SpringerWienNewYork

Michael Hertl (ed.)

Autoimmune Diseases of the Skin

Pathogenesis, Diagnosis, Management

Second, revised
and enlarged edition

SpringerWienNewYork

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This book was supported by *Gesellschaft für Autoimmun-Krankheiten e.V.*,
Schönkirchen bei Kiel

Cover illustration: M. Hertl
Typesetting: Composition & Design Services, Minsk 220027, Belarus
Printing: Druckerei Theiss GmbH, A-9431 St. Stefan im Lavanttal
Printed on acid-free and chlorine-free bleached paper
SPIN: 10975923

With 77 partly coloured Figures

Library of Congress Control Number: 2005920465

ISBN 3-211-20686-8 SpringerWienNewYork
ISBN 3-211-83598-9 1st edition SpringerWienNewYork

Foreword

Based on recent advances in the understanding of the immunological pathogenesis of many chronic inflammatory disorders there is increasing evidence that several of them are characterized and potentially mediated by autoimmune phenomena. Classical examples are rheumatoid arthritis, myasthenia gravis, pemphigus vulgaris, lupus erythematosus and multiple sclerosis. Others, such as psoriasis vulgaris, some less well-characterized collagen vascular disorders, vasculitides and a subtype of chronic urticaria have a more or less pronounced autoimmune background that has to be considered in the overall management of these disorders. A significant portion of autoimmune diseases precipitate primarily or secondarily at the skin. Understanding the cutaneous symptoms may be therefore crucial for the diagnosis, classification and therapeutic management of organ-specific and systemic disorders that require special attention by the physician.

This book is set out to present the most recent scientific and clinically relevant state-of-the-art-knowledge on the broad spectrum of autoimmune disorders affecting the skin. It is meant to provide the most recent information on these disorders for clinicians as well as practicioners in dermatology, medicine, rheumatology, ENT, pediatrics, ophthalmology, orthopedics etc and for basic scientists interested in human autoimmunity. Each book chapter dealing with a distinct cutaneous autoimmmune disorder consists of an introduction focusing on the state of knowledge regarding pathogenesis and epidemiology followed by a practical guide how to identify and handle the particular disorder(s). Special attention is paid to genuine cutaneous autoimmune disorders such as autoimmune bullous skin disorders including pemphigus, pemphigoid and epidermolysis bullosa acquisita. These disorders can be considered as paradigms of organ-specific autoimmune disorders because autoantigens and autoantibody-mediated pathogenesis are well-characterized.

Major progress has been made in the diagnosis and classification of collagen vascular disorders such as systemic sclerosis, lupus erythematosus, dermatomyositis and overlap syndromes. These advances have provided the basis for more specific therapeutic interventions. Recent pathogenetic findings in psoriasis, lichen planus and chronic urticaria have led to novel therapeutic concepts that will replace the “classical” symptomatic treatments that have been established for decades. One striking example is the therapeutic effect of biologics in severe psoriasis vulgaris and psoriatic arthritis and the

modulatory effect of high dose immunoglobulins in dermatomyositis and severe vasculitides. In addition to the book chapters on distinct clinical cutaneous disorders, the introductory chapter explains basic immunological principles leading to autoimmunity and the final chapter gives an overview of the mode of action of novel immunomodulatory drugs. The present book which is edited by my co-worker Dr. Michael Hertl is set out to combine major scientific advances in the understanding of autoimmunity with the clinical presentation and management of these disorders. I am convinced that the book constitutes a very successful effort to provide a handbook for those who are scientifically or clinically interested in autoimmune disorders of the skin. I wish the editor and the authors success with this endeavor.

Erlangen, July 2001 *Gerold Schuler*

Preface to the First Edition

Hundred years ago, Paul Ehrlich speculated whether an individual is able to produce toxic autoantibodies and about the implications of such antibodies for disease. The contention that an alteration of the body fluids causes disease followed the traditional teachings of Hipppocrates and Galen that disease results from dysfunction of the four humors. However, Ehrlich introduced the novel concept of antigen specificity that was based on his side chain theory of antibody formation: (1) antibodies are naturally occuring substances that serve as receptors on the cell surface; (2) the specificity of antibody for antigen is determined by a unique stereochemical configuration of atoms that permits the antibody to bind tightly and chemically to its appropriate antigen; (3) the number of different combining sites structures available is so great that each one differs from the others, with little or no cross reactivity among them; (4) and in order to induce active antibody formation, it is only necessary that appropriate receptors be present on the cells for antigen to interact with them and so stimulate their overproduction and liberation into the blood. According to this description by Paul Ehrlich, the antibody ap-peared to be a polymorphous cytoplasmic agent with a unique feature – a highly organized combining site (the haptophore group) that determined its unique antigen specificity.

It was Bordet who showed that anti-erythrocyte antibodies were capable of mediating immune hemolysis giving rise to the idea that self-produced hemolytic antibodies might assist in destroying autologous erythrocytes.

This and similar findings including the description of cytotoxic antibodies against a variety of other cell types prompted Ehrlich to say: "… the organism possesses certain contrivances by means of which the immunity reaction, so easily produced by all kinds of cells, is prevented from acting against the organism's own elements and so giving rise to autotoxins … so that we might be justified in speaking of a 'horror autotoxicus' of the organism. These contrivances are naturally of the highest importance for the individual" (P. Ehrlich and J. Morgenroth, Berlin. Klin. Wochenschr., 1901).

When Metalnikov was the first to demonstrate the generation of autoantibodies that were cytotoxic against spermatozoa *in vitro*, Ehrlich questioned that they were able to induce pathology *in vivo*.

It took, however, more than fourty years that some distinct organ-specific immune disorders were categorized as true autoimmune diseases. Among the first identified were autoimmune orchitis, allergic encephalomyelitis, autoimmune

thyroiditis, pemphigus vulgaris and bullous pemphigoid. Noteworthy, some of these disorders are exclusively mediated by circulating autoantibodies such as the hemolytic anemias, thrombocytopenia, pemphigus, and pemphigoid while others, such as allergic autoimmune encephalomyelitis and autoimmune thyroiditis require the transfer of immunocompetent cells in addition to autoantibodies.

