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STIFTUNG PROFESSOR DR. MAX CLOËTTA

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Prof. Dr. Margot Thome-Miazza
«Molecular mechanisms controlling lymphocyte proliferation and survival»»

Prof. Dr. Walter Reith
«Regulation of antigen presentation in the immune system»

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VORWORT

Professor Marco Baggiolini
Präsident des Stiftungsrates

Die Liste der Preisträger der letzten zehn Jahre widerspiegelt Gebiete und Errungenschaften der aktuellen forschenden Medizin in der Schweiz. Die Akteure sind mir noch lebhaft in Erinnerung, durch ihre Arbeit, einzelne Veröffentlichungen, ihren Vortrag an der Feier und zum Teil auch durch ihre Umgebung, durch Mitarbeiter und Verwandte, die sich über den Erfolg freuten. Jedes Jahr sind mehrere von ihnen als Gäste dabei und bilden zusammen mit dem Stiftungsrat, dem effizienten Sekretariat und vielen langjährigen Förderern aus akademischen und wirtschaftlichen Kreisen den feierlichen Rahmen der Preisverleihung. Der Stifter und seine Familie sind dank ihrer steten Förderung sehr erfolgreich gewesen, das kann man abschätzen anhand der Resultate der unterstützten Forschung und der Karrieren, die sie ermöglicht haben. Zusätzlich ist ihnen etwas Einzigartiges gelungen: über die Jahrzehnte haben sie eine angesehene und traditionsbewusste Cloëtta-Gemeinschaft gebildet.

Die Forschungsgebiete, die unsere Stiftung auszeichnet, entsprechen den internationalen Trends. Prominent sind die **Infektionskrankheiten**, die biologischen, molekularen und epidemiologischen Studien ihrer Erreger mit alten und neuen Varianten und die Mechanismen der **Immunabwehr** mit ihrer Vielfalt und Komplexität, der gelegentlichen Extravaganz – die den Forschenden verblüfft – und den krankmachenden Mechanismen der **Autoimmunität**. Das Studium der Erreger und der Immunabwehr wird immer wichtiger, und es ist zu hoffen, dass in einer baldigen Zukunft unser Preis Fortschritte auf dem Gebiet der Vakzine auszeichnen wird. Immer gegenwärtig, als eine Art Welttheater-Kulisse der Medizin, ist die **Entzündung** als ambivalentes Phänomen, das sich zwischen Heilung und Krankheit bewegt und grosse klinische Bedeutung behalten hat. Trotz vieler Erkenntnisse hat die Entzündungsforschung interessanterweise über Jahrtausende wenig

Fortschritte gemacht. Die Diagnose ist im Wesentlichen bei den Grundsymptomen der Antike geblieben: *rubor, calor, tumor, dolor,* und therapeutisch hat das Wundermolekül Aspirin immer noch den sichtbaren Glanz eines Goldstandards.

Gegenüber dem Schwerpunkt Infektion und Immunität finden wir unter den Preisträgern der letzten zehn Jahre eine erfreuliche Zahl von «Solisten», die eigene Wege beschritten haben. Sie befassen sich mit Signalmolekülen, Signalübertragung, Genetik, Gentranskription, Biorhythmen, Apoptose und anderen Fragen der Grundlagenforschung. Sie gehen Risiken ein, sie sind Artisten, die ohne Netz auf dem hohen Seil der Innovation tanzen. In einer Zeit, in der einleuchtende, absehbare, ja nahezu sichere Forschungsvorhaben eher die Gunst der Geldgeber finden, sind die «Solisten» für die Cloëtta-Gemeinschaft immer wichtiger. Der medizinische Ausschuss unseres Stiftungsrats ist an der Neuheitsfront besonders aufmerksam und dürfte vielleicht noch risikofreudiger sein, mit den Preisen und bei der Vergabe der begehrten und wichtigen Cloëtta-Forschungsstellen an junge, unabhängige Forscher.

Es muss immer wieder in Erinnerung gerufen werden, dass eine gemeinnützige Institution wie die Stiftung Prof. Dr. Max Cloëtta ihren anspruchsvollen Zweck nur dann erfüllen kann, wenn ihr ausgewiesene Fachleute unentgeltlich ihr grosses Wissen zur Verfügung stellen.

Dr. Hans-Ulrich Doerig trat im Sommer 2009 in Folge seiner Wahl zum Präsidenten des Verwaltungsrates der Credit Suisse aus dem Stiftungsrat zurück, dem er seit 1995 als Mitglied und seit 1997 als Vizepräsident angehört hatte. Die Stiftung und die Cloëtta-Gemeinschaft danken ihm für sein Engagement.

Je länger eine Stiftung besteht, desto häufiger muss sie auch Abschied nehmen von Menschen, die sie geprägt haben. Dr. Hans W. Kopp ist am 25. Januar 2009 nach kurzer, schwerer Krankheit verstorben. Als Willensvollstrecker des Stifters Dr. Antoine Cloëtta und Präsident des Stiftungsrates seit der Errichtung der Stiftung 1973 bis 1995 hat er diese massgeblich geformt. So wurde unter seiner Federführung, zu-

sammen mit den Mitgliedern des Medizinischen Ausschusses, 1982 das Forschungsstellen-Programm gegründet, das eine beachtliche Zahl von Forscherinnen und Forschern in einer wichtigen Phase ihrer Karriere unterstützt und das nach bald drei Jahrzehnten seines Bestehens an Aktualität nichts eingebüsst hat.

Heute werden (wieder!) zwei Immunologen ausgezeichnet.

Professor Margot Thome-Miazza aus dem Departement für Biochemie der Fakultät für Biologie und Medizin der Universität Lausanne wird ausgezeichnet für ihre Arbeiten zu den Mechanismen der Aktivierung der T-Lymphozyten bei der Immunabwehr. Sie hat eine Reihe von beteiligten Molekülen untersucht: Proteinkinasen, die im Aktivierungsprozess eingreifen, und einen Komplex aus drei Proteinen (CARMA1, BCL10 und MALT1), der durch die Aktivierung von NFkappa B die Vermehrung der Lymphozyten bewirkt und ihre Lebensdauer verlängert. In Fortsetzung dieser Arbeiten hat sie die Erhöhung der Adhäsion der Lymphozyten durch MALT1 nachgewiesen und weitere Funktionen von MALT1 und BCL10 beschrieben, die therapeutische Ansatzpunkte eröffnen könnten. Die Laudatio für Professor Thome-Miazza hält Professor Jürg Tschopp vom Departement Biochemie an der Universität Lausanne.

