Department of Dermatology

Division of Immune Modulation

Address
Hartmannstraße 14
91052 Erlangen
Phone: +49 9131 8536725
Fax: +49 9131 8535799
www.immunmodulation.uk-erlangen.de

Head of Division
Prof. Dr. Alexander Steinkasserer, PhD

Contact
Prof. Dr. Alexander Steinkasserer, PhD
Phone: +49 9131 8536725
Fax: +49 9131 8535799
alexander.steinkasserer@uk-erlangen.de

Research focus

- Immune-modulation in autoimmunity and transplantation
- Transcriptional *in vivo* targeting of Dendritic cells (DC)
- Signal transduction of CD83 in DC and regulatory T cells
- Immune-modulation by TSLP and CD83
- Interaction of DC and viruses

Structure of the Division

Professorship: 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 research projects.

Immune-modulation in autoimmunity and transplantation

PI: PD Dr. E. Zinser

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 paralyses 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, B cells as well as microglia cells. This allows the elucidation of the biological function of CD83 expression in these specific cell populations. In addition, the group is currently investigating the precise function of sCD83-mediated immune-regulatory and tolerogenic mechanisms using a murine model of cornel allograft transplantation. By detailed functional examinations, we aim to elucidate how sCD83 induced corneal allograft tolerance is maintained directly by immune cells of the donor graft and to use this knowledge to develop future therapeutic strategies

Transcriptional *in vivo* targeting of Dendritic cells (DC)

PI: 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.

Signal transduction of CD83 in DC and regulatory T cells

PI: Prof. Dr. A. Steinkasserer

This group concentrates on structural analyses and characterization of CD83 related signal transduction pathways. Specific interaction partners have been identified using a Ligand-Based Receptor Capture assay and will now be further evaluated. In addition, the three-dimensional structure of the extracellular CD83 domain has been established up to a resolution of 1.7Å, using X-ray crystallography. To identify possible binding motifs in silico, a bioinformatic modeling study has been performed. Using our recently generated DC specific CD83 conditional KO animals, we discovered that CD83 modulates proinflammatory TLR2/4 signaling pathways, thereby potently regulating immune responses in a DC dependent manner. Regarding regulatory T cells, we reported for the first time that CD83 is essential for the resolution of inflammation, since deletion of CD83 on these cells causes a massive over activation of the immune system with exacerbated autoimmune reactions, as observed in animal models for arthritis and inflammatory bowel disease (IBD). In follow up studies we will now elucidate the precise underlying mechanisms and use this knowledge for the development of future therapeutic intervention strategies for patients suffering from autoimmune disorders.

Immune-modulation by TSLP and CD83

PI: PD Dr. M. Lechmann

TSLP (Thymic Stromal Lymphopoietin) 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 IBD, 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. With regard to the therapeutic application of sCD83, a study in an animal model of IBD, 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. L. Grosche

DC play a pivotal role in the induction of protective antiviral immune responses. The focus of this project group is the identification of virus-specific immune evasion mechanisms during herpesviral infections of DCs, by herpes simplex virus type-1 (HSV-1) and human cytomegalovirus (HCMV). Regarding this, we have shown that HSV-1 as well as HCMV downmodulate the expression of the surface molecule CD83 on infected mature DCs via a proteasome-dependent mechanism, which subsequently leads to hampered antiviral immune responses. A second HSV-1- and HCMV-mediated immune evasion mechanism is the inhibition of mDC migration. This was shown to be caused, among others, by rapid induction of mDC adhesion. The precise molecular mechanism is currently under investigation. Furthermore, this group is interested in the characterization of HSV-1 replication in immature versus mature DCs. Contrary to previous hypotheses, we showed that HSV-1 indeed establishes its complete gene expression cascade in mature DCs. However, supernatants of mature DCs, in contrast to immature DCs, barely contain any infectious progeny virions, and almost exclusively contain non-infectious L-particles. We have proven that HSV-1 capsids are trapped inside the nucleus of mature DCs, while immature DCs facilitate an autophagy dependent complete viral replication cycle. An additional project deals with the analysis of non-infectious L-particles, due to their ability to transfer functional viral proteins to un-infected bystander cells. Thus, L-particles constitute an additional immune evasion strategy of HSV-1, since they can also modulate bystander cells for viral benefit.

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.

Selected publications

Heilingloh CS, Klingl S, Egerer-Sieber C, Schmid B, Weiler S, Mühl-Zürbes P, Hofmann J, Stump JD, Sticht H, Kummer M, Steinkasserer A, Muller YA. Crystal structure of the extracellular domain of the human dendritic cell surface marker CD83. J Mol Biol. 2017 Apr 21;429(8):1227-1243

Horvatinovich JM, Grogan EW, Norris M, Steinkasserer A, Lemos H, Mellor AL, Tcherepanova IY, Nicolette CA, DeBenedette MA. Soluble CD83 Inhibits T Cell Activation by Binding to the TLR4/MD-2 Complex on CD14+ Monocytes. J Immunol. 2017, 198(6):2286-2301

Hammer A, Waschbisch A, Knippertz I, Zinser E, Berg J, Jörg S, Kristina Kuhbandner K, David C, Pi J, Bayas A, De-Hyung Lee, Haghikia A, Gold R, Steinkasserer A, Linker RA. Role of Nrf2 Signaling for Effects of Fumaric Acid Esters on Dendritic Cells. Front. Immunol. 2017 Dec 22;8:1922

Grosche L, Draßner C, Mühl-Zürbes P, Kamm L, Le-Trilling V, Trilling M, Steinkasserer A, Heilingloh CS. Human Cytomegalovirus-Induced Degradation of CYTIP Modulates Dendritic Cell Adhesion and Migration. Front Immunol., 2017 Apr 21;8:461

Grosche L, Kummer M, Steinkasserer A. What Goes Around, Comes Around - HSV-1 Replication in Monocyte-Derived Dendritic Cells. Front Microbiol. 2017 Nov 7;8:2149

Döbbeler M et al. CD83 expression is essential for Treg cell differentiation and stability. JCI insight, 2018, 3(11). pii: 99712

International cooperations

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

Dr. C. Nicolette, Argos Therapeutics, Durham: USA