The existence of immunological tolerance was the logical consequence of Paul Ehrlich's postulate that there was a "horror autotoxicus" a mechanism that inhibited formation of potentially harmful autoantibodies to self *in vivo*. It was Owen to show that dizygotic calves whose circulation was connected *in utero* were unable to respond to each other's antigens after birth. Out of this and similar observations, the clonal deletion theory was invented by Burnet meaning that antigen present during embryonic life would somehow cause destruction of self-reactive clones. The observation that adult animals could be rendered unresponsive to foreign antigens by the administration of large doses of the antigen led to the notion that immunological tolerance could be also acquired.

The recognition of different central and peripheral immune mechanisms leading to immunological tolerance are all based on Ehrlich's concept of "horror autotoxicus", *i.e.* acquired or active immune regulation of unwanted immune responses against self. The finding that B lymphocytes generally require the help of T lymphocytes in their antibody response to a defined antigenic stimulus led to the discovery of distinct immune cell subsets including helper cells, cytotoxic cells and regulatory cells. The identification of the idiotype-anti idiotype network was born out of the discovery that the antigen binding site of the antibody itsself can act as an antigen for anti-idiotypic antibodies. Anti-idiotypic immune responses are part of the physiological immune surveillance aimed at limiting the extent of an immune response.

The identification of different lineages of antigen presenting cells has taken away much attention from T lymphocytes as the exclusive regulators of immune and autoimmune responses. Major interest has recently focused on dendritic cells, bone marrow-derived antigen presenting cells with potent capacity to induce primary T-cell-mediated immune responses. However, accumulating evidence has demonstrated that the dendritic cell system bears much more plasticity than originally thought. Dendritic cells can arise from several different types of progenitor cells and different functional types of dendritic cells can be generated from the same precursor. It thus appears that dendritic cells have the potential to modulate immune responses within the wide spectrum of immunity on the one hand and immunological tolerance on the other hand.

The rapid development of immunological research has also provided major insights in the pathogenesis of autoimmune disorders which has implications for classification, diagnosis and therapy of these disorders. Classical examples for well-characterized autoimmune disorders are myasthenia gravis, pemphigus vulgaris, and hemolytic anemia. Furthermore, the availability of recombinant forms of the major autoantigens of these disorders has

provided critical tools to investigate autoimmunity versus immunological tolerance to these self proteins in affected patients and healthy individuals.

The increasing understanding of the mechanisms that lead to immunological tolerance to self and the role that HLA and non-HLA alleles play in antigen recognition by autoaggressive T cells may also lead to novel therapeutic strategies. Several clinical studies have sought to restore immunological tolerance to self by the administration of modified self peptides, such as the administration of altered peptide ligands of myelin proteins in multiple sclerosis. Immature dendritic cells hold great promise as highly efficient tools to induce immunological tolerance to defined self proteins or peptides as demonstrated in murine allograft rejection models. They may induce tolerance by inducing antigen-specific anergy of autoreactive T cells and/ or by the induction of regulatory T lymphocytes that inhibit the activation of autoaggressive T cells.

I am very grateful that internationally leading experts in the field of cutaneous autoimmune disorders spontaneously agreed to provide comprehensive and well-illustrated overviews of the major autoimmune disorders of the skin. It was truly fun to interact with all of them! In addition, I would like to acknowledge the support and efforts of Springer Verlag in making this kind of book possible. We hope that the concept of this book will indeed help to broaden the understanding of cutaneous autoimmune disorders for those working in the many clinical disciplines which are involved in the care of these patients. Finally, I thank my wife for her continous support and her help and criticism during the development of this book.

Erlangen, July 2001 *Michael Hertl*

Preface to the Second Edition

Thanks to the positive reception of the first edition of the book by the medical community both in Europe and in the USA, the present book has come to its second edition. All the chapters have been thoroughly revised and two new chapters on Vitiligo and Alopecia areata were included.

We hope that the present book will continue to provide state-of-the-art knowledge for those who are interested and clinically involved with autoimmune disorders of the skin.

The present edition of the book is dedicated to my clinical teacher, Professor Gerd-Klaus Steigleder, on the occasion of his 80th birthday.

Marburg, January 2005 *Michael Hertl*

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1 Pathogenesis of Autoimmune Disease

Martin Röcken and Tilo Biedermann

Autoimmunity and Autoimmune Disease

The term autoimmunity signifies the presence of specific memory-type immune reactions that are directed against one or more self-epitopes. Under most conditions, autoimmunity is determined in terms of immunoglobulins that react with either unknown or well-defined human antigens. Today it is supposed that the production of these autoantibodies requires prior activation of potentially autoreactive B cells by memory T cells. These T cells must not only recognize a closely related peptide structure. Importantly, these T cells can stimulate B cells only when primed by activated antigen presenting cells.

Autoimmunity is a relatively frequent event. Most likely, any individual raises immune reactions against numerous self antigens. This autoimmunity leads only very rarely to overt autoimmune disease. Therefore, the development of autoimmune disease requires trespassing of a large number of additional security levels, beyond autoimmune reactivity (Schwartz 1998). This is illustrated by two frequent clinical phenomena: One of the best examples are antinuclear antibodies (ANA), which are found in even more than 50% of the female population older than 50 years. Compared to this frequency, ANA-associated autoimmune diseases are relatively rare and affect less than 2% (Rubin 1997). The other is that only very few autoimmune diseases progress continuously. Most of them progress during short waves of disease activity and in between these waves have long periods of quiescence. Since autoreactive T and B cells do normally not disappear during these periods of quiescence, a series of control mechanisms protect from manifest autoimmune disease.