Professor Walter Reith aus dem Departement für Pathologie und Immunologie der Universität Genf erhält den Preis für seine langjährige Forschung auf dem Gebiet der sogenannten Histokompatibilität, die von Oberflächenproteinen vom Typ MHC der Klasse II vermittelt wird. Durch die MHC-Proteine unterscheiden die Zellen des Immunsystems zwischen eigenem Gewebe, das geschont, und fremdem Gewebe, etwa bei Tumoren und Infektionen, das vom Immunsystem zerstört wird. Professor Reith hat die Mechanismen der Expression der Erkennungsproteine und ihre Regulation untersucht sowie ihre Rolle bei Zuständen von Immundefizienz beschrieben. Seine Laudatio hält Professor Walter Schaffner vom Institut für Molekularbiologie an der Universität Zürich.

DER CLOËTTA-PREIS 2009
WIRD VERLIEHEN

FRAU PROFESSOR DOKTOR

MARGOT THOME-MIAZZA

GEBOREN 1965
ASSISTENZPROFESSORIN
AM DEPARTEMENT FÜR BIOCHEMIE
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FORSCHUNGSARBEITEN AUF DEM GEBIET DER IMMUNOLOGIE
UND DES AKTIVIERENS DER LYMPHOZYTEN.

ZÜRICH, 20. NOVEMBER 2009

FÜR DEN STIFTUNGSRAT:

DER PRÄSIDENT

DER VIZEPRÄSIDENT

EIN MITGLIED

Prof. Dr. Margot Thome-Miazza

CURRICULUM VITAE

Name:	Thome-Miazza
First name:	Margot
Date of birth:	October 9th, 1965
Place of birth:	Stuttgart, Germany
Marital status:	Married, two children

Education and Training

1985	High School Diploma, Filderstadt, Germany
1986–1992	Undergraduate and graduate studies of Biochemistry University of Tübingen, Germany, and University of Arizona, USA
1993–1995	Doctoral thesis: «Identification of ligands of the tyrosine kinase p56lck» Laboratory of Dr. O. Acuto, Department of Molecular Immunology, Pasteur Institute, Paris, France
1996–1998	Postdoctoral fellow at the University of Lausanne, Switzerland Research project: «Signaling mechanisms in apoptosis» Laboratory of Prof. Dr. J. Tschopp, Institute of Biochemistry

Positions

1999–2004	Research assistant (Maître Assistant), University of Lausanne Research interest: «Signaling mechanisms regulating NF-kB activation» Laboratory of Prof. Dr. J. Tschopp, Institute of Biochemistry
2004–2009	SNF fellow Professor, University of Lausanne, Dept. of Biochemistry Research interest: «Molecular mechanisms of NF-kB activation in T-cells and monocytes»
2009–	Associate professor, University of Lausanne, Dept. of Biochemistry, Research interest: «Signaling mechanisms controlling T-cell activation and lymphoma development»

Honors and awards

1993–1995	Doctoral fellowship from Boehringer Ingelheim Fonds (Germany)
1996–1998	EMBO long term postdoctoral fellowship (EMBO, Germany)
2004–2010	Swiss National Science Foundation Fellow Professorship
2009	Research Prize, Leenaards Foundation
2009	Prize Prof. Dr. Max Cloëtta

Memberships

Member and Assessor of the Swiss Society of Biochemistry
Editorial Board Member of the European Journal of Immunology

Recent research support

Swiss National Science Foundation
Swiss Cancer League
Novartis Foundation
Vontobel Foundation
Pierre Mercier Foundation
Emma Muschamp Foundation
Leenards Foundation

KEY PUBLICATIONS

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*shared first authorship

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MOLECULAR MECHANISMS CONTROLLING LYMPHOCYTE PROLIFERATION AND SURVIVAL

Margot Thome-Miazza

The human body is exposed daily to potentially harmful infectious and non-infectious agents, and has therefore developed efficient defense systems. Lymphocytes are cells of the immune system that play a prime role in the defense against infectious agents, but also contribute to the efficient elimination of malignant cells. Lymphocytes become activated upon detection of molecular changes associated with infection or malignancy, and subsequently undergo a clonal expansion that serves to multiply a subset of cells that are most suited to eliminate the detected infectious agent or tumor cell. Subsequently, lymphocyte numbers retract, and excessive lymphocytes die because of both, a lack of sufficient growth factors in their environment and an active, ligand-induced mechanism of cell death induction (**Fig. 1**). The remaining surviving lymphocytes, also called memory lymphocytes, provide efficient protection of the body upon a later infection by the same infectious agent.

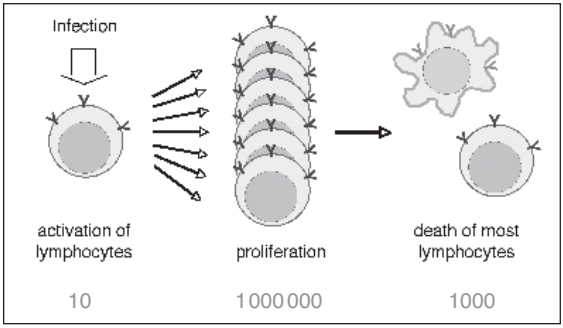

Figure 1: Lymphocyte expansion and elimination during a normal immune response. *Upon recognition of an infectious agent by the lymphocyte's cell surface receptor, lymphocytes get activated and expand approximately 100.000 fold within few days. Subsequently to the elimination of the infectious agent, most of the lymphocytes die and only a limited number of so-called memory lymphocytes remain, which protect the individual against a subsequent infection by the same pathogen.*

It is the correct control of every step in the process of activation, expansion and subsequent elimination of lymphocytes that assures an efficient adaptive immune response. Deregulation of the activation step leads to immunodeficiency, while inefficient elimination of reactive lymphocytes has been associated with autoimmune disease and development of lymphocyte-derived cancers, such as lymphoma and leukemia. Moreover, persistent activation of lymphocytes by grafted tissues, recognized by the immune system as a foreign and thus potentially harmful agent, is responsible for the rejection of organ transplants (**Fig. 2**).

