UNIVERSITY HOSPITAL

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
- CD83 induced immune regenerative processes and resolution of inflammation
- Immune-modulation in autoimmunity and transplantation
- Transcriptional *in vivo* targeting of Dendritic cells (DC)
- Cell-specific biologic function of CD83 expressing immune cells
- Interaction of DC and viruses

Structure of the Division

Professorship: 1
Personnel: 18
- Scientists: 10 (thereof funded externally: 8)
- Graduate students: 5

Research

The *translational research*, i.e. the translation of basic research findings into new and applicable therapeutic strategies for patients, is the prime focus within 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. In addition, we focus our research efforts torwards immune-mediated regenerative processes during wound healing and resolution of inflammation.

CD83 induced immune-regenerative effects and resolution of inflammation
PI: Dr. D. Royzman, Prof. Dr. A. Steinkasserer
The timely coordinated and site specific resolution of inflammation and the subsequently induced immune-mediated regeneration processes of cells and tissues, are absolutely vital to inhibit chronification and long term damage. This is true for inflammatory disorders of the joint and intestinal tissues, such as in rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), as well as for wound healing processes. Since the recombinantly expressed soluble CD83 (sCD83) molecule has been shown to induce antigen-specific immune tolerance and resolution of inflammation, we investigated the effects of sCD83 in the context of preclinical RA models. Herein, sCD83-treated mice showed a significantly ameliorated disease progression, a reduced inflammatory milieu as well as an accelerated resolution of inflammation. Noteworthy, sCD83 treated animals were even protected from a flare up reaction, without any additional sCD83-applications. Furthermore, we discovered for the first time, that sCD83 treated animals show an inhibitory effect on the formation of bone-resorbing cells, i.e. osteoclasts. Based on these results, the major focus of the research group lies now in the translation of these basic murine results into the human setting, in order to establish new sCD83 based therapeutic strategies for RA patients. In addition, we investigate the pro-regenerative capacities of sCD83 in the context of wound healing. This project is based on the previous observation that both the systemic as well as the local sCD83 application resulted in a significantly improved and accelerated wound closure, using a murine model. In particular, this was characterized by an increased vessel formation within the wound areas and accelerated regenerative healing processes. Currently, we investigate the sCD83-mediated molecular and cellular processes in the course of wound healing, to elucidate the underlying mechanisms. In addition, the potential of sCD83 to induce long lasting wound healing and regeneration processes, for future treatment options for elderly patients suffering from chronic wounds or patients with wound-healing disorders, will be investigated.

Immunmodulation in autoimmunity and transplantation
PI: PD Dr. E. Zinser
The project group focuses on the immuno-modulatory properties of soluble CD83. Using this molecule, we inhibited the inflammation and disease associated symptoms in different murine autoimmune models. Furthermore, also the rejection of heart-, skin-, and cornea-transplants was reduced/ prevented by the sCD83 treatment. Regarding the mode of action, we found, that sCD83 induces regulatory T cells (Treg) and that the indoleamine 2,3-dioxygenase (IDO) plays a major mechanistic role.
Using conditional KO animals, where CD83 is specifically deleted in CX3CR1^{+} macrophages (MΦ), we are currently investigating the role of CD83 within these important immune cells. MΦ are the body's own phagocytes, responsible for detecting, engulfing and destroying pathogens as well as apoptotic/necrotic cell debris. Moreover, MΦ play an important role upon tissue regeneration after injury. Distinct MΦ populations will be characterized under steady state and inflammatory conditions by modern high resolution microscopy, immunological assays and proteomics analyses.
In addition, the group is actually investigating the precise function of sCD83-mediated immune-regulatory mechanisms using a murine model of corneal allograft transplantation. Within this subproject, we analyse whether the pre-treatment of donor tissue with sCD83 induces corneal allograft tolerance and inhibits rejection within the acceptor. Data established in the context of this project provide the basis for new therapeutic strategies in the field of transplant immunology.

Transcriptional *in vivo* targeting of Dendritic cells (DCs)
PI: Dr. I. Knippertz
This research group focuses on two main key topics: (i) transcriptional targeting of dendritic cells for the development of new vaccination strategies, and (ii) the activation of the aryl hydrocarbon receptor (AhR) for the induction of tolerogenic DCs.
Regarding the first topic, we aim to develop a new vaccine for the treatment of patients suffering from cancer or chronic viral infections (e.g. HIV). Currently, new therapeutic vaccination strategies, using adenoviral vectors as well as nanoparticles, are in development to target DCs directly in patients. To ensure specific therapeutic gene expression only in mature immune-stimulating DCs, we use the DC-specific human CD83 promoter, which allows the transcriptional targeting of these DCs. Hence, different therapeutic adenoviruses as well as nanoparticles will be generated, allowing the induction of potent anti-tumoral or anti-viral immune responses, directly in patients.
The second emphasis of our group is to study the mechanisms by which different AhR agonists modulate the phenotype and function of DCs, thereby influencing the immune response in physiology and pathophysiology. In this context, we recently showed, that DCs treated with the AhR ligand Quercetin, a naturally occurring flavonoid, developed a tolerogenic phenotype. Currently, we analyse the underlying molecular mechanisms of AhR activation by Quercetin and other endogenous agonists. The long term aim is the development of new treatment options for patients suffering from autoimmune diseases.

