Translational Immunology

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Giant Cell Arteritis – towards a better understanding of pathogenesis

Giant cell arteritis (GCA) is a primary vasculitis of unknown etiology. Disease manifests as an inflammatory syndrome and ischemic symptoms resulting from stenosis of inflamed arteries. There is strong evidence that T cells play an important role in disease induction 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 specifically the immunological target of the T cells.

Characterization of the immunological milieu and the T cell compartment in GCA

Using multiparameter flow cytometry immunophenotyping and multiplexed cytokine measurements we determined the immunological milieu in 42 study subjects (16 GCA patients at diagnosis, 13 disease controls and 13 non-inflammatory, age-matched controls). We identified IL-6 as the main cytokine differentiating between GCA and controls (Fig. 1). Similarly, the IL-8 was higher in GCA, while the other cytokines showed no significant difference to controls. This finding nicely fits the clinical data showing good response of treatment with an anti-IL6 receptor antagonist. Using multi-color flow cytometry we confirmed that T regulatory cells seemed to be reduced in GCA compared to controls. Th1 T cells were comparable between the groups, while high IL-17-producing CD4+ and CD8+ T cells were more frequent in GCA compared to all controls (Fig. 2). However, the majority of GCA patients had normal frequencies of Th17 T cells, suggesting that distinct patient subgroups might exist. As part of the analysis between the clinical presentation and immunological data we are currently investigating this.

Determination of the T cell repertoire in GCA

As next steps, we aim to determine the T cell receptor (TCR) repertoire in patients with GCA. Specifically, we want to test whether the T cells in the inflamed tissue of GCA patients or self-reactive T cells in the peripheral blood are oligoclonally expanded. This information can be used to screen for the immunological target of the T cells.

The role of autoantibodies targeting 14-3-3 protein isoforms in GCA

A recent study suggested that antibodies against isoforms of the so-called 14-3-3 protein (an intracellular regulatory protein) may be useful as biomarkers in large-vessel avsculitis (LVV), i.e. GCA and Takayasu's arteritis. This study was done in patients with aortic aneurysm due to LVV, i.e. those with a late complication of vasculitis. Here, we performed an analysis to assess the presence of these Autoantibodies 'at GCA diagnosis'. If present they would have the high potential as biomarkers/autoantibodies for the diagnosis and monitoring of treatment effects as in other autoimmune diseases (e.g. systemic lupus, ANCA vasculitis). To test this, antibodies against three isoforms of 14-3-3 (γ, ε, and ζ) were measured in 51 LVV patients, and 42 controls (including non-inflammatory and inflammatory diseases), using an multiplexed bead-based immunoassay and immunoprecipitation assays. The positive threshold was defined based on values found in young healthy controls. Anti-14-3-3 IgG antibodies were compared between GCA patients and controls to assess their diagnostic performance as a biomarker. Antibodies against all three 14-3-3 isoforms were detected in GCA patients as well as in age-matched inflammatory and non-inflammatory controls. Amongst LVV patients, detection of antibodies targeting 14-3-3 ε and ζ was associated with more severe disease, specifically stroke or aortitis. Thus, we could conclude that detection of antibodies against 14-3-3 proteins at the time of GCA diagnosis is not disease-specific. Their presence at high levels in LVV with stroke, aortitis and – in a previous study – with aneurysm formation may indicate their value as potential biomarkers for extensive large vessel inflammation. The relevance of 14-3-3 antibodies in non-LVV patients needs to be tested in larger cohorts.

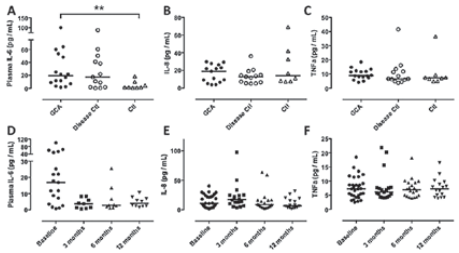

Fig. 1: Cytokine profiles in GCA and controls. (A–C) Mesoscale measurements for three representative proinflammatory cytokines – IL-6, Il-8 and Il-1 – are displayed. IL-6 levels were high in GCA and inflammatory controls. The latter includes many patients with polymyalgia rheumatica (PMR) a disease sharing many features with GCA, including the good response to anti-IL6 therapy (Tocilizumab). **(D–E)** Longitudinal measurements indicate that upon therapy IL6 levels drop dramatically. Kruskal-Wallis test with Dunn's correction was applied. *P < 0.05.

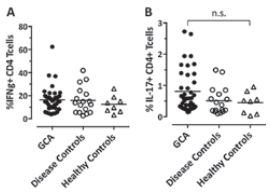

Fig. 2: A subset of GCA patients is characterized by high Th17 T cells. The percentage of IL-17-producing CD4+ T cells in lymphocytes of GCA patients, disease controls and healthy controls was determined by flow cytometry using PMA stimulation assays. Data is expressed as % positive for the respective cytokine amongst CD4 T cells. n = 42 (23 GCA, 12 disease controls, 7 healthy controls)

Selected Publications

Bigler MB, Egli SB, Hysek CM, Hoenger G, Schmied L, Baldin FS, Marquardsen FA, Recher M, Liechti ME, Hess C, *et al.* (2015). Stress-Induced *In Vivo* Recruitment of Human Cytotoxic Natural Killer Cells Favors Subsets with Distinct Receptor Profiles and Associates with Increased Epinephrine Levels. PLoS One 10, e0145635

Berger CT, Greiff V, John S, Koenig KF, Bigler MB, Recher M, Hess C and Daikeler T (2015). Risk factors for pneumocystis pneumonia in giant cell arteritis: a single-centre cohort study. Clin Exp Rheumatol 33, S-122–125

Berger CT, Greiff V, Mehling M, Fritz S, Meier MA, Hoenger G, Conen A, Recher M, Battegay M, Reddy ST, *et al.* (2015). Influenza vaccine response profiles are affected by vaccine preparation and preexisting immunity, but not HIV infection. Human vaccines & immunotherapeutics 11, 391-396

Berger CT, Llano A, Carlson JM, Brumme ZL, Brockman MA, Cedeno S, Harrigan PR, Kaufmann DE, Heckerman D, Meyerhans A, *et al.* (2015). Immune screening identifies novel T cell targets encoded by antisense reading frames of HIV-1. J Virol 89, 4015–4019

Thoens C, Berger C, Trippler M, Siemann H, Lutterbeck M, Broering R, Schlaak J, Heinemann FM, Heinold A, Nattermann J, *et al.* (2014). KIR2DL3(+)NKG2A(-) natural killer cells are associated with protection from productive hepatitis C virus infection in people who inject drugs. J Hepatol 61, 475–481

Connection to Clinical Practice

PD Dr. Thomas Daikeler
and Prof. Dr. Christoph Hess
Division of Rheumatology
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The Basler 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 a prospective interdisciplinary cohort of patients with GCA. 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.