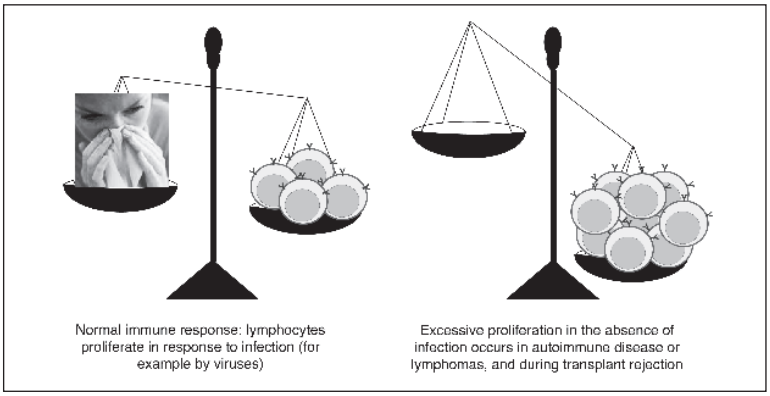

Figure 2: Consequence of excessive lymphocyte proliferation. *Normally, lymphocytes proliferate in response to infection, but excessive lymphocytes are subsequently eliminated by cell death. Excessive lymphocyte proliferation in the absence of infection can cause autoimmune disease or lead to lymphoid malignancies such as leukemia or lymphomas. Exaggerated lymphocyte responses are also responsible for the rejection of transplanted organs.*

Several lines of evidence support the need for further research on mechanisms controlling normal and pathological lymphocyte activation. On the one hand, there is a dramatic increase in autoimmune diseases worldwide, and the number of organ transplantations is continually rising. There is thus an increased need for effective and well-tolerated immunosuppressive strategies. On the other hand, a better understanding of signaling pathways leading to aberrant lymphocyte proliferation will help in the treatment of leukemias and lymphomas.

Here, I will review some of the key features that control lymphocyte activation and survival, with a special focus on lymphocyte cell surface receptors and intracellular signaling cascades that are initiated upon triggering of these receptors, and that we have studied in detail over the last thirteen years.

Steps controlling the activation and proliferation of lymphocytes

Every lymphocyte carries at its cell surface a unique receptor, the antigen receptor, which is capable of recognizing foreign antigens. Foreign or non-self antigens can be distinguished from self-antigens based on their molecular structure, and are recognized as foreign because of a prior developmental selection that allows only those lymphocytes to mature who do not have an antigen receptor cross-reacting with self-antigens, and because of additional mechanisms of peripheral tolerance that suppress autoimmunity in specific tissues (1, 2). Triggering of the antigen receptor initiates a cascade of intracellular signaling events that lead to the activation of lymphocytes, which multiply and participate actively in the immune response. So-called B-lymphocytes do so by producing protective antibodies, while another subset of lymphocytes, the T-lymphocytes, help B-lymphocytes or react by direct killing of infected or tumor cells. The signaling cascade that controls these lymphocyte responses co-ordinates many types of cellular reactions (**Fig. 3**).

Antigen receptor-induced cellular reactions include changes in the shape of the cell that allow the lymphocyte to attach tightly to the antigen-presenting cell, changes in cell metabolism required for rapid proliferation, but also changes in the expression of sets of genes that control the differentiation and survival of the activated lymphocyte. Alterations in cellular shape are linked to changes in the actin cytoskeleton that are triggered by antigen recognition. How the antigen receptor controls the actin cytoskeleton is the subject of intense research efforts (3). Most of these focus on proteins of the WASP/WAVE family and their binding partners, which promote the incorporation of soluble actin monomers into filamentous strands of actin by the Arp2/3 complex (4). Such newly forming actin filaments are thought to push

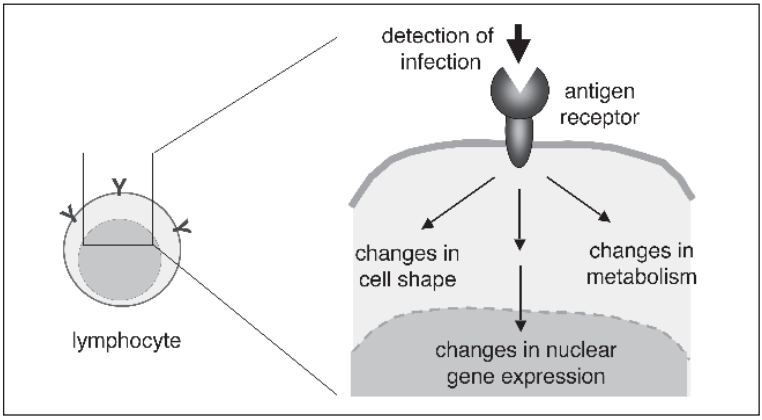

Figure 3: Cellular changes induced by detection of infection through the antigen receptor. *Triggering of the receptor leads to molecular signaling pathways (indicated by arrows) that control changes in the shape, metabolism and gene expression of the activated lymphocyte.*

membrane protrusions forward and to thereby extend the cell surface. This process is important to allow the T-cell to make efficient contacts with antigen-presenting cells, and can be mimicked *in vitro* by allowing T-lymphocytes to form conjugates with antigen-presenting cells (APCs), or to spread out on plates that are coated with agonistic T-cell receptor antibodies (5). When studying T-lymphocytes that are deficient in the protein BCL10, we observed that these cells were impaired in their capacity to form T-cell/APC conjugates or to spread out on anti-TCR coated plates (6). This was linked to a nearly total absence of T-cell receptor-induced actin polymerization (6). How exactly BCL10 controls actin polymerization is not yet understood; it is likely that BCL10 acts upstream in the signaling pathway leading from T-cell receptor engagement to the activation of WASP/WAVE family proteins, but further work is required to assess the exact contribution of BCL10. Most of our recent work has however focused on the role of BCL10 and its binding partners, CARMA1 and MALT1, in the T-cell receptor-induced transcription of genes that are relevant to lymphocyte proliferation and which will be discussed in detail below.

