Clinical Neuro-immunology

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Molecular and immunological analysis of Multiple Sclerosis

Our research focuses the molecular and immunological analysis of multiple sclerosis (MS), an inflammatory, demyelinating central nervous system (CNS) disease. We have two main research lines: 1) genomic investigations (including genetic, transcriptional and protein expression analysis) and 2) studies on B cell involvement in MS pathogenesis. Both approaches provide tools and markers for immunomonitoring of current and newly emerging treatments.

Immune regulation by microRNAs in MS

MicroRNAs (miRNAs), small non-coding RNA molecules, which modulate gene-expression of >50% of all protein-encoding genes, and are key regulators of a wide variety of biological processes, e.g. cell proliferation, differentiation, apoptosis and organ development. Our cellular miRNA studies in immune cells from MS patients have revealed distinct expression profiles compared with those in healthy volunteers. We have also shown that natalizumab, the treatment for relapsing-remitting MS, has diverse effects on miRNA expression. We uncovered recently a specific effect of natalizumab on the expression of miR-126 and miR-10 and their potential target, POU2AF1, an important regulator of the transcription factor Spi-B, which binds to unique sequences of the JC virus and plays a critical role in driving virus activity (Meira *et al.*, 2014, 2016, Fig. 1). Natalizumab treatment has been associated with the development of progressive multifocal leukoencephalopathy (PML), a severe opportunistic infection of the CNS caused by reactivation of the latent JC virus. We are presently evaluating the expression of miR-126/10 and POU2AF1 as biomarkers for a PML risk in MS patients treated with natalizumab. Another focus of our research is extracellular miRNAs, stored in extracellular vesicles (EVs), in serum and CSF from MS patients. Our aim is to get new insights into the functional role of EVs in immune regulation and cell-to-cell communication in MS.

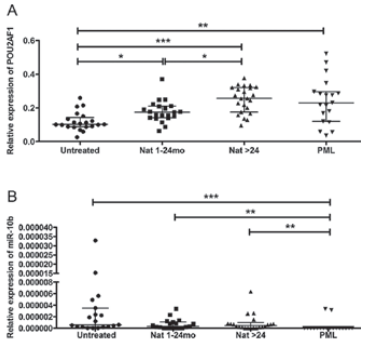

Fig. 1: Transcriptional expression of POU2AF1 (A) and miR-10b (B) in untreated, natalizumab treated RRMS (1–24mo; >24mo) and natalizumab associated PML patients. Relative expression levels (median with interquartile range) are depicted. ***p<0.001; **p<0.01, *p<0.05.

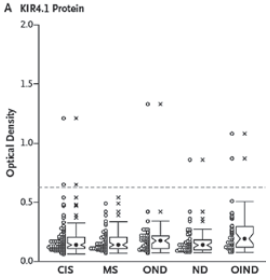

Fig. 2: KIR4.1 protein ELISA: 141 patients with clinically isolated syndrome (CIS, n=82) or multiple sclerosis (MS, n=59) and 131 controls (other (non-inflammatory) neurological diseases (OND) n=48, neurodegenerative diseases (ND) n=48, other inflammatory neurological diseases (OIND) n=35). Anti-KIR4.1 reactivity is expressed as the mean optical density (OD) of duplicate measurements. The distribution of OD KIR4.1 protein by group is shown in notched box-and-whisker plots, each accompanied by histograms of the same data. The dashed horizontal line represents a cut-off value of 0.628 (5 standard deviations (SD) above the mean of an unblinded OND control group1, n=10). Statistical comparison between the groups revealed no significant differences (Kruskal-Wallis rank sum test for five groups: p=0.16).

