Dendritic cell research: Department of Dermatology and Venereology, Innsbruck, Austria

Immunobiology of dendritic cells

(please see also www.langerhanscell.com)

(Nikolaus Romani, PhD, Associate Professor; Christine Heufler-Tiefenthaler, PhD, Associate Professor; Patrizia Stoitzner, PhD, Privatdozentin and coworkers)

Dendritic cells are leukocytes that are highly specialized for the generation of T cell-dependent immune responses. They are crucially involved in the activation of T lymphocytes, the regulation of T helper cytokine patterns (Th1 - interferon-gamma producing helper T cells versus Th2 - interleukin-4 producing helper T cells), the activation and development of cytotoxic T lymphocytes, the production of antibodies (via T cell help), and the activation of macrophages (via interferon-gamma). Dendritic cells are the only cells of the body that are able to initiate primary immune responses. Thus, they are critically positioned at the onset of any primary immune reaction (primary infection, vaccination, autoimmune reactions). Langerhans cells have long been known to investigative dermatologists; they are the dendritic cells of the epidermis.

Dendritic cell research has a long-standing tradition at the Department of Dermatology. It has its roots in the pioneering work on Langerhans cells of Professors Klaus Wolff, Georg Stingl and Peter Fritsch. Dendritic cell research was extendend and deepened under Professor Gerold Schuler (1983-1995). There is an active and long-lasting relationship with the laboratory of Professor Ralph M. Steinman, discoverer of dendritic cells and Lasker Awardee 2007 ("American Nobel Prize"), at the Rockefeller University in New York (http://www.rockefeller.edu). Important data that helped to better understand the biology of dendritic cells have been corroborated in our labs as can be seen from an attached list of selected publications.
Three major dendritic cell-related research areas are presently covered:

Research with special emphasis on molecular aspects of dendritic cell function (Christine Heufler). Much of the molecular basis for the outstanding immunostimulatory functions of dendritic cells is still unknown. By means of modern methods in molecular biology (e.g., differential display, microarray gene technology) novel molecules that are relevant to the function of dendritic cells are being identified, isolated and characterized. Both human and murine dendritic cells are investigated. Several interesting molecules have already been found (Tiefenthaler et al., 1999; Boehm, Hofer et al, 2003, Hofer et al 2006); further molecules will follow.

At present (October 2010) the following researchers are part of the group: Dr.rer.nat. Valeska Heib (Post-Doc), Dr.med. Daniela Grabher (PhD student), Margit Auffinger (technician), Susanne Neyer (technician).

Research with special emphasis on cellular aspects of dendritic cell function (Nikolaus Romani and Patrizia Stoitzner). In the human system (i.e., with dendritic cells from human blood or skin) we are studying the antigen processing and presentation machinery with special regard to the state of maturation of dendritic cells. The MHC class I pathway ("cross-presentation") is being investigated, in particular. Another research focus is the analysis of the role of dendritic cells in the regulation of the "quality of T cell responses", i.e., during the differentiation of helper T cells into Th1 (i.e., interferon-gamma producing) or Th2 cells (interleukin-4 producing) or Th17 cells. In both research areas, dendritic cells of the skin (Langerhans cells) are specifically considered. A central theme in the murine system is the regulation of dendritic cell migration in the skin. This problem is being studied in skin explant culture models as well as in the classical in vivo model of contact hypersensitivity. Moreover, state-of-the-art mouse models (e.g., Langerhans cell ablation models) are employed. The immunogenic properties of Langerhans cells in the context of immunotherapy of cancer, in particular melanoma have developed into the main focus of the lab. The question will be pursued how Langerhans cells can best be harnessed for these purposes. More details can be found on our separate website: www.langerhanscell.com. Electronmicroscopy serves as a valuable supporting method in many aspects.