T-cell receptor induced changes in gene expression are controlled by transcription factors that bind specific target sequences in the genome and thereby increase or inhibit the transcription of sets of target genes (7). Two transcription factors are particularly important for lymphocyte activation: the nuclear factor of activated T-cells (NFAT) and the nuclear factor kappa B (NF-κB), which coordinately regulate the expression of genes such as interleukin-2, a cytokine that promotes T-lymphocyte proliferation *in vitro* (8). Because of their pivotal role in lymphocyte activation, both NFAT and NF-κB activating pathways are attractive targets for therapeutic immuno-modulation. The signaling events activating the transcription factors NFAT and NF-κB have been intensively studied during the last two decades. Both transcription factors are kept in an inactive form in the cytoplasm of resting cells, and translocate into the nucleus upon antigen receptor triggering, but the underlying molecular mechanisms controlling nuclear import of NFAT and NF-κB are distinct (**Fig. 4**).

In resting T-lymphocytes, NFAT is kept in the cytoplasm in an inactive, highly phosphorylated form that cannot enter the nucleus. Antigen receptor triggering induces a rise in the concentration of intracellular calcium that leads to activation of the calcium dependent Ser/Thr phophatase Calcineurin. The resulting de-phosphorylation of NFAT leads to exposure of its nuclear localization site and nuclear import of NFAT to induce transcription of genes (9, 10). NFAT-dependent gene transcription is pivotal to the adaptive immune response, and targeting the NFAT pathway is presently one of the most efficient immunosuppressive strategies. Inhibition of NFAT activation is achieved by treatment with Cyclosporin A, a compound that can enter the cell and bind to its cytoplasmic binding protein Cyclophilin. The Cyclosporin A/Cyclophilin complex in turn binds and inhibits the phosphatase Calcineurin (9). Cyclosporine and its derivatives are used to prevent transplant rejection and graft versus host disease, but also to treat certain severe forms of auto-immune diseases and immune-mediated skin diseases.

The activity of the transcription factor NF-κB is regulated by another series of signaling events that are triggered by antigen receptor engagement (11, 12). NF-κB is kept in the cytoplasm through binding to its inhibitor, the inhibitor of kappaB (IκB), and requires the proteolytic

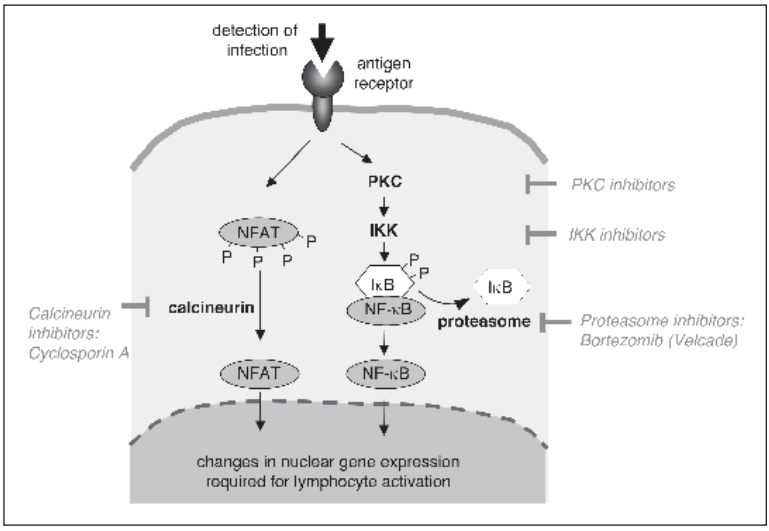

Fig. 4: Summary of key signaling events that control NFAT- and NF-κB dependent gene transcription in antigen receptor-triggered lymphocytes. *Antigen receptor triggering activates the transcription factor NFAT through its dephosphorylation, mediated by the phosphatase calcineurin. Calcineurin inhibitors, such as cyclosporine A, efficiently dampen lymphocyte-dependent immune responses and are thus used to prevent transplant rejection or treat certain auto-immune or inflammatory diseases. Therapeutic targeting of the NF-κB pathway has recently gained interest through the identification of enzymatic activities that control key steps in the pathway. These include the proteolytic activity of the proteasome, required to degrade the NF-κB inhibitor IκB, and the kinase activity of PKC family members and of the IκB kinase (IKK) complex.*

degradation of IκB by the proteasome to allow its nuclear entry. This critical step is controlled through receptor-mediated activation of the IκB kinase (IKK) complex, which phosphorylates IκB and thereby targets it for ubiquitination-dependent degradation (13). Many laboratories including ours have studied the signaling events that mediate the antigen-receptor-induced activation of IKK. One of the earliest events upon antigen receptor engagement is the activation of tyrosine kinases, which in turn activate Ser/Thr kinases of the PKC family, PKCθ (in T-cells) and PKCθ (in B-cells) that are required for IKK activation. Over the last 10 years, we and others have focused on the identification and

molecular characterization of molecular compounds controlling the NF-κB pathway downstream of PKC and upstream of IKK. This has led to the identification of the CBM complex, a protein complex comprising the proteins CARMA1, BCL10 and MALT1 which plays a central role in antigen receptor-induced NF-κB activation downstream of PKC and upstream of the IKK complex (**Fig. 5**) (11).