T and B Cells

T cells are small lymphocytes that are characterized by their antigen recognition structure, the T cell receptor (TCR). According to the current state of

knowledge, the TCR is only functional as a cell bound structure. Due to the low affinity for free peptide (Weber et al. 1992), the TCR recognizes only antigens that are presented by major histocompatibility complex (MHC) molecules. The TCR acts in concert with an array of additional surface structures. The most important are the co-receptors, the CD4 and CD8 molecules. The CD8 molecule determines the interaction of the TCR with MHC class I and the CD4 molecule with MHC class II. Appropriate activation of T cells requires a series of additional events, such as adhesion molecules and costimulatory molecules (reviewed in Biedermann et al. 2003).

B cells are characterized by the production of antigen recognition structures, the B cell receptor and immunoglobulins. They produce immunoglobulins mainly when stimulated appropriately through T-B-cell interactions (Lanzavecchia 1985). However, besides antigen specific signals, induction of immunoglobulin production by B cells requires CD40-CD40L interactions and cytokines (Banchereau et al. 1994). In contrast to the TCR, immunoglobulins may have a very high affinity for their specific antigen. They recognize free antigen and their major function seems to be the binding to either cell-bound or free antigens.

T cells develop in the thymus and B cells in the bone marrow. Importantly, the structure of the TCR is definitely determined in the thymus. Thus, the thymus constitutes an important site of education which ultimately determines the specificity of the ensuing T cells (Kisielow and von Boehmer 1995). In contrast, the structure of the immunoglobulin recognition site is not terminally fixed when B cells leave the bone marrow and mature B cells undergo somatic mutation and the affinity of the antigen recognition site of secreted immunoglobulins can mature during the course of immune responses.

Thymic Maturation and Selection of T Cells

Precursor T cells develop within the bone marrow and reach the thymus through the blood. These immature precursor cells undergo a series of activation and maturation events that ultimately result in a precursor population that expresses a TCR and both, CD4 and CD8 molecules. The TCR expresses two independent immunoglobulin-like chains, the α- and the β-chain. The β-chain is expressed together with a pre-α-chain; the definite TCR α-chain replaces the pre-α-chain prior to the development of the CD4+CD8+, double positive status. Normally, T cells express only one pair of TCR α/β-chains. This subsequent replacement of the pre-α-chain by a definite TCR-α-chain however, may lead to the occurrence of T cells which express two receptors, one single β-chain assorted with two different and independent α-chains. Thus, one T cell may have two, entirely independent specificities (Kretz-Rommel and Rubin 2000; Stockinger 1999).

Once the double positive status is achieved, T cells interact with thymic MHC molecules. This interaction of the double positive cells, which are highly sensitive to death signals, will decide their further outcome as most of the double positive cells die during this selection process. T cells with relatively high affinity for peptide loaded and possible also empty MHC molecules die through induction of apoptosis. T cells that express a TCR with an affinity that is too low for recognizing peptide loaded MHC molecules die from neglect. Only a small proportion of T cells, smaller than 10%, survives this selection and leaves the thymus as a single positive T cell, expressing either CD4 or CD8 and a TCR (Bouneaud et al. 2000; Kisielow et al. 1988; Rocha and von Boehmer, 1991). During thymic selection, TCR structures with high affinity for self may not only lead to deletion; another mode is temporary suppression of the TCR. If a T cell with two distinct TCR α-chains then receives at the same time a survival signal by the second receptor, this cell may become positively selected and result in a peripheral T cell population with two distinct TCR; one corresponding to an autoreative receptor (*Fig. 1*).

Tolerance of Self-Reactive T and B Cells

Central Tolerance and Peripheral Tolerance

The thymus and the apoptosis and paralysis occurring during the development of B cells recognizing abundant antigens in the periphery delete about 90% of self-reactive T and B cells. This phenomenon is termed as central tolerance. However, roughly 10% of these cells survive (Blackman et al. 1990; Kisielow et al. 1988). Moreover, not all antigens are presented in thymus, bone marrow or peripheral blood. In one individual, all cells express the same MHC class I and a large spectrum of common minor antigens. However, each cell also expresses its own set of antigens that is related to its function and localization. Thus, the mature immune system encounters a larger spectrum of antigens in the periphery than in the thymus. Tolerance against these antigens requires a multitude of mechanisms which are summarized under the term *peripheral tolerance*. While *central tolerance* is mainly based on deletion of potentially autoreactive T cells, a larger spectrum of mechanisms constitutes *peripheral tolerance* (Arnold et al. 1993; Rocken and Shevach 1996).

Mechanisms of Peripheral Tolerance

One mechanism of peripheral tolerance may be deletion, too. Deletion is mainly associated with the sudden appearance of a large number of antigens. This mechanism has been demonstrated for antigens that were presented in large numbers, thus during infection or following injection of superantigens

