Translational Neuro-immunology

Matthias Mehling
SNSF Ambizione-SCORE
Department of Biomedicine
Division of Neurology
University Hospital Basel

Group Members
Andrea Amstad
(MD Student)
Corina Frick
(MD-PhD Student)

Single cell lymphocyte migration in multiple sclerosis

Individual cell-migration is fundamental to protective immunity but plays also a central role in the pathogenesis of autoimmune diseases. Our general aim is to assess migration characteristics of primary human T cells within specific subpopulations on a single cell level in health and in autoimmunity.

Orchestrated migration of T cells provides the basis for their precise positioning within lymphoid and non-lymphoid tissues. Conversely, migration of autoreactive lymphocytes is fundamental to the pathogenesis of autoimmune diseases, such as multiple sclerosis (MS). The importance of T cell migration in the pathogenesis of MS is supported by the fact that two highly efficacious drugs for the treatment of MS (fingolimod and natalizumab) act on T cell migration.

Most of our insight into T cell migration is based on the monitoring of bulk cell populations in animal models. For human T cells, a relatively limited set of migration-characteristics have been recapitulated *in vitro*, again mostly by using bulk cell populations and probing the peripheral blood lymphocyte compartment. While important understanding of mechanisms underlying T cell migration derives from these studies, a potential heterogeneity of migration between individual cells is not interrogated using this approach. Also, clinical samples containing only small numbers of T cells are not amenable for analysis using classical *in vitro* migration assays. Specifically, understanding the migration characteristics of T cells derived from cerebrospinal fluid of MS patients –the closest routinely accessible approximation to pathogenic cells in this disease– would be of particular interest.

In recent years, introduction of microfabrication technologies resulted in the generation of so-called microfluidic devices, which allow monitoring of cells on a single-cell level with high spatio-temporal resolution. We have developed microfluidic devices specifically designed to studying the migration characteristics of primary human T cells. These devices allow a highly precise build-up of soluble and immobilized chemokine gradients. Characterizing migration properties of individual human CD4+ memory T cells *ex vivo*, we have already established the proof of concept that this technique can overcome previous limitations of standard migration assays. With the help of microfluidics we aim at assessing migration characteristics of immune cells derived from the cerebrospinal fluid of patients with MS and relate these findings with clinical phenotypes.

Selected Publications

Schwarz J, Bierbaum V, Merrin J, Frank T, Hauschild R, Bollenbach T, Tay S, Sixt M, Mehling M. A microfluidic device for measuring cell migration towards substrate-bound and soluble chemokine gradients. Sci Rep. 2016 Nov 7;6:36440

Mehling M, Frank T, Albayrak C, Tay S. (2015) Real-time tracking, retrieval and gene expression analysis of migrating human T cells. Lab Chip 15, 1276–1283

Mehling M, Tay S. (2014). Microfluidic cell culture. Curr. Opin. Biotechnol. 25, 95–102

Mehling M, Brinkmann V, Burgener A-V, Gubser P, Luster A, Kappos L, Hess C. (2013) Homing frequency of human T cells inferred from peripheral blood depletion kinetics after sphingosine-1-phosphate receptor blockade. Journal of Allergy and Clinical Immunology 131, 1440–1443.e7

Mehling M, Hilbert P, Fritz S, Durovic B, Eichin D, Gasser O, Kuhle J, Klimkait T, Lindberg RL, Kappos L, Hess C. Antigen-specific adaptive immune responses in fingolimod-treated multiple sclerosis patients. Ann Neurol. 2011 Feb;69(2):408–13

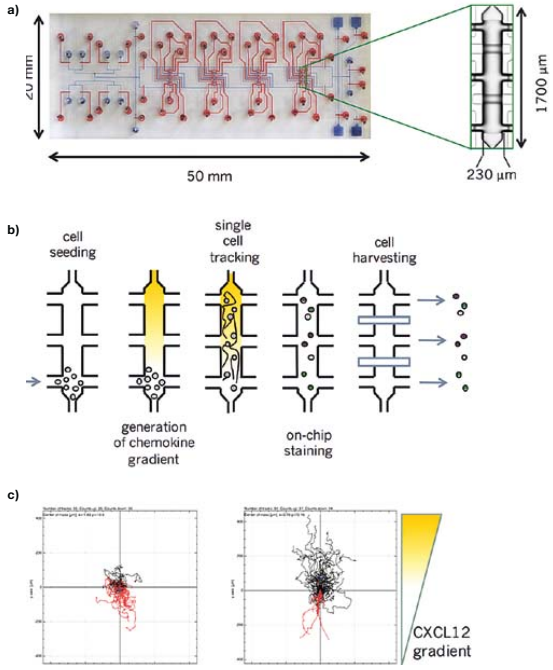

Fig. 1: Overview and geometry of microfluidic chemotaxis and cell retrieval device. **(a)** Actual photograph of the device (blue structures: flow channels; red structures: control channels) and one magnified migration chamber. **(b)** Schematic overview of the functionality of an individual microfluidic migration chamber for assessing single cell migration in highly controllable chemokine gradients. **(c)** Trajectories of migrating primary human CD4+ central memory T cells plotted on a common starting point in the absence (left panel) and presence (right panel) of a CXCL12 gradient.

Connection to Clinical Practice

Prof. Dr. Ludwig Kappos
Prof. Tobias Derfuss
Neurology Department

Relating migration-characteristics of MS cerebrospinal fluid T cells with clinical phenotypes

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The disease affects worldwide over 2.5 million individuals and is the most common cause of neurological disability in young adults. Autoreactive immune responses in the CNS, mediated by encephalitogenic lymphocytes are thought to play central roles in the initiation and propagation of MS pathology. Priming of encephalitogenic T cells presumably occurs in secondary lymphoid tissues (SLT) outside the CNS. Thus, migration of these cells – or their precursors – to SLT, and from SLT to the CNS are crucial steps in the immunopathogenesis of MS. To assess migration characteristics of T cells derived from patients with MS our Translational Neuroimmunology Laboratory works in close collaboration to the Division of Neurology of the University Hospital Basel, which includes a MS Outpatient Clinic. This provides access to samples from a unique and well defined population of MS-patients with different stages and courses of the disease and different treatments including experimental therapies in clinical development.