Through combined bioinformatic, biochemical and genetic approaches, we have identified CARMA1 as a scaffold protein that mediates NF-κB activation through recruitment of the adaptor protein BCL10 (14, 15), and that is essential for lymphocyte activation and proliferation (16). BCL10 in turn binds constitutively to the signaling protein MALT1, and it is thought that a major role of the assembled CARMA1-BCL10-MALT1 (CBM) complex is to mediate IKK activation via additional proteins such as the ubiquitin ligase TRAF6 and the Ser/Thr kinase TAK1 that control the activity of the IKK complex through its ubiquitination and phosphorylation, respectively (17). Recently, we and others could show that MALT1 is not only an adaptor protein, but that it has an enzymatic (proteolytic) activity that is essential for optimal lymphocyte activation (18, 19) (**Fig. 5**). Using a fluorogenic MALT1 substrate, we could show that MALT1 activity peaks 30 min after antigen receptor stimulation and returns to baseline levels after approximately one hour (19). This suggests that MALT1 activity is tightly regulated by unknown molecular mechanisms that are the focus of ongoing studies. Through the development of a cell-permeable inhibitor for MALT1, we could show that the protease activity of MALT1 is required for optimal NF-κB activation and cytokine production of activated T-cells (19). In addition, we found that MALT1-dependent cleavage of BCL10 affects the adhesion of T-cells to extracellular matrix proteins or cellular adhesion molecules (19), which might facilitate the binding of T-cells to antigen-presenting cells or to the endothelium of blood vessels in inflamed tissues during lymphocyte extravasation (20, 21).

With the identification of essential enzymatic activities controlling the NF-κB pathway, strategies to therapeutically interfere with NF-κB activation in lymphocytes have started to emerge (**Fig. 4 and 5**). Proteasomal inhibitors such as Bortezomib (Velcade) block NF-κB

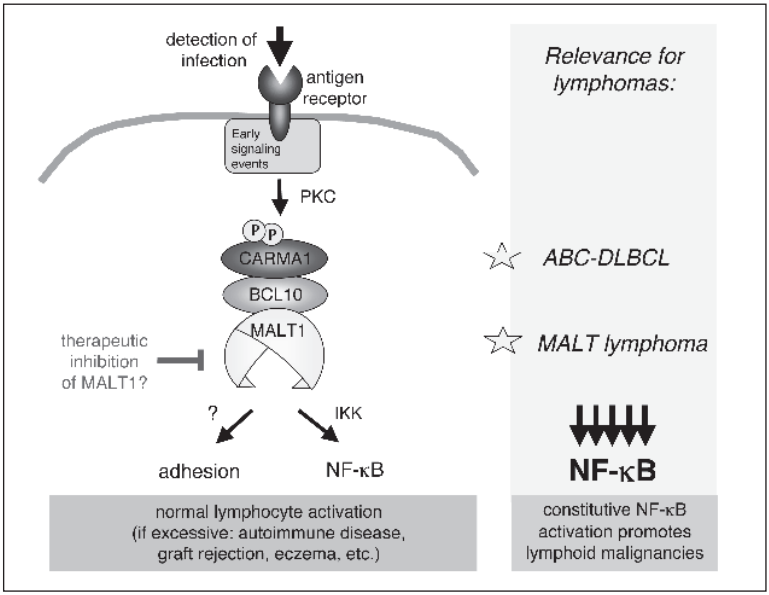

Fig. 5: Role of CBM proteins in lymphocyte activation. *Antigen receptor engagement triggers early signaling events that lead to activation of kinases of the PKC family. The proteins CARMA1, BCL10 and MALT1 control NF-κB activation upstream of the IKK complex, but also affect T-cell adhesion via unknown mechanisms. MALT1 has protease activity that is essential for both, adhesion and NF-κB activation. Therapeutic inhibition of MALT1 might be useful to treat diseases with exaggerated lymphocyte activaton, such as autoimmundiseases or eczema, or to prevent the rejection of organ transplants by activated lymphocytes. Oncogenic mutations in genes encoding CBM proteins have been reported in MALT lymphoma and the activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL), suggesting a possible further application for MALT1 inhibitors.*

activation in lymphocytes but also in many other cells, and also interfere more generally with proteasomal protein degradation. Therefore, proteasome inhibitors have toxic side effects that prevent their use for immuno-suppression, but still allow for the treatment of hematopoietic malignancies such as multiple myeloma, which is characterized by constitutive NF-κB activation (22). Similar problems have to be considered when thinking of possible applications for IKK inhibitors, which inhibit NF-κB activation in all cell types. Nevertheless, IKK inhibitors

are now in preclinical trials for immunosuppression and cancer therapy (23, 24). Since MALT1 deficiency preferentially affects adaptive immune responses (25), inhibition of MALT1 might become an interesting approach for inhibition of NF-κB activation specifically in lymphocytes, either for immuno-suppression or to treat lymphoid malignancies characterized by constitutive MALT1 activation (see below).

Uncontrolled lymphocyte proliferation and lymphoma development

Several lines of evidence support the idea that aberrant NF-kB activation in lymphocytes is associated with the development of lymphomas (26, 27). At least two types of lymphoma have been directly linked to mutations in the genes encoding CARMA1, BCL10 or MALT1 (**Fig. 5**): diffuse large B-cell lymphoma (DLBCL), which is the most common form of lymphoma in adults, and lymphomas of the mucosa-associated lymphoid tissue (so-called MALT lymphomas), a rather rare form of lymphoma (27, 28). DLBCL can be classified into at least three subtypes based on the gene expression profile (27). The so-called activated B-cell (ABC) subtype of DLBCL is characterized by constitutive activation of NF-kB and high levels of expression of NF-kB target genes (27). It was shown that silencing of the expression of CARMA1, BCL10 or MALT1 leads to impaired survival of cell lines derived from ABC-DLBCL (29), suggesting that the CARMA1-BCL10-MALT1 pathway is responsible for constitutive NF-kB activation in this type of lymphoma. Subsequently, oncogenic mutations in CARMA1 have been identified in patients with ABC-DLBCL, identifying CARMA1 as a bona fide oncogene (30). Using cell lines derived from patients with ABC DLBCL, we could recently show that MALT1 is constitutively active in these cell lines, and that MALT1 activity can be induced by oncogenic mutants of CARMA1 (Hailfinger et al., in press). Interestingly, the proliferation and survival of ABC DLBCL cell lines in vitro was strongly impaired by treatment with a MALT1 inhibitor, suggesting that MALT1 protease activity could be a disease-specific drug target (Hailfinger et al., in press). Further work is required to assess whether MALT1 protease activity is also relevant for the growth of MALT lymphomas and potentially of other malignancies associated with constitutive NF-κB activation.