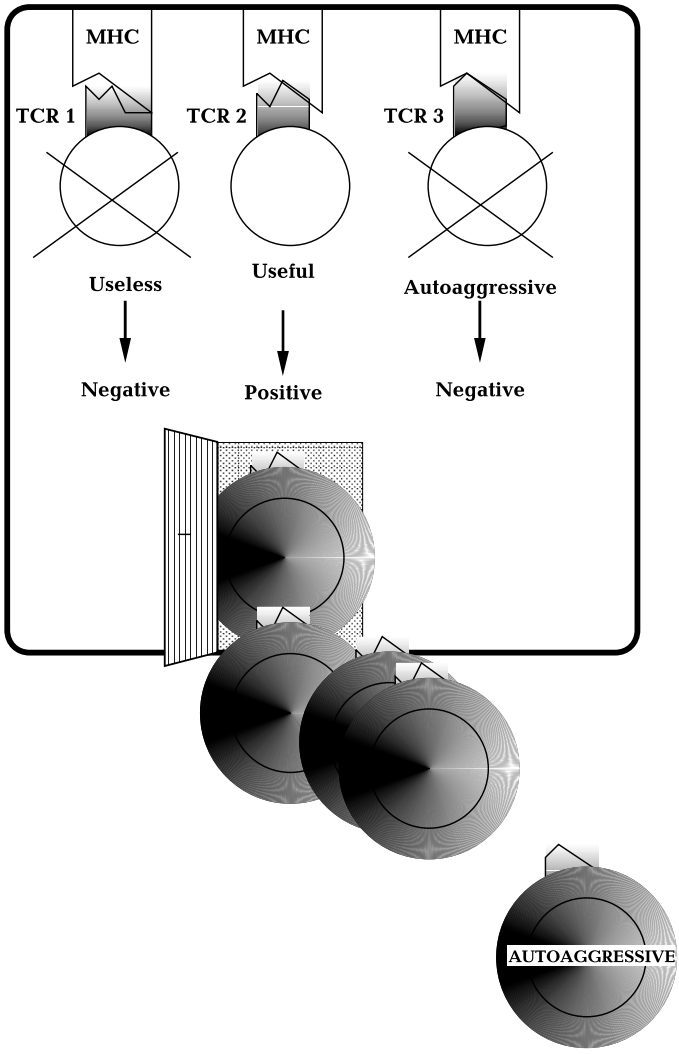

Fig. 1. Modes of intrathymic selection of T cells. T cells with a very high affinity T cell receptor (TCR) for self major histocompatibility complexes (MHC) die from active deletion, those with an intermediate affinity are positively selected and those with low affinity will die from neglect

(Moskophidis et al. 1993; Webb et al. 1990). Whether this mechanism applies also under physiological conditions is not clear. But it may become relevant during tissue destruction, when large quantities of self-antigens are presented, thus in the case of skin burning, viral infections of skin, muscle or other organs or following a stroke. However, this phenomenon has not yet been analyzed in more detail.

Another mechanism is suppression of TCR expression. This has been shown with pregnant mice expressing a transgenic TCR that recognizes the foreign MHC class I molecule expressed by the father and the fetus. The level of this transgenic TCR is high before and after pregnancy, but low during pregnancy. These T cells are also functionally silenced. During pregnancy, female mice become even tolerant to otherwise highly immunogenic tumor cells expressing this same antigen (Alferink et al. 1998). Thus, suppression of a TCR expression is closely associated with the occurrence of peripheral tolerance and may contribute to it. These data, even though very elegant, do not exclude that other mechanisms significantly contribute to peripheral tolerance (Alferink et al. 1998; Schonrich et al. 1991).

One important example demonstrating the requirement for additional mechanisms was given by mice that simultaneously express a peptide antigen of the lymphocytic choriomeningitis virus (LCMV) by the endocrine pancreas and T cells with a TCR transgenic for the LCMV peptide (Ohashi et al. 1991; Oldstone et al. 1991). These animals have autoreactive CD8+ T cells that are functionally normal, express normal levels of the TCR and kill peptide loaded targets in vitro to the same extend as transgenic T cells from control animals. Nevertheless, these animals do not develop overt autoimmune disease, showing that, besides the target organ, the expression of an endogenous potentially immunogenic peptide and normal levels of TCR, other signals are required for the induction of autoimmune disease. Such a situation may be the consequence of 'ignorance' of the target structure by the autoreactive T cells (Ohashi et al. 1991). Ignorance may be the consequence of missing adhesion molecules or the absence of co-stimulatory signals (von Herrath et al. 1995). However, it may also be due to expression of autoantigens at immunologically privileged sites, the expression of apoptosis inducing molecules capable of killing activated T cells or secondary to local silencing of activated T cells that recognize target tissues in the absence of co-stimulatory molecules.

Reactivity and mode of action are not only given by the TCR and the spectrum of co-stimulatory T cells expressed by T cells. Most importantly, T cell functions are determined by the cytokines they produce. Naive T cells produce only interleukin (IL-) 2 when stimulated by peptides and professional antigen presenting cells (APC; (Weinberg et al. 1990). Subsequently, T cells develop towards memory cells that are theoretically capable of producing a large spectrum of cytokines. Today it is established that T cells normally do not secrete a random pattern of cytokines, but differentiate into phenotypes that produce distinct sets of cytokines associated with well defined functional phenotypes (Mosmann and Sad 1996; Rocken et al. 1992; Rocken et al. 1996).

T cells that produce predominantly IL-2 and interferon-γ (IFNγ) are associated with inflammatory, cell mediated immune responses. When expressing the CD4 molecule they are named Th1, when expressing the CD8 molecule, they are named Tc1 cells and induce 'type 1' immune responses (Arnold et al. 1993; Racke et al. 1994; Katz et al. 1995; Kolb et al. 1995; Powrie 1995; Rocken et al. 1996; Adorini and Sinigaglia 1997). These types of immune responses are

required for the control of infections with viruses, funghi or parasites. However, when directed against autoantigens, they may cause inflammatory autoimmune diseases. These inflammatory autoimmune diseases are normally well localized to one single organ or a group of organs that share a common antigen. These T cells do not only induce direct tissue destruction, they also induce B cells to produce complement binding antibodies, which may enhance local inflammation and tissue destruction, as it is the case in patients with bullous pemphigoid (Budinger et al. 1998).

The most important counterpart of 'type 1' immune responses are 'type 2' responses. They are induced by CD4+ T cells capable of producing IL-4 and IL-13. These two cytokines seem to suppress multiple pro-inflammatory effector functions by macrophages, such as production of tumor necrosis factor (TNF). Th2 cells are primarily known by their capacity to switch the immunoglobulin isotype of human B cells towards IgE and probably also IgG4 (Mosmann and Coffman 1989). Thus, Th2 cells do not generally extinct immune responses. They may even induce autoimmune responses and probably also autoimmune disease, such as pemphigus vulgaris, which is associated with autoantibodies of the IgG4 isotype and little local inflammation (Goldman et al. 1991; Hertl et al. 1998). However, when directed against epitopes that are associated with type 1-mediated inflammatory autoimmune disease, type 2 immune responses may exert anti-inflammatory, protective effects. Treating Th1 mediated diseases with Th2 cells or the cytokine IL-4 that most potently induces Th2 and suppresses Th1 has been demonstrated in animal models of organ specific autoimmune disease and skin inflammation. Most importantly, however, this therapeutic strategy was also effective in humans suffering from psoriasis, a Th1 mediated autoimmune disease of the skin (Ghoreschi et al. 2003).