B cells and their targets in MS

B-cells have a major role in the pathogenesis of MS. Depletion of B-cells leads to a remarkable amelioration of the disease. The mechanisms by which B-cells impact MS are however incompletely understood. Our research focuses on the identification of novel B-cell autoantigens and the characterization of the interaction of autoaggressive B-cells with the CNS. We could show that antibodies against native myelin oligodendrocyte glycoprotein (MOG) identify a subset of patients with neuromyelitis optica (Pröbstel *et al.*, 2015). Antibodies against the potassium channel KIR4.1 have been suggested as a biomarker in MS. Using eukaryotic expression of this protein we could show that the prominently described antibody reactivities are directed against other proteins than KIR4.1 and that the assay as published is not useful for clinical practice (Pröbstel *et al.*, 2016, Fig 2). Currently, we are using transgenic animals to better characterize the pathogenic mechanisms of B cells in the animal model of MS. We identified the co-capture of membrane antigens by the B cell receptor as a key step in initiating an autoimmune response. This work will be continued in analyzing the capacity of B cell to migrate to peripheral tissues and harvest their cognate and non-cognate antigens from the tissue. This phenomenon of membrane capture will also be used to identify novel autoantigens in MS.

Immunomonitoring of new treatments and biomarker research

The mode of action of many current disease modifying treatments is often not well understood. We aim to get a better understanding of the mode of action and thereby identify candidates for treatment response biomarkers. Currently, we are recruiting MS patients that start treatment with dimethyl fumarate. Immune cells of the blood as well as serum will be analyzed for immunological markers, and miRNA/RNA expression profiles that could potentially correlate with the clinical response to treatment. Combination of these biomarkers with a standardized clinical and neuroradiologic assessment will hopefully provide means to better characterize the heterogeneous MS patient populations and to predict the disease course and the treatment response.

Connection to Clinical Practice

Our Laboratory is closely connected to the MS Outpatient Clinic of the Department of Neurology, University Hospital Basel that cares for more than 1000 MS patients per year. This allows access to a population of MS-patients in different stages of the disease. There is also a close collaboration with the Division of Neuroradiology and the Medical Image Analysis Centre (MIAC) that enables characterization of patients with cutting edge neuroimaging techniques. Our Clinical MS Research Group plays a key role in organizing and conducting international therapeutic studies in MS, e.g. with siponimod, amiselimod (Kappos L, 2016), the humanized monoclonal antibodies ocrelizumab, daclizumab, and GNbAC1. These trials provide unique possibilities to apply basic research approaches to understand disease mechanisms and therapeutic responses. Development of biomarkers needs prospective, standardized, and high-quality clinical and neuroradiological data from large patient cohorts to allow for validation and implementation in clinical practice. The Swiss MS Cohort Study (SMSC), supported by the Swiss MS Society and coordinated by our MS Group was initiated in 2012. It aims at building and maintaining a long-term cohort of Swiss MS patients with clinical and MRI follow-up data as well as sampling of body fluids.

Selected Publications

Meira M, Sievers C, Hoffmann F, Derfuss T, Kuhle J, Kappos L, Lindberg RL. (2014) MiR-126: a novel route for natalizumab action? Multiple sclerosis (Houndmills, Basingstoke, England) 20, 1363–1370

Meira M, Sievers C, Hoffmann F, Haghikia A, Rasenack M, Décard BF, Kuhle J, Derfuss T, Kappos L, Lindberg RLP. (2016) Natalizumab-induced POU2AF1/Spi-B upregulation: A possible route for PML development. Neurology® Neuroimmunology & Neuroinflammation 3, e223

Pröbstel A-K, Kuhle J, Lecourt A-C, Vock I, Sanderson NSR, Kappos L, Derfuss T. (2016) Multiple Sclerosis and Antibodies against KIR4.1. New England Journal of Medicine 374, 1496–1498

Pröbstel A-K, Rudolf G, Dornmair K, Collongues N, Chanson J-B, Sanderson NS, Lindberg RL, Kappos L, de Seze J, Derfuss T. (2015) Anti-MOG antibodies are present in a subgroup of patients with a neuromyelitis optica phenotype. Journal of Neuroinflammation 12, 1–7

Kappos L, Arnold DL, Bar-Or A, Camm J, Derfuss T, Kieseier BC, Sprenger T, Greenough K, Ni P, Harada T. Amiselimod (MT-1303) in relapsing multiple sclerosis. A randomised, double blind, placebo-controlled, multicentre phase II trial of a selective sphingosine 1-phosphate 1 (S1P1) receptor modulator. Lancet Neurology 2016 (in press)