Mechanisms that limit the survival of proliferating lymphocytes

The antigen receptor-induced NF-κB activation in lymphocytes is usually transient, and allows lymphocytes to proliferate and survive during a limited window of time of a few days. This assures the transient NF-κB-dependent upregulation of gene products such as cytokines, that act as growth factors to promote cellular growth and proliferation, but also of proteins that transiently make the cells resistant to cell death, such as Bcl-2 and FLIP family proteins. During the retraction phase of the immune response, the level of expression of these proteins drops down, and as a result, the cells become susceptible to cell death. This inherently programmed form of cell death of lymphocytes, also called activation-induced cell death (AICD) is thought to be the result of both, growth factor deprivation and an active fratricide-dependent mechanism of cell death induction through the death receptor Fas and its ligand, Fas ligand (FasL) (31). The molecular mechanism of Fas signaling has been studied extensively (**Fig. 6A**).

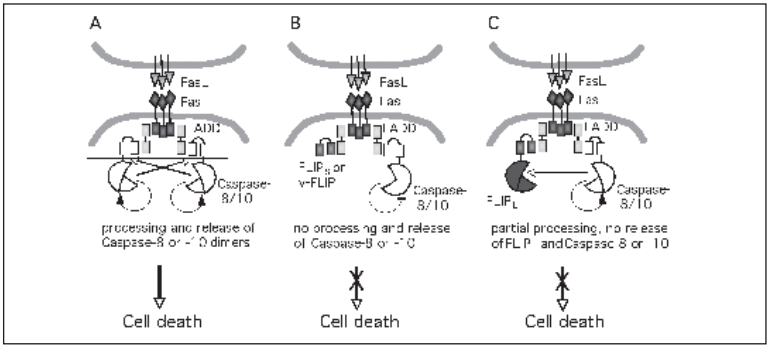

Fig. 6: Role of FLIP proteins in cell death protection of lymphocytes. *Lymphocytes can be triggered to die by membrane-bound FasL, which is expressed on activated lymphocytes. FasL induced trimerization of the death receptor Fas, which assembles a signaling complex that leads to autoprocessing-mediated activation and release of caspase-8 and -10 into the cytosol, to cleave many cellular proteins involved in the execution phase of programmed cell death (**A**). FLIP proteins are structurally homologous to Caspase-8/10, and block Fas-induced cell death by interfering with Caspase-8/10 activation (**B** and **C**). c-FLIPS and v-FLIPs are thought to block Caspase-8 or -10 processing and release, while c-FLIPL allows partial processing of these caspases but no release.*

Fas has a cytoplasmic death domain (DD), and binding of the membrane-bound, trimeric form of FasL to the receptor results in the recruitment of the adapter molecule FADD (Fas-associated protein with death-domain) to the receptor via a DD/DD interaction. FADD also contains an N-terminal death effector domain (DED), which in turn recruits the DED-containing proteases of the caspase family, caspase-8 (formerly called FLICE) and caspase-10 (formerly called FLICE-2), to form a receptor-bound signaling complex (31). It is thought that this process brings two or more caspase-8 (or -10) molecules into close proximity at the receptor level, and allows them to proteolytically activate each other. Active caspase-8/-10 molecules lacking the N-terminal DEDs will then be released into the cytoplasm and initiate apoptosis by subsequent cleavage and activation of downstream effector caspases (caspases-3, -6, -7) and of cellular proteins involved in the execution phase of the cell death program (**Fig. 6A**).

My postdoctoral work has led to the identification and functional characterization of a new class of proteins that prevent Fas receptor-induced cell death (32–34). These cellular caspase-8/FLICE-inhibitory proteins (c-FLIP proteins) are structurally homologous to the Fas associated Caspases-8 and -10, and interfere with their activation by the receptor by preventing their recruitment and/or full processing at the receptor-associated signaling complex (**Fig. 6, B** and **C**).

Two major splice isoforms of cellular FLIP have been described. The long splice isoform, c-FLIP$_L$, contains two DEDs and a protease-like domain, and therefore ressembles Caspase-8 in its overall structure, but lacks critical amino acid residues important for protease activity (**Fig. 6C**). The short isoform, c-FLIP$_S$, lacks the protease-like domain and contains only two N-terminal DEDs that correspond in structure to the FADD-binding N-terminus of Caspase-8 (**Fig. 6B**). FLIPL was found highly expressed in freshly activated T-cells, but is down-regulated upon prolonged stimulation in presence of IL-2, suggesting that decreased FLIP expression levels may sensitize activated T-cells to Fas-induced apoptosis and thus to the termination of the immune response by activation-induced cell death (33, 35, 36). On the other hand, increased expression levels of the short splice isoform of FLIP,

c-FLIP$_S$, has been found in memory T-cell models *in vitro*, suggesting that upregulation of c-FLIP$_S$ could contribute to the increased FasL-resistance of memory T-cells (37, 38). In addition to protecting the lymphocytes from receptor-induced cell death, FLIP proteins can also actively promote lymphocyte activation and proliferation (34). This is most likely mediated by proteins of the TRAF (TNF receptor associated factor) family that bind to c-FLIP$_L$ and certain viral FLIP proteins (39, 40). Viral FLIP (v-FLIP) proteins are present in lymphotropic herpesviruses such as the equine herpesvirus-2 (EHV-2), the herpesvirus saimiri (HVS), but also the human Kaposi sarcoma-associated herpesvirus (human herpesvirus-8, HHV-8 (32, 41, 42). The expression of these v-FLIP proteins is thought to prevent or delay the elimination of herpesvirus-infected cells by cytotoxic T-lymphocytes, by interfering with Fas-receptor-induced cell death signaling (32, 43). Protection against death receptor-induced apoptosis is clearly the best-described function of viral FLIPs, however, additional functions have been discovered. We could recently show that the Kaposi sarcoma-associated v-FLIP protein K13 protects infected cells against superoxide-induced cell death by massive upregulation of manganese superoxide dismutase (MnSOD) (44). The human poxvirus molluscum contagiosum virus (MCV), which infects keratinocytes, contains two quite different v-FLIP variants with unusually long C-terminal extensions. We could show that one of these, the FLIP protein MC159, contains C-terminal binding sites for TRAF2 and TRAF3 that are dispensable for short term protection, but required for efficient long-term protection of cells against Fas-induced apoptosis, an effect that correlated with impaired stimulation-induced internalization of the Fas receptor (40).

