Department of Dermatology
Division of Immune Modulation

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Research Focus
• Immune-modulation in autoimmunity and transplantation by soluble CD83
• Transcriptional in vivo targeting of dendritic cells (DC) using the human CD83 promoter
• Intracellular signal transduction of CD83 in DC
• Immune-modulation by TSLP and CD83
• Interaction of DC and viruses

Structure of the Division
Professorships: 1
Personnel: 20
• Scientists: 12 (thereof funded externally: 10)
• Graduate students: 7

Research
The translation research, i.e. the translation of basic research findings into new and applicable therapeutic strategies for patients, is within the prime focus of our research Division. Immune modulation, in the context of autoimmune disorders and transplantation as well as tumor- and infectious diseases, are in the center of our recent projects.

Immune-modulation in autoimmunity and transplantation by soluble CD83
Pt: Dr. E. Zinner
The project group focuses on the immuno-suppressive properties of soluble CD83 (sCD83). Using a recombinantly expressed sCD83 molecule, it was possible to inhibit the paralyzes associated with EAE, an animal model for the early, inflammatory phase of Multiple Sclerosis in a prophylactic as well as in a therapeutic setting. Furthermore, also the rejection of heart-, skin-, and cornea-transplants could be prevented by the use of sCD83. Regarding the mode of action of sCD83, we could show that it induces regulatory T cell (Treg) and that indoleamine 2,3-dioxygenase (IDO) plays a major role. Interestingly, a naturally occurring sCD83 molecule has been identified in the serum of tumor patients, whereby high concentrations of sCD83 correlated with a reduced treatment free survival in CLL patients, indicating its relevance also in tumor patients. The therapeutic potential as well as the mode of action of sCD83 is currently under investigation using murine arthritis models as well as conditional KO animals whereby CD83 is specifically deleted only in DC, Treg or in B cells. This allows the elucidation of the biological function of CD83 expression in specific cell populations.

Transcriptional in vivo targeting of dendritic cells (DC) using the human CD83 promoter
Pt: Dr. I. Knippertz
Focus of the research group is the transcriptional targeting of DC and Treg for the treatment of cancer, chronic viral infections, and autoimmune diseases. Regarding this transcriptional targeting strategy, the human DC- and maturation specific CD83 promoter has been successfully characterized in the past. The membrane-bound CD83 molecule is a 45 kDa glycoprotein expressed on the surface of mature, immunogenic DC. Since CD83 is not expressed on immature, tolerogenic DC, its regulatory DNA region, the CD83 promoter, is of high interest in the context of DC-mediated in vivo vaccination strategies directly in patients. For this purpose, therapeutic adenoviruses and nanoparticles are currently generated encoding different immune-modulatory and therapeutic transgenes under the control of the cell type- and stadium specific CD83 promoter. The potency of these therapeutic vectors will then be determined in vivo in humanized tumor mouse models. Recent data from our Division demonstrated CD83 not only to be expressed by mature DC, but also by activated Treg. Interestingly, transcriptional regulation is different in DC and Treg. Therefore, another aim of our group is the characterization of the CD83 promoter in activated Treg, e.g. by ChiP-Seq for the development of new transcriptional targeting strategies for the treatment of autoimmune diseases. The third emphasis of our group is to study the mechanisms by which different Aryl hydrocarbon receptor (AhR)-agonists modulate DC-specific CD83 expression on transcriptional level, thereby modulating the immune response in physiology and pathophysiology. Bioinformatic analyses revealed two transcription factor binding sites for AhR within the human CD83 promoter region which have been proven experimentally afterwards. The incubation of DC with different AhR-agonists in vitro led to a specific downregulation of CD83, accompanied with an altered cytokine secretion profile and T cell stimulatory capacity. The underlying molecular mechanisms are currently under investigation.

Intracellular signal transduction of CD83 in DC
Pt: Prof. Dr. A. Steinkasserer
The main research focus of the project concentrates on structural- and signal transduction pathway analyses of the membrane bound CD83 molecule. Specific binding domains/partners have been identified using a yeast two hybrid screen. Site directed mutagenesis-, transfection-, immune-precipitation-, and co-immunofluorescence-studies have been used to further characterize the protein-protein interaction, the N-linked glycosylation, and the activation of mCD83 on a molecular level. To identify possible binding motifs in silico, a bioinformatic modeling study has been performed. The elucidation of the mCD83 signaling pathway in mature human DC will open new and specific therapeutic targets.

