such 'escape' is a major challenge for vaccine design. An influenza vaccine protecting us from all potentially occurring viral variants remains the holy grail of influenza vaccine research. The current influenza vaccination strategy of yearly vaccination with adapted strains aims to counteract viral escape. To better understand the factors influencing vaccine responses in healthy and immunosup-pressed individuals, we study the immune responses following influenza vaccina-tion in these subjects. In the setting of seasonal influenza vaccination, we found that in immunosuppressed subjects (i.e. HIV infection) the response profiles (i.e. a multidimensional vector that includes time and antigen specificity) are similar to those in healthy, whereas the magnitude of the response is dampened (Berger CT. Human Vaccine Immunother, 2015). In a follow-up study on healthy subjects we could show that the vaccine response to the influenza vaccine is moreover strong-ly affected by the previous vaccination history. We found evidence that the vaccine response can become skewed, rendering the subject prone to viral escape (Big-ler, M. B. et al. (in preparation)).

We are currently expanding these findings in a prospective clinical study of repeat-ed annual influenza vaccination over three consecutive seasons from 2018–2021. We investigate the evolution of the B cell responses by immunophenotyping and B cell receptor sequencing, and by defining the antibody functions and cross-reac-tivity. Specifically, we aim to dissect whether adaptations in the vaccine formula-tion recruit new naïve B cells to the overall influenza response (i.e. broaden the re-sponse) or mainly boost/adapt the preexisting immunity (i.e. skew the response). Using a systems approach, this data may allow formulating predictions based on the pre-vaccination profile and repertoire. This may help identifying (i) who is in need for yearly vaccination, and (ii) which antigenic difference between subse-quent vaccinations induce diversification of the vaccine response. Ultimately, we aim to apply this towards more personalized rather than one-size-fits-all vaccina-tion strategies, to reduce the risk of vaccine failure.

The immunological targets in autoimmune vasculitis

Autoimmune diseases occur when the immune system attacks self-proteins. Un-derstanding the target of the immune response in autoimmune disease may enable developing therapies interfering with the cause of immunopathogenesis directly. Target identification moreover allows developing tools to measure autoimmunity. Clinically relevant autoantibodies have been described in various autoimmune dis-ease. Immunological biomarkers in predominantly T cell-mediated autoimmune diseases have not yet been established for clinical use.

Giant cell arteritis (GCA) is a T cell-mediated, inflammatory disease of unknown etiology. GCA exclusively affects the large arteries. Disease manifests as an in-flammatory syndrome and ischemic symptoms resulting from stenosis of inflamed arteries. There is strong evidence that T cells play an important role in disease in-duction and/or maintenance. The pathogenesis remains, however, unknown. One of the goals of our lab is to unravel the events leading to disease and more specif-ically the immunological target of the T cells. We study this within the framework

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of a prospective single-center GCA cohort at the university hospital Basel that we are running with the rheumatology clinic. All patients seen at our institution with clinical suspicion of GCA are enrolled. The cohort-data entails a comprehensive set of clinical, routine laboratory, pathological (biopsy), and vascular diagnostic (ultrasound duplex studies and PET studies) information, as well as the longitudinal biobanking of blood and serum samples. This cohort is a precious source to address translational research questions (e.g. Kistner A *et al.,* Rheumatology 2017; Berger CT *et al.,* Rheumatology 2018; Berger CT *et al.,* Annals of the Rheumatic Diseases 2019).

The main current focus is to analyze the inflammatory infiltrate in the artery biopsies of GCA patients. We use next-generation sequencing of the TCRαβ repertoire to identify the expansion of dominant T cell clones in biopsies from patients. Using the collected information on the TCR repertoire, we then aim to identify the target of the expanded T cell clones. To do so, we established a workflow to transfect the identified TCRαβ of expanded T cells into TCRαβ-deficient Jurkat. The thereby generated set of transfected TCRαβ-Jurkat cells is used as reporter cell lines to screen against putative targets of the transfected TCR. For this antigen discovery studies we use an unsupervised ('MHC class II ligandome of artery tissue') and a supervised (viral antigen) screening approach (Bigler MB *et al.,* Arthritis and Rheumatology 2018). Identifying the source of the antigen that T cells recognize in GCA will inform on the potential disease-causing processes. This may pave the way for novel approaches (i) to prevent GCA by identifying subjects at risk, and (ii) to develop immune-therapies aimed at improving antigen-specific tolerance.

