Experimental Immunology

Gennaro De Libero
Department of Biomedicine
Tumorimmunology
University Hospital Basel

Group Members
Lena Angman
(Technician)
Salvatore Calogero
(PhD Student)
Dr. Marco Cavallari*
(Postdoc)
Dr. Pauline Cullen Baumann
(Administrative Assistant)
Dr. Daniela Di Blasi
(Postdoc)
Berenice Fischer
(Undergraduate Student)
Celine Furtwängler*
Dr. Artem Kalinichenko
(Postdoc)
Dr. Marco Lepore
(Postdoc)
Dr. Lucia Mori
(Research Associate)
Adrijana Perkovic*
Nirojan Rajah*
Tobias Rutishauser
(External Collaborator)
Sebastiano Sansano*
(Technician)
Dr. Mathias Schmaler
(Postdoc)

Dr. Julian Spagnuolo
(Postdoc)
Dr. Alessandro Vacchini
(Postdoc)

*left during report period

Adaptive and innate T cells specific for non-peptidic antigens: the diseases' perspective

Antigen recognition is a central event in immune response and the immune system has evolved a series of receptors, which recognize a variety of antigens and activate specific immune cells. T lymphocytes express membrane-bound T cell receptors (TCR) that recognize complexes composed of antigen-presenting molecules and antigens. In addition to small peptides, T cells may also recognize lipids, glycolipids, and small metabolites of endogenous or microbial origin. Our studies in humans revealed that these latter T cells are as abundant as peptide-specific ones. Our goal is to understand the role of non-peptide-specific T cells in the immune response, and their participation in diseases.

Our studies cover the following three main areas. The first one is lipid-specific T cell immunity. Our aim is understanding the mechanisms leading to lipid recognition by T cells, how lipid antigens interact with the lipid-presenting CD1 molecules, and how lipid-specific T cells participate in the recognition of tumor cells (in human cancer), of mycobacteria-infected cells (in tuberculosis) and of self lipids (in autoimmune diseases). We have investigated the mechanisms how complex lipids are processed by lipases and hydrolases, how the lipid antigens are transported within the antigen-presenting cells, how they are loaded on CD1 molecules. These studies led to the establishment of novel anti-bacterial vaccines taking advantage of lipid-specific T cells providing help to B cells secreting sugar-specific antibodies. We have also identified novel tumor-associated lipid antigens, which will be further exploited in leukaemia immunotherapy.

The second type of studies investigate the biology of TCR γδ cells. We identified butyrophilin 3A1 as the relevant molecule for the activation of human T cells expressing the TCR Vγ9-Vδ2 heterodimers by microbial and self-metabolites. These metabolites accumulate in some tumor cells and specifically stimulate TCR Vγ9-Vδ2 cells. We established a human TCR Vγ9-Vδ2 transgenic mouse model that is being utilized to explore the anti-tumor function of this T cell population.

The third type of studies focus on T cells restricted to the MHC-class-I-related molecule, MR1. These T cells are stimulated by metabolites generated in the vitamin B2 pathway and are called mucosal-associated T (MAIT) cells as they preferentially localize in mucosal tissues, liver and skin. We found that the TCR gene repertoire of these cells is remarkably oligoclonal both in peripheral blood and liver, inferring preferential stimulation of selected T cell clones *in vivo*. Unique aminoacids were detected in the CDR3 regions of skin-derived MR1-restricted T cells, possibly due to selective expansion following stimulation with metabolites produced by the skin-resident microflora. Biochemical purification revealed a complex array of stimulatory antigens, including vitamin B2-unrelated ones.

In order to understand the functional role of MR1-restricted T cells, systematic and sequential studies are ongoing. First, by single cell transcriptomics analyses of MAIT cells we discovered functionally different cell populations, whose roles in liver and gut diseases are being investigated. Secondly, by multidimensional flow-cytometry we identified the phenotypic correlates of these distinct populations. To this aim, panels of monoclonal antibodies have been optimized to allow the characterization of T cells within human healthy and diseased tissues. Thirdly, individual cell populations are being investigated after sorting, cloning and *in vitro* activation. These studies are revealing how tissue-resident MR1-restricted T cells specialize in their functions and participate in disease evolution.
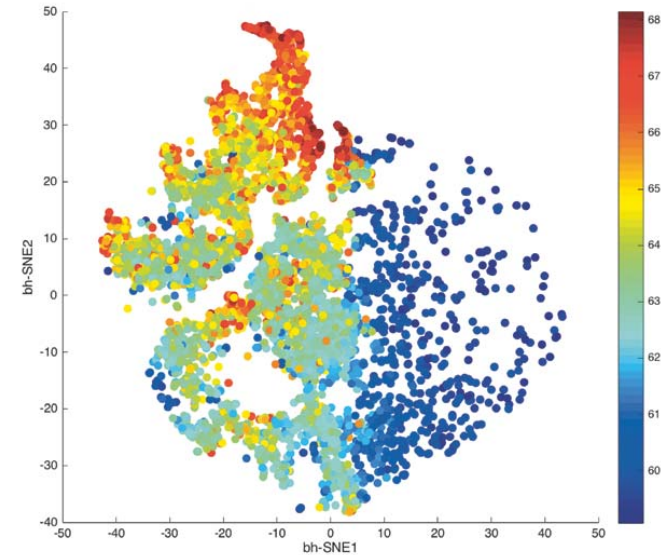
Fig. 1: Populations of MAIT cells identified by multidimensional flow cytometry. Differential expression of 14 surface markers upon stimulation with microbial metabolites. Colors indicate antigen responsiveness: non-reacting cells (blue) highly reacting cells (red).

Selected Publications

Mori L, Lepore M, De Libero G. 2016. The Immunology of CD1- and MR1-Restricted T Cells. Annu Rev Immunol 34: 479–510

Singhal A, Jie L, Kumar P, Hong GS, Leow MK, Paleja B, Tsenova L, Kurepina N, Chen J, Zolezzi F, Kreiswirth B, Poidinger M, Chee C, Kaplan G, Wang YT, De Libero G. 2014. Metformin as adjunct antituberculosis therapy. Sci Transl Med 6: 263ra159

Lepore M, de Lalla C, Gundimeda SR, Gsellinger H, Consonni M, Garavaglia C, Sansano S, Piccolo F, Scelfo A, Haussinger D, Montagna D, Locatelli F, Bonini C, Bondanza A, Forcina A, Li Z, Ni G, Ciceri F, Jeno P, Xia C, Mori L, Dellabona P, Casorati G, De Libero G. 2014. A novel self-lipid antigen targets human T cells against CD1c+ leukemias. J Exp Med

Cavallari M, Stallforth P, Kalinichenko A, Rathwell DC, Gronewold TM, Adibekian A, Mori L, Landmann R, Seeberger PH, De Libero G. 2014. A semisynthetic carbohydrate-lipid vaccine that protects against S. pneumoniae in mice. Nat Chem Biol 10: 950–6

Lepore M, Kalinichenko A, Colone A, Paleja B, Singhal A, Tschumi A, Lee B, Poidinger M, Zolezzi F, Quagliata L, Sander P, Newell E, Bertoletti A, Terracciano L, De Libero G, Mori L. 2014. Parallel T-cell cloning and deep sequencing of human MAIT cells reveal stable oligoclonal TCRbeta repertoire. Nat Commun 5: 3866