Cell-specific biologic function of CD83 expressing immune cells
PI: Dr. A. Wild
This group focusses on the biologic function of the CD83 molecule, expressed by specific immune cells, including DCs, Tregs as well as microglia. Using cell-type specific conditional KO (cKO) mouse strains, we demonstrated that DC-expressed CD83 plays an important part in resolution of inflammation, since autoimmune responses are severely aggravated in these cKO mice. On the other hand, due to this over activation, bacterial infections are cleared much better. On cellular level, we found that CD83-deficent DCs are characterized by a pro-inflammatory cytokine profile and inhibited tolerogenic and regulatory processes. The underlying molecular mechanisms, leading to the differentiation of this particular cellular phenotype, are currently under investigation. In studies, using CD83 cKO Tregs, we have shown that CD83 is essential for the differentiation and stability of this particular T cell subset, and now we investigate the underlying mechanisms. Moreover, we analyze cKO-strains, in which CD83 is specifically depleted in microglial cells, of the central nervous system (CNS). Using these mice, we have discovered that CD83 is associated with both, a homeostatic and a reparative phenotype in these CNS cells.

Currently, we are investigating the effect of CD83 deletion, using preclinical models for autoimmune neuro-inflammation. Preliminary data show, that CD83 cKO mice develop axacerbated disease symptoms. Within this basic research project, we will generate valuable insights to development new therapies for inflammatory autoimmune disorders of the CNS, in the future.

Interaction of DCs and viruses

PI: Dr. A. Birzer

This research group focuses on the interaction of DCs and specific viruses, including herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and HCMV. To induce potent immune responses against pathogens, e.g. viruses, DCs play a pivotal role. Thus, it is not surprising that many viruses developed specific immune escape mechanisms during their coevolution with the host. We are particularly interested to elucidate the molecular mechanisms leading to such immune escape strategies. In this regard we recently reported, that both adhesion and migration of human DCs are targeted by HSV-1 and HSV-2. Enhanced DC-adhesion leads to impaired migration of these cells into the draining lymph nodes and subsequently to reduced anti-viral immune responses.

Moreover, we discovered that HSV-1 specifically modulates the IL-6 signaling pathway in human mature DCs (mDCs). Using FACS analyses we showed that IL-6 receptor surface expression was strongly impaired on directly HSV-1-infected mDCs. Surprisingly, this was also the case when we analyzed uninfected, bystander mDCs. This is facilitated by so called non-infectious light (L)-particles, which in comparison to infectious heavy (H)-particles do not contain the viral capsid and thus miss the viral genome. However, these particles contain many viral proteins which are sufficient to down-modulate IL-6 receptor expression on mDCs. To obtain further insights regarding the precise protein composition of these non-infectious L-particles, we performed mass spectrometry analyses and compared L- particles with infectious H-particles.

In addition, we are interested in the DC-specific viral replication cycle and compared immature DCs (iDCs) with mDCs, and observed a very interesting difference between these cells. Surprisingly, only iDCs generate infectious H-particles, while mDCs only facilitate the production of non-infectious L-particles. Mechanistically, we found that HSV-1 capsids are trapped within the nucleus in mDCs, thereby inhibiting the viral replication cycle. In sharp contrast, iDCs facilitate an autophagy-dependent degradation of the nuclear lamin layer and thus induce the completion of the viral replication cycle, leading to the generation of infectious viral particles. This represents a new and very interesting mDC-specific mechanism to inhibit viral replication.

Teaching

We teach students from the degree courses “molecular medicine” as well as “biology”, in the fields of molecular and cellular immunology. The teaching takes place in form of lectures, seminars as well as practical courses. In addition, we supervise Bachelor, Master and PhD students.

Selected publications

Birzer A, Krawczyk A, Draßner C, Kuhnt C, Mühl-Zürbes P, Heilingloh CS, Steinkasserer A, Popella L. HSV-1 Modulates IL-6 Receptor Expression on Human Dendritic Cells. Front Immunol. 2020 Aug 26;11:1970. doi: 10.3389/fimmu.2020.01970. PMID: 32983130; PMCID: PMC7479228.

Royzman D, Andreev D, Stich L, Rauh M, Bäuerle T, Ellmann S, Boon L, Kindermann M, Peckert K, Bozec A, Schett G, Steinkasserer A, Zinser E. Soluble CD83 Triggers Resolution of Arthritis and Sustained Inflammation Control in IDO Dependent Manner. Front Immunol. 2019 Apr 2;10:633.

Turan A, Grosche L, Krawczyk A, Mühl-Zürbes P, Drassner C, Düthorn A, Kummer M, Hasenberg M, Voortmann S, Jastrow H, Dörrie J, Schaft N, Kraner M, Döhner K, Sodeik B, Steinkasserer A, Heilingloh CS. Autophagic degradation of lamins facilitates the nuclear egress of herpes simplex virus type 1. J Cell Biol. 2019 Feb 4;218(2):508-523.

Wild AB, Krzyzak L, Peckert K, Stich L, Kuhnt C, Butterhof A, Seitz C, Mattner J, Grüner N, Gänsbauer M, Purtak M, Soulat D, Winkler TH, Nitschke L, Zinser E, Steinkasserer A. CD83 orchestrates immunity toward self and non-self in dendritic cells. JCI Insight. 2019 Oct 17;4(20):e126246.

Zinser E, Naumann R, Wild AB, Michalski J, Deinzer A, Stich L, Kuhnt C, Steinkasserer A, Knippertz I. Endogenous Expression of the Human CD83 Attenuates EAE Symptoms in Humanized Transgenic Mice and Increases the Activity of Regulatory T Cells. Front Immunol. 2019 Jun 25; 10:1442. doi: 10.3389/fimmu.2019.01442.

International cooperations

Prof.Dr. M. Berezovski, Department of Chemistry and Biomolecular Sciences: Canada

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

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

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

Prof. Dr. M. G. Manz, University of Zurich, Zurich: Switzerland