A third, probably increasingly important population are IL-10 producing regulatory or Tr cells. In contrast to all other phenotypes, these Tr cells seem to have the exquisite capacity of turning immune responses off. This regulatory effect may be of great importance in the treatment of autoimmune diseases, since Tr are obviously capable of silencing both, type 1 and type 2 immune responses (Groux et al. 1997; Akdis et al. 2000). Referring to the historical attribution given to $CD8^+$ T cells, suppressor T cells experience a time of renaissance. These $CD4^+$ T cells are capable to suppress autoaggressive immune reactions and were found to express CD25, GITR, CTLA-4, and most importantly a specific transcription factor, forkhead box p3 (Foxp3) (Bluestone and Tang 2004). Foxp3 is not only a marker for these Tr, it is of functional importance for the suppressive mode of action of Tr (Walker et al. 2003; Fontenot et al. 2003). As a consequence, patients deficient in the Foxp3 transcription factor develop a multiorgan autoimmune disease (Kriegel et al. 2004). Tr cells are very difficult to induce and grow to expand in vitro and probably also in vivo, but finding Foxp3 and increasingly elucidating the underlaying mechanisms of Tr development will help to answer the questions in regard to the significance these cells may play in the therapy of autoimmune disease.

Activation and Differentiation of T Cells

All organs are drained by dendritic APC (DC). These DC are normally considered as potent stimulators of T cells that prime primarily for interferon-γ (IFNγ) producing CD4+ and CD8+ T cells (Schuler and Steinman 1997; Schuler et al. 1997; Banchereau and Steinman 1998). DC acquire this capacity following antigen uptake while they migrate to the draining lymph nodes. This capacity in activating and stimulating T cells to become efficient effector cells, capable of mediating inflammatory immune responses and of inducing immunoglobulin production by B cells, requires a certain activation status by these APC. Thus APC co-express adhesion molecules that permit adherence of naive and activated T cells. They express a panel of co-stimulatory molecules that are required for the activation of specifically binding T cells and, in addition, they produce cytokines. Both, the sum of cell bound signals and of APC derived cytokines results not only in the stimulation and maturation of the specific T cells but also determines their differentiation. Thus, the maturation process that APC and DC undergo during their migration from the periphery to the draining lymph node will ultimately determine, whether the primary activation of T cells may lead to type 1, type 2 or Tr T cells. Depending on the functional T cell phenotype they induce, APC and DC are operationally termed DC1, DC2 or DCr (Kalinski et al. 1999; Moser and Murphy 2000) (*Fig. 2*).

When residing in peripheral organs, DC are continuously processing numerous antigens delivered by the local milieu. At this stage, DC have little migratory and antigen presenting capacity. Recent data suggest that the few immature and quiescent DC that migrate from peripheral organs to the draining lymph node are not capable of activating T cells to become autoaggressive. They seem either to contribute to the phenomenon of 'ignorance' or to promote the differentiation of naive but potentially autoreactive T cells towards an immunosuppressive Tr phenotype (Jonuleit et al. 2000). In sharp contrast, DC start to mature and to leave their residing site after an appropriate stimulus. Among those innate signals highly conserved so called 'pathogen associated molecular pattern' (PAMP) derived from infectious agents, such as bacterial DNA, bind to Toll-like receptors (TLR) and are increasingly recognized as most relevant activators of DC. These innate signals transform APC not only from an antigen processing towards an antigen presenting cell, capable of attracting naive and memory T cells into lymph nodes. These innate signals also determine the differentiation of APC towards either a DC1, DC2 or DCr phenotype and, in consequence, their capacity to direct the functional phenotype of the future immune response, directed against either self or foreign antigens (Banchereau and Steinman 1998; Kalinski et al. 1999; Moser and Murphy 2000). This concept was expanded by disclosing regulatory mechanisms underlaying DC induced immune responses. Thus, PAMPs present during the initial activation of DC generally instruct DC to produce

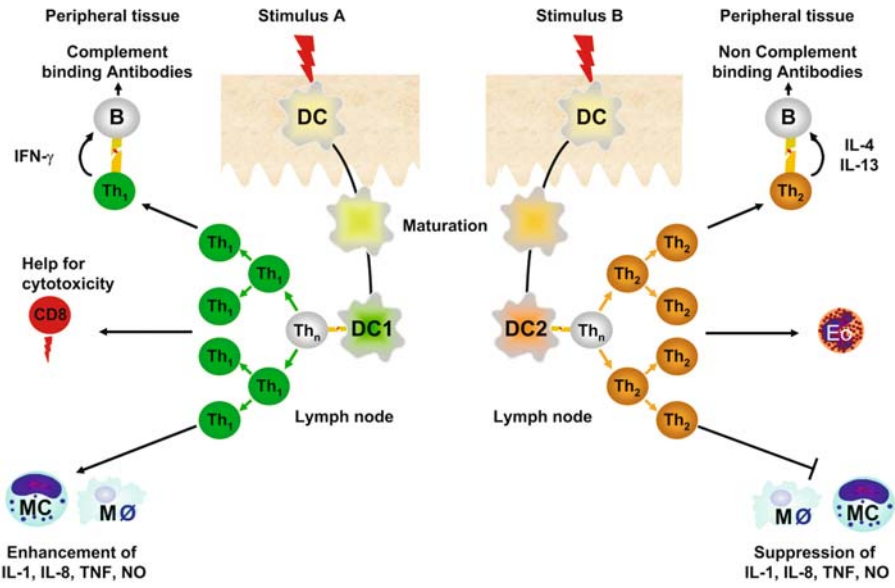

Fig. 2. Differentiation of T helper (Th) cells into either IFNγ producing Th1 or IL-4 producing Th2 cells. The differentiation of Th into either Th1 or Th2 phenotypes is driven by the functional phenotype of the stimulating dendritic cells (DC), draining the site of inflammation. The 'innate' stimuli initiating both, activation and migration of the DC, also influences the differentiation of these migrating DC into either a DC1 or DC2 phenotype

IL-12 and PAMPs tend to promote Th1 development leading to a proper anti-infectious immunity (*Fig. 2, 3*). However, some PAMPs and other signals lead to an inappropriate Th2 immunity in response to microbes (*Fig. 2*). Interestingly, these Th2 reactions can be switched to effective Th1 reactions, a mechanism that may also regulate autoimmunity. Paradoxically, IL-4 is a potent factor driving this switch, because IL-4 instructs activated DC to produce IL-12 and promotes Th1 cell development (Biedermann et al. 2001). These paradox functional consequences achieved by IL-4 were investigated by the sequential analysis of immune responses. Immune responses in general develop via the consecutive activation of DC and then T cells. Thus, the contrasting effects of IL-4 on immune responses with opposing functional phenotypes are a result from IL-4 signaling in early DC activation leading to a Th1 phenotype and from IL-4 induced T cell differentiation inducing Th2 cells during a later stage.