Selected Publications

Deigendesch N, Hirsiger JR, Bigler MB, Ghosh A, Harder D, Jauch A, Espinosa JM, Recher M, Navarini A, Daikeler T, Berger CT. Tumoural soft tissue calcification in Down syndrome: association with heterozygous germline SAMD9 mutation and hyperactive type I interferon signaling. Rheumatology (Oxford). 2020 Jun 28:keaa301. doi: 10.1093/rheumatology/keaa301.

Hirsiger JR*, Fuchs, PS*, Häusermann P, Müller-Durovic B, Daikeler T, Recher M, Hirsch HH, Terracciano L, Berger CT. Syphilis reactivates latent EBV reservoir via TLR2 and BCR activation. Open Forum Infectious Diseases 2019 Sep; 6(9): ofz317.

Berger CT, Rebholz-Chaves B, Recher M, Manigold T, Daikeler T. Serial IL-6 measurements in patients with Tocilizumab treated large-vessel vasculitis detect infections and may predict early relapses. Ann Rheum Dis. 2019 Jul;78(7):1012–1014.

Recher M, Hirsiger JR, Bigler MB, Iff M, Lemaître B, Scherer K, Häusermann P, Siegrist CA, Berger CT. Immune system correlates of extensive limb swelling in response to conjugated pneumococcal vaccination. NPJ Vaccines. 2018 May 18;3:17. doi: 10.1038/s41541-018-0059-3. eCollection 2018.

Bigler MB, Hirsiger JR, Recher M, Mehling M, Daikeler T, Berger CT. Varicella Zoster Virus-specific T cell responses in untreated Giant Cell Arteritis. Arthritis Rheumatol. 2018 Feb;70(2):318–320. [Research Letter].

Kistner A, Bigler MB, Glatz K, Egli SB, Baldin FS, Marquardsen FA, Mehling M, Rentsch KM, Staub D, Aschwanden M, Recher M, Daikeler T, Berger CT. Characteristics of autoantibodies targeting 14-3-3 proteins and their association with clinical features in newly diagnosed giant cell arteritis. Rheumatology (Oxford). 2017 May 1;56(5):829–834.

Connection to Clinical Practice

PD Dr. Thomas Daikeler
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The Swiss Giant Cell Arteritis Cohort
Giant cell arteritis (GCA) is the most prevalent of the primary vasculitis syndromes with an increasing disease incidence. Patients typically present with constitutional symptoms, headache, and a systemic inflammatory syndrome. To date therapy of GCA is based largely on steroids, and guided by parameters reflecting disease activity only partially, as indicated by recent imaging-studies. Furthermore, intensity and duration of steroid therapy remain a matter of debate, and no consensus exists in defining remission. Both GCA itself and the steroid based therapy are associated with significant morbidity. Improving diagnostic accuracy and monitoring of disease activity thus would be of great importance. To study these clinical problems, we established in 2011 a prospective interdisciplinary cohort of patients with GCA at the University Hospital Basel. Since 2020, we co-lead a Swiss Cohort for GCA that involves all University Hospitals in Switzerland. In the Relevant clinical data, laboratory parameters, serum and peripheral blood mononuclear cells from all patients are collected at longitudinal time-points. Vascular disease activity is assessed using new technologies such as color-coded duplex ultrasound and positron emission tomography. Thereby we aim at integrating clinical data, imaging studies, and extended immunological and histomorphological assessments for a more detailed understanding of the immunopathogenesis of GCA. This may help to (i) further develop precise, ideally non-invasive, tools to diagnose and monitor disease activity, and (ii) generate strategies towards interfering with specific pathways associated with disease activity and/or complications.