Immune-modulation by TSLP and CD83
Pt: Dr. M. Lechmann
This research group is interested in the regulatory mechanisms balancing TH1/TH17/TH2 immune responses on the one hand and in the development and activation of regulatory T cells in vivo on the other hand. It is focusing on two modulators of the immune system, namely the thymic stromal lymphopoietin (TSLP) and CD83 protein. TSLP is thought to be the "missing link" between DC activation and allergic responses. To further analyze the role of TSLP in vivo, a TSLP KO-mouse was generated. Using this KO-mouse, the function of TSLP was addressed in different inflammatory and infectious diseases models as well as in models for autoimmunity. It was demonstrated that TSLP has an important protective function in the development of chronic inflammatory bowel diseases, is capable to directly stimulate intestinal epithelial cells and promotes the regeneration of the epithelial barrier. In the second project, the CD83-specific reporter mouse was generated which now allows us to carry out in vivo monitoring of CD83 expressing cells. In this project, the expression and function of CD83 in T cell subpopulations is of particular interest. We reported that CD83-positive T cells had mainly the phenotype of...
regulatory T cells as well as Treg-like suppressor functions in vitro and in vivo. Based on these findings the group now investigates, using a Treg-specific conditional CD83 KO-mouse, the influence of CD83 on differentiation and function of regulatory T cells. Third, with regard to the therapeutic application of sCD83, a study in an animal model of inflammatory bowel disease, i.e. the DNBS-induced colitis, has been performed. Interestingly sCD83 treatment ameliorated DNBS-induced colitis, whereby these animals showed less severe progress of disease and significant faster recovery. Essential for this immunomodulatory function of sCD83 was the induction of the IDO. The immunomodulatory sCD83 is also endogenously expressed in inflamed colonic tissue. The questions which cells express CD83 in the intestine and which immune cell types and intestinal epithelial cells are direct targets of CD83 as well as how CD83 modulates intestinal homeostasis and pathogenesis are currently under investigation.

Interaction of DC and viruses

PI: Dr. C. Heilinloh

This project group analyzes the impact of viral infections on dendritic cells (DC). Particular attention has been given to HSV-1 and HCMV infections. In this respect, the group identified several new immune-escape mechanisms. For instance, the infection of DC with HSV-1 leads to a complete degradation of CD83 which correlates with a reduced immuno-stimulatory capacity of these infected DC. Our group demonstrated that the viral immediate early protein ICP0 induces a proteasomal CD83 degradation which interestingly is independent of its E3 ubiquitin ligase function and the ubiquitin machinery. Furthermore, infection of mature DC with HCMV also induces a proteasomal degradation of the CD83 molecule with immediate-early kinetics. The exact mechanism of these degradation mechanisms is subject of current research. Furthermore, the group is also interested in the replication of HSV-1 in mature DC. In contrast to earlier publications, the replication of HSV-1 in mature DC could be reported recently. In this regard, we were able to show that HSV-1 infected mature DC release so-called L particles which contain several viral proteins, but lack capsid and DNA. These non-infectious L particles were shown to be able to transfer functional viral proteins to uninfected bystander DC inducing e.g. CD83 degradation, revealing important biological functions of these particles during lytic replication. Therefore, the transfer of viral proteins by L particles to uninfected bystander cells may represent an additional strategy for viral immune escape. An additional project deals with the HSV-1 mediated modulation of DC migration. In this respect we showed that HSV-1 induces the adhesion of mDC which in turn reduces chemokine mediated DC-migration which is an absolutely essential step in order to induce potent antiviral immune responses.

Teaching

The co-workers of the Division teach students of molecular medicine and biology in the field of molecular and cellular immunology. The training takes place in form of lectures, seminars, practical courses as well as Bachelor’s, Master’s, and PhD theses. In addition, the SFB 643 (compare own report) was coordinated together with the Department of Dermatology.

Selected Publications


International Cooperations

Prof. Dr. H. Wang, Lawson Health Research Institute, University of Western Ontario, London: Canada

Prof. Dr. C.C. Figdor, Nijmegen Center for Molecular Life Sciences, Nijmegen: The Netherlands

Prof. Dr. R.D. Everett, MRC-Center for Virus Research, University of Glasgow, Glasgow: UK

Prof. Dr. N. Romani, Department of Dermatology, Medical University Innsbruck, Innsbruck: Austria

Prof. Dr. U. Grohmann, University of Perugia, Perugia: Italy