In addition to TLR signaling, there are also PAMP and TLR independent pathways that drive T cell immunity through DC modulation. Thus, apoptotic cell material and activated NK cells can also prime DC to produce IL-12 and to induce CD8 T cell memory responses, a mechanism that may be also underlaying an activation of autoreactive lymphocytes (Mocikat et al. 2003) (*Fig. 3*).

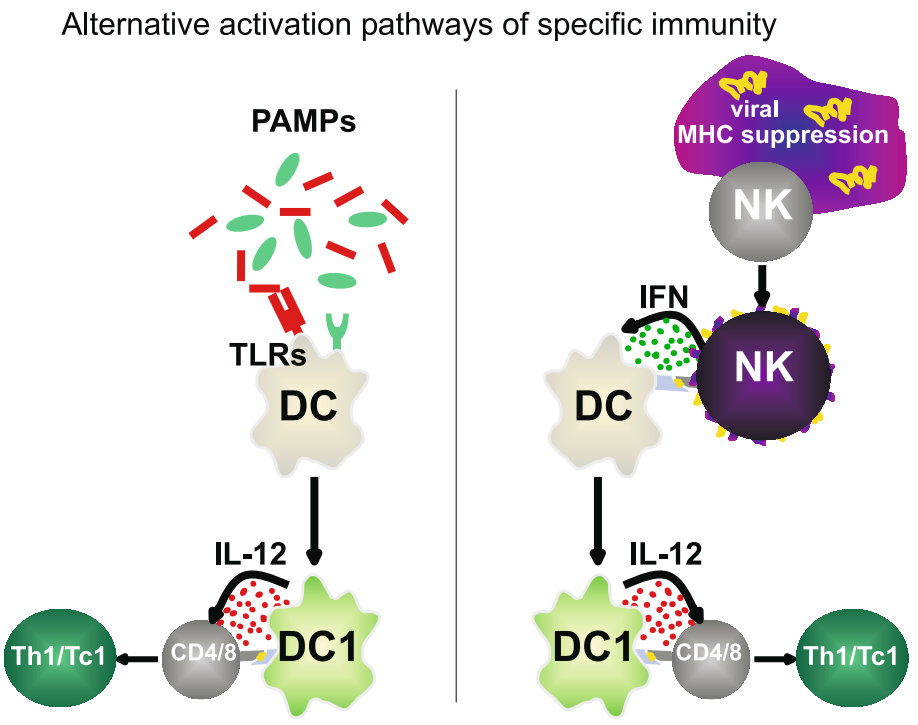

Fig. 3. PAMPs tend to induce IL-12 producing DC1 that control the development of IFNγ producing Th1 or Tc1 cells. These type 1 immune responses are effective against microbes but may also be involved in tissue destruction during autoimmune diseases. Alternatively, DC1 may also be generated under the influence of activated natural killer (NK) cells and lead to Th1 or Tc1 cells

Activation of Self-Reactive T and B Cells

Autoimmune diseases require the presence of autoreactive T cells and, in the case of immunoglobulin mediated diseases, of autoreactive B cells. In view of the potent and large number of regulatory mechanisms that protect against autoimmune disease, activation of autoreactive T and B cells is thought to require a series of destabilizing events. One important aspect is the activation and reactivation of potentially autoreactive T cells (Rocken et al. 1992). However, induction of autoreative T cells or B cells alone does not induce or predispose for autoimmune diseases. For example, in individuals, which are genetically predisposed of developing autoimmune diabetes, the relative risk of becoming diabetes increases significantly if their T cells respond vigorously against endogenous antigens from pancreatic islet cells. In sharp contrast, individuals from the same population are largely protected against autoimmune diabetes, when they exert high immunoglobulin titers but weak T cell responses

against the same antigens (Harrison et al. 1993). This further underlines that 'reactivity' does not equal autoimmune disease.

One of the fundamental questions that are still unanswered yields with the primary event leading to the induction of autoreactivity. Some data suggest that, in the presence of an appropriate genetic background, minimal events such as normal tissue necrosis may be sufficient for the induction of, perhaps even potentially harmful, autoreactivity (Albert et al. 1998; Matzinger and Anderson 2001).

Most data suggest that a series of tolerance inducing mechanisms normally inhibits T and B cells to react against many autoantigens (Naucler et al. 1996). Therefore, stimuli that induce reactivity against these autoantigens have to overcome the diverse tolerance inducing barriers. Epidemiologic data suggest that the realization of autoimmune diseases is often preceded by infectious diseases and attention was given to the events by which infections may abolish the status of tolerance (Sinha et al. 1990; Matzinger 1994). At least three mechanisms are thought to contribute to this phenomenon: reactivation of tolerant T and B cells, induction of autoreactive T cells by molecular mimicry and modification of the cytokine pattern during the course of infectious diseases.