The working group of Prof. Matthias Schmuth, MD and Dr. Sandrine Dubrac is closely associated with the dendritic cell groups. While primarily dealing with the barrier function of the skin, this group also studies the role of skin dendritic cells in regulation the barrier and vice versa. The role of nuclear hormone receptors is studied in particular. (http://www2.i-med.ac.at/dermatologie/epiderm_d.html)

At present (October 2010) the following researchers are part of the group: Privatdozentin Patrizia Stoitzner, PhD, Dr.phil. Franz Koch, Vincent Flacher, PhD (Post-Doc), Christoph Tripp, PhD (Post-Doc), Mag.rer.nat. Florian Sparber (PhD Student).

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Research with special emphasis on the clinical application of dendritic cells for immunotherapy of malignant tumors (Nikolaus Romani and Susanne Ebner). Research efforts of the past years have led to the development of a method to generate large numbers of dendritic cells from monocytes of the blood (Romani et al., 1994; Romani et al., 1996). This method is now widely being used. The concomitant identification of tumor-specific molecules (tumor antigens) has for the first time rendered realistic the application of dendritic cells for immunotherapy of tumors. The rationale is to use dendritic cells as a powerful adjuvant to generate anti-tumor immune responses. In principle, dendritic cells from the blood of patients are grown in vitro, "loaded" with tumor antigens (peptides), and re-infused into the patients in
order to elicit a potent cytotoxic anti-tumor T cell response. This approach has proven
successful in several mouse models. Several clinical trials are currently on the way. In essence,
the concept of dendritic cell therapy could be validated in humans. We are collaborating with
Professor Gerold Schuler (Dermatology, University of Erlangen; http://www.derma.uni-
erlangen.de ). Further studies are being designed. Malignant melanoma is the main target for
these promising approaches. Many of these acitivities were performed within the framework of a
"Competence Center” and will be continued within the large Tyrolean research consortium
„Onctyrol - center for personalized cancer medicine“ (www.onctyrol.at). There, our
Dermatology group has joined forces with the group of Prof. Martin Thurnher (http://www.uro-
innsbruck.at/ImmunologischesLabor/index.htm) and thereby formed the Cell Therapy Unit.
At present (October 2010) the following researchers are part of the group: Van Anh Nguyen, MD, Univ.-Doz.,
Markus Forstner (technician), Daniela Reider (technician), Christina Fürhapter (technician), Nikolaus Romani,
PhD and as clinical partners Georg Weinlich, MD and Klaus Eisendle, MD,PhD.

Selected dendritic cell-relevant publications (as of October 2010)

Nguyen VA, Dubrac S, Huter O, Del Frari B, Romani N, Ebner S. CD34+ derived Langerhans cell-like cells are

Romani N, Flacher V, Tripp CH, Sparber F, Ebner S, Stoitzner P. Targeting skin dendritic cells to improve
intradermal vaccination. Current Topics in Microbiology & Immunology, in press, 2010

Sparber F, Tripp CH, Hermann M, Romani N, Stoitzen P. Langerhans cells and dermal dendritic cells capture
protein antigens in the skin: possible targets for vaccination through skin. Immunobiology, 215:770-779, 2010

Stoitzner P, Sparber F, Tripp CH. Langerhans cells as targets for immunotherapy against skin cancer. Immunol
Cell Biol, 88:431-437, 2010 (Review Article)

Dubrac S, Schmuth M, Ebner S. Atopic Dermatitis: The role of Langerhans cells in disease pathogenesis. Immunol
Cell Biol, 88:400-409, 2010 (Review Article)

Romani N, Thurnher M, Idoyaga J, Steinman RM, Flacher V. Targeting of antigens to skin dendritic cells:

Romani N, Clausen BE, Stoitzner P. Langerhans Cells & More: Langerin-expressing dendritic cell subsets in the

Invest Dermatol, 130: 331-335, 2010 (Meeting Report)

Tripp CH, Ebner S, Ratzinger G, Romani N, Stoitzner P. Conditioning of the injection site with CpG enhances the
migration of adoptively transferred dendritic cells and endogenous CD8+ T cell responses. J Immunother, 33:115-
125, 2010


Tripp CH, Sparber F, Hermans IF, Romani N, Stoitzner P. Glycolipids injected into the skin are presented to NKT

Langerhans cells are critical in the development of atopic dermatitis-like inflammation and symptoms in mice. J
Cell Mol Med, 13:2658-2672
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