Interestingly, we recently found elevated levels of c-FLIP expression in DLBCL cell lines of the ABC subtype, and these were reduced through pretreatment with the MALT1 inhibitor (Hailfinger et al., in press) because the expression of the FLIP proteins themselves is controlled by the transcription factor NF-κB (45, 46). Thus, NF-κB targets such as cellular FLIP proteins may have an important role in the resistance of these particularly aggressive lymphomas against chemotherapeutic or immune response-mediated attempts to stop the disease.

Implications for the design of new immunosuppressive or anti-lymphoma therapies

The study of intracellular signaling pathways that control the proliferation and survival of lymphocytes has led to the identification and characterization of several key components and regulators of these pathways. Proteins that have an enzymatic activity are of particular interest, because of the possibility to develop pharmaceutical inhibitors with therapeutic applications. Calcineurin inhibitors such as cyclosporine A inhibit the antigen receptor-mediated activation of the NFAT pathway and are widely used in immunosuppressive therapies, but have side effects that are due to the ubiquitous expression of NFAT family members in other tissues. New strategies are under development, such as targeting protein kinase C-family members that are specifically expressed in lymphocytes and control the activity of both, the NFAT and NF-κB pathway in lymphocytes (47–49). Therapeutic targeting of signaling components specific to the NF-κB pathway has gained interest because of the discovery of its deregulation in certain types of cancers (26), but also because of its predominant role in controlling many aspects of the immune response (50). The better understanding of NF-κB regulation therefore holds the promise to develop drugs that can either interfere with the pathway to dampen exaggerated immune responses, or to inhibit cellular proliferation in specific subtypes of lymphomas characterized by constitutive NF-κB activation. MALT1 and its binding partners, CARMA1 and BCL10 are key players in this pathway (11, 29), but also affect other T-cell responses such as cytoskeleton-dependent changes in the lymphocyte cell shape (6) and an increased adhesiveness to antigen presenting cells (19). The further elucidation of these and possibly other, yet to be discovered functions of these proteins is a challenge for our future research.

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LE PRIX CLOËTTA 2009
EST DÉCERNÉ À

MONSIEUR LE PROFESSEUR

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KEY PUBLICATIONS

1. Clausen B.E., J.M. Waldburger, F. Schwenk, E. Barras, B. Mach, K. Rajewski, I. Förster and W. Reith (1998). Residual MHC class II expression on mature dendritic cells and activated B-cells in RFX5-deficient mice. *Immunity* **8**, 143–155.

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REGULATION OF ANTIGEN PRESENTATION IN THE IMMUNE SYSTEM

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The bodies of humans and other animals constitute a vast and appealing resource-rich milieu in which foreign microorganisms can live, feed, reproduce and shelter from the harsh and hostile external environment. We are therefore continuously subjected to onslaughts by a wide variety of potentially pathogenic organisms, including myriads of different viruses, bacteria, fungi, and unicellular and multicellular parasites. To combat the establishment and propagation of infections we are equipped with a complex network of molecules, cells and tissues collectively referred to as the immune system. Our immune system is specialized for recognizing and alerting us to the presence of foreign organisms, for mounting efficacious and multifaceted immune responses that are tailored for combating and eliminating diverse infectious agents, and for providing long-lasting immunity preventing the recurrence of previously encountered infections. Because of these key functions, the immune system is essential for survival. In the absence of a fully functional immune system – as is for instance the case in hereditary and acquired immunodeficiency diseases, or following the administration of immunosuppressive drugs to treat autoimmune diseases, avoid transplant rejection or attenuate graft versus host disease – even minor infections can take hold and prove fatal.

In parallel to fighting and clearing infections, our immune system also plays a key role in recognizing and eliminating tumors. Conversely, it must remain tolerant to healthy self-tissues, and avoid mounting unwanted immune responses directed against therapeutic drugs or innocuous foreign molecules, such as those found in ingested nutrients, plant pollen or cat dander. The loss of self-tolerance, and the inability to avoid vigorous reactions against medicaments, nutrients or harmless substances, lead to pathological immune responses and hypersensitivity reactions that underpin autoimmune diseases and allergies.

The initiation and development of protective immune responses directed against infectious agents and tumors in the context of an immune system that remains self-tolerant and avoids hyper-reactivity to beneficial or harmless compounds is strictly dependent on the ability to recognize and distinguish between self or innocuous antigens and foreign antigens derived from infectious organisms. Major Histocompatibility Complex (MHC) molecules play a central role in this process because they serve as cell-surface display cases specialized for presenting peptide antigens to the immune system.

Expression and function of MHC class II molecules

T-lymphocytes constitute a population of diverse cell types implicated at various levels in the initiation, propagation and regulation of protective immune responses directed against infectious agents and tumors, as well as in the maintenance of self-tolerance. Most major types of T-cells carry a receptor – called the T-cell receptor (TCR) – that is dedicated for the recognition of peptide antigens bound to MHC molecules expressed at the surface of other cell types. Of prime importance for appropriate functioning of the immune system in health and disease are T-cells carrying the CD4 co-receptor. The TCRs of $CD4^+$ T-cells recognize peptides presented by MHC class II (MHCII) molecules displayed at the surface of specialized cells of the immune system (**Figure 1**). Peptides presented by MHCII molecules are derived mainly from extracellular or membrane-bound proteins that have been internalized and degraded in endosomal/lysosomal compartments.