Breaking T and B Cell Tolerance

Experiments with transgenic or non- transgenic mice have shown that, in principle, tolerant T and B cells can be reactivated by infectious agents. Infections are capable of restoring in silenced T cells the capacity to produce cytokines (Rocken et al. 1992; Racke et al. 1994). This phenomenon was extended to the situation of transplantation induced tolerance (Ehl et al. 1998). Similarly, reactivity and immunoglobulin production by B cells that were silenced either by exogenous or transgenic endogenous antigens can be restored with mitogens, including bacteria derived lipopolisacchrides (Louis et al. 1973; Goodnow et al. 1991). Even though these experiments have shown that infectious agents can abolish solid T and B cell tolerance there are little data showing that this reactivation of tolerant T and B cells can also lead to autoimmune disease. One first example suggesting such a situation is given by double transgenic mice that bear a TCR recognizing a transgenic self-antigen expressed by hepatocytes. Injection of bacterial DNA motifs that activate DC and promote DC1-development by these activated DC did also induce transient liver damage, as evidenced by an increase of transaminases. However, this phenomenon was short lived and no data are available proving that autoimmune disease can be the direct consequence of polyclonal T cell activation (Limmer et al. 1998). In small animal models, induction of autoimmune disease by bacterial DNA motifs or more complex bacterial lysates such as complete Freund's adjuvans required, in addition, always immunization

with an antigen that mimics peptide motifs of the targeted self antigen (Bachmaier et al. 1999). Thus, in normal mice bacterial DNA motifs triggered the myocarditis only when co-administered with an altered self-peptide, derived from chlamydia.

These data suggest that immunization against antigens that are structurally related to self-antigens are essential for the induction of autoimmunity. This concept is further supported by functional and structural analysis of T cell epitopes of infectious agents and potential self-antigens. Chlamydia peptides can share functional similarities with peptides expressed by mammalian heart muscle, while other infectious agents share important peptide sequences with potential self-antigens such as myelin basic protein. This aspect is especially significant since molecular mimicry does not require molecular identity. Studies with altered peptide ligands have shown that induction of cytokine production or T cell proliferation requires only poor structural relation as long as important anchor positions are conserved (Gautam et al. 1994; Wucherpfennig and Strominger 1995). Various examples suggest that this may be of relevance for autoimmune diseases of the skin. Thus, the first eruption of the juvenile type of psoriasis is preceded by streptococcal infections in most patients (Prinz 1999) and lichen planus is associated in a large number of patients with an acute or chronic liver disease (Chuang et al. 1999). In some patients lichen planus may even be provoked by active or even passive vaccination against hepatitis (Tessari et al. 1996; Degitz and Röcken 1997).

Despite the experimental prove for both, re-activation of tolerant T cells and for molecular mimicry, the exact role of infections in the pathogenesis of autoimmune diseases remains open. One important alternative would be the direct infection and molecular alteration through infectious disease. One important example is chronic active hepatitis, where relatively weak immune responses follow the slowly progressing wave of infected hepatocytes and thus slowly destroy the liver. In this situation, activation of the T cell mediated immune responses, associated with a short aggravation of the hepatitis may lead to reduction and control of the viral load and cure from chronic progressive hepatitis (Berg et al. 1997; Gerlach et al. 1999; Moradpour and Blum 1999). In the skin a very similar phenomenon is visible during fungal infections. The border, the clinically manifest eczema, reflects the immune reaction against a large burden of fungi. Inside the inflammatory margin, the eczema and the fungal load are significantly milder. In the case of fast growing fungi, the eczema may present as a policyclic disease (*Fig. 4*).

A third level where infections could directly interfere with autoreactive T cells is the pattern of cytokines that T cells produce. Thus, infection with the nematode nippostrongylus brasiliensis can not only restore reactivity in silenced $CD4^+$ T cells but also induce IL-4 production by these silenced T cells (Rocken et al. 1992; Rocken et al. 1994; Rocken et al. 1996).

In conclusion, increasing understanding of the TLR-mediated activation if innate immune cells and their link to adaptive immunity has helped to create a concept that also applies to the activation of autoreactive T and B cells.

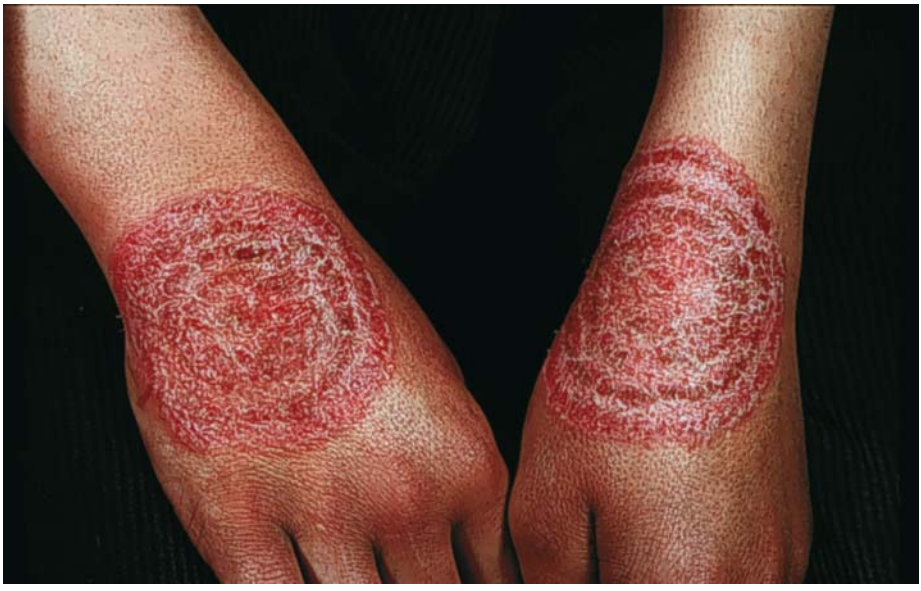

Fig. 4. Waves of inflammation as reflected by the migrating margins of eczema found during tinea infection

Thus in a series of models, activating innate immunity via TLR has turned on or increased the adaptive immune response. These data emphasize the power of infectious diseases in mounting immune responses and in modulating the cytokine phenotype of established immune responses. PAMPs binding to TLR and regulating the transcription of pro-inflammatory genes through NFκB are the basis for this new understanding. Thus, PAMPs like immunostimulatory DNA binding TLR9, like lipopolysachharides binding TLR4 and others are capable of activating DC, B cells, and probably also T cells. Instructing IL-12 producing DC via TLR9 can be achieved by injection of TLR9 ligands into mice. Using the model of progressive, Th2-mediated leishmaniasis infection in susceptible BALB/c mice, Zimmermann et al. showed that immunostimulatory DNA motifs are capable of reverting even fully established type 2 immune responses into IFNγ dominated type 1 immune responses and DTHR (Zimmermann et al. 1998). Thus, injection of immunostimulatory DNA motifs and triggering TLR9 overcame the tolerance towards the parasite and restored control over *Leishmania major* in animals with a large parasite burden. In view of such a powerful Th1-inducing capacity, it was likely that similar immunostimulatory motifs are also capable of breaking self-tolerance and induce autoreactive Th1/Tc1 cells that cause inflammatory tissue destruction. Indeed, it was shown very recently that viruses provide TLR signals required for bypassing regulatory T cell-mediated tolerance (Yang et al. 2004). PAMPs may therefore be considered as the leading group of danger signals

that nature provides and that may also lead to activation of autoreactive T and B cells.

In addition to PAMPs derived from microbes, there is increasing evidence suggesting that endogenous ligands can also trigger TLR and activate autoreactive lymphocytes (Ulevitch 2004). Systemic lupus erythematosus is characterized by the production of autoantibodies against nucleic-acid-containing macromolecules such as chromatin or ribonucleoprotein particles. DC and B cells are effectively activated by immune complexes containing chromatin, a process that involves TLR9. This activation leads to proliferation of autoreactive T and B cells providing direct evidence for TLR promoted autoimmunity mediated by endogeneous ligands (Leadbetter et al. 2002; Boulé et al. 2004).

Autoimmune Disease

Autoimmunity is a prerequisite for autoimmune disease. However, the events that lead from autoimmunity to an overt inflammatory disease are still unclear. Production and release of TNF seems to be important for this step, but the exact role of this cytokine is far from being elucidated (Green and Flavell 2000). Without any doubt, autoreactive T cells are not only associated with autoimmune diseases but can directly cause the disease. Analysis from mice with non obese diabetes (NOD) revealed that both, $CD4^+$ and $CD8^+$ T cells are required for the induction of both, autoimmune inflammation and autoimmune disease (Bendelac et al. 1987). Similarly, transfer of MBP-reactive T cells (Mokhtarian et al. 1984) and even more precisely, MBP-reactive $CD4^+$ T cells of the Th1 phenotype alone are capable of inducing severe autoimmune encephalitis, when transferred into naive mice (Racke et al. 1994).

T Cells

A comparison of various models for organ-specific, inflammatory autoimmune disease unrevaled that organ specific inflammatory autoimmune diseases are primarily induced by T cells of the proinflammatory Th1 phenotype. It is assumed that both, $CD4^+$ and $CD8^+$ T cells are involved under most conditions, but the exact role of $CD8^+$ T cells remains unclear. Adoptive transfer of polarized Th1 cells alone is normally enough for inducing the disease. In this context it is of interest that ex vivo analysis of the cytokine phenotype of T cells associated with inflammatory autoimmune diseases normally reflects a type 1 phenotype. This is valid for models of autoimmue diseases in small animals and for the analysis of autoimmune responses in humans with organ-specific autoimmune disease such as autoimmune diabetes (Kolb et al. 1995), multiple sclerosis (Martin et al. 1992; Zhang et al. 1998) or psoriasis (Austin et al. 1999; Vollmer et al. 1994).

B Cells and Immunoglobulins

Probably the best example for an immunoglobulin-mediated disease is pemphigus vugaris. In patients, this disease is associated with little inflammation and seems to be directly mediated by the binding of autoreactive immunoglobulins to the desmogleins that guarantee the adherence between keratinocytes (Amagai et al. 1991). Indeed, transfer of patient sera and monoclonal antibodies directed against desmoglein 3 into the skin of new-born mice can directly induce acanthosis (Rock et al. 1989). This critical role for a direct binding of immunoglobulins to desmoglein structures is further supported by the observation that in patients with pemphigus vugaris the disease activity correlates closely with the serum levels of the autoantibodies (Hertl 2000). Such a close association is unusual for other autoimmune diseases, including lupus erythematosus or bullous pemphigoid. For comparisons, bullous pemphigoid is of special interest. It is also an immunoglobulin mediated bullous skin disease. In sharp contrast to pemphigus vulgaris, the clinical manifestation of bullous pemphigoid does not only require deposition of autoantigens but also an inflammatory milieu that causes detachment of the basement membrane (Liu et al. 1998; Liu et al. 2000). Consequently, transfer of specific sera or immunoglobulins under the skin of new born nude mice alone is not sufficient for the induction of blisters. It requires, in addition, activation of the complement cascade and inflammation, involving the recruitment of granulocytes (Liu et al. 1995).

Tissue Damage and Type 1 T Cells

Type 1 T cells are associated with two distinct types of tissue damage. One type of tissue damage is characterized by a sterile inflammation, the other with the strong accumulation of polymorphonuclear granulocytes.

Sterile type 1 responses are found in lichen planus, multiple sclerosis or autoimmune diabetes. They are associated with activated macrophages, which seem to be the effector cells of these immune responses. Like macrophages that are stimulated in vitro in the presence of IFNγ, they produce large amounts of TNF, oxygen radicals, NO and other mediators of inflammation (Stenger and Modlin 1999). Activated $CD8^+$ T cells with potent killer functions seem also to be involved (Zinkernagel 1996). In concert, these mediators can cause severe tissue destruction that ultimately results in compensatory scar formation. Due to the capacity of the skin to regenerate even severe tissue damage, lichen planus heals under most conditions without scaring. However, persistent alopecia, onychodystrophy or even scars of the normal skin are potential complications (*Fig. 5A*).

Under other conditions, type 1 mediated autoimmune diseases are associated with a strong infiltrate by PMN. Such a constellation characterizes psoriasis,