Key MHCII-positive cells include thymic epithelial cells (TEC) in the cortical (cTEC) and medullary (mTEC) compartments of the thymus, and cells that are specialized for the capture and presentation of antigens, collectively referred to as professional antigen presenting cells (APC) (**Figure 1**) (reviewed in 1–4). APC include B-lymphocytes, cells belonging to the monocyte-macrophage lineage, and various dendritic cell (DC) subtypes. Within these cell lineages, MHCII expression is fine-tuned as a function of developmental stage, activation status, interactions with other cells, and/or exposure to extracellular stimuli in-

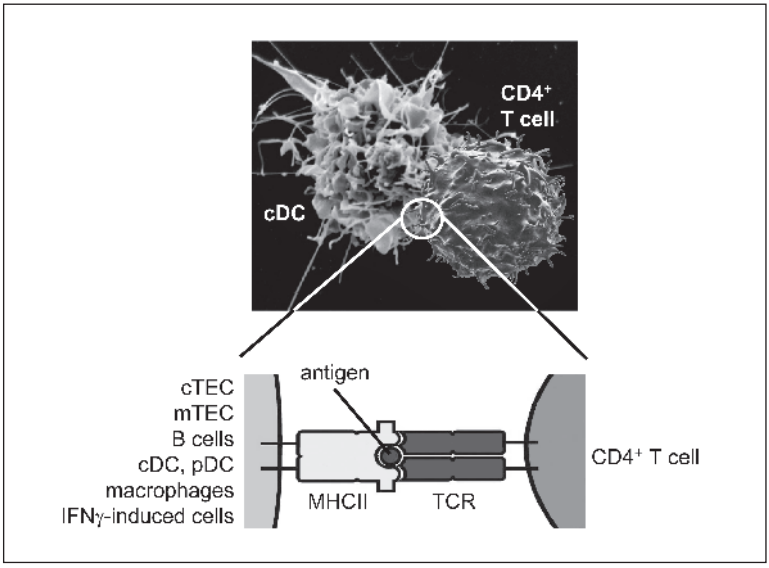

Figure 1. *Expression and function of MHCII molecules. MHCII molecules are heterodimeric transmembrane glycoproteins proteins expressed at the surface of specialized cells of the immune system, including cortical thymic epithelial cells (cTEC), medullary thymic epithelial cells (mTEC), B-cells, various different types of dendritic cell including conventional DC (cDC) and plasmacytoid DC (pDC), and cells belonging to the monocyte-macrophage lineage. MHCII expression is also induced on other cell types when they are stimulated with IFNγ. MHCII molecules present peptides to the antigen receptor (TCR) of CD4⁺ T-cells.*

cluding cytokines, inflammatory signals and microbial compounds (1–4). Most other cell types – such as fibroblasts, endothelial cells and epithelial cells in various tissues – generally lack constitutive MHCII expression. However, the majority of these MHCII-negative cells can be induced to activate MHCII expression by exposure to interferon-γ (IFNγ) (1–4), thereby licensing them to participate as «non-professional» APC during ongoing immune responses.

MHCII-mediated antigen presentation is essential for several key processes in the immune system. MHCII expression in the thymus guides

the development of $CD4^+$ thymocytes and shapes the antigen-specificity of their TCR repertoire. MHCII-positive cTEC drive positive selection (survival) of $CD4^+$ thymocytes carrying TCR capable of interacting with self MHCII molecules. MHCII-positive mTEC and DC in the medulla establish self-tolerance by promoting the negative selection (deletion) of autoreactive $CD4^+$ thymocytes carrying TCR specific for self-antigens. Thymic MHCII expression is also implicated in the selection of regulatory $CD4^+$ T-cells (Treg), which are critical for maintaining peripheral tolerance by inhibiting autoreactive T-cells that have evaded negative selection in the thymus. In the periphery, MHCII-mediated antigen presentation by APC controls $CD4^+$ T-cell activation and thus orchestrates the initiation, regulation and development of antigen-specific immune responses directed against pathogens and tumors, as well as against self-antigens during the course of autoimmune diseases. MHCII-mediated antigen presentation by DC plays a dual role. Under steady-state non-inflammatory conditions, immature DC help to maintain peripheral tolerance. Conversely, following activation by infections and/or inflammatory signals, DC adopt a mature phenotype that converts them into potent APC for the activation of naïve T-cells and the initiation of immune responses. MHCII expression by B-cells allows them to collaborate with $CD4^+$ T-cells for the generation of high-affinity antibody responses. Finally, MHCII expression by macrophages is critical for their ability to receive help from $CD4^+$ T-cells for the elimination of intracellular pathogens.

Regulation of MHCII expression; lessons from a severe hereditary immunodeficiency syndrome

The immunological processes implicating MHCII-mediated antigen presentation all depend on a strict cell-type specific and quantitatively controlled pattern of MHCII expression. Deficient or inappropriate MHCII expression therefore has profound pathological consequences. This has prompted us and others to engage in an intensive and long-lasting research effort aimed at understanding the molecular mechanisms that regulate the expression of MHCII genes (reviewed in 1–6).

MHCII molecules are heterodimeric (α/β chain) transmembrane glycoproteins. In man there are three MHCII isotypes (HLA-DR, -DQ and –DP) while in mice there are only two (H-2A and H-2E). Intracellular routing and peptide loading of MHCII molecules is controlled by their association with an accessory protein called the invariant chain (Ii) and two non-classical MHCII-like molecules called HLA-DM (H-2M in mice) and HLA-DO (H-2O in mice). The α and β chain genes of all classical and non-classical MHCII molecules are clustered together in the genome, in the class II region of the MHC locus. Expression of the MHCII, Ii and HLA-DM (H-2M) genes is tightly coregulated. HLA-DO (H-2O) expression is also coregulated, albeit in a more cell type restricted pattern limited to B-cells, mTEC and certain DC subtypes. Coordinate expression is controlled at the level of transcription by a highly-conserved regulatory module (S-Y module) found in the promoter of each gene (**Figure 2**) (1–6). The S-Y module is a transcriptional enhancer consisting of four conserved cis-acting DNA sequences – known as the S, X, X2 and Y boxes – present in a tightly constrained order, orientation and spacing (**Figure 2**) (1–6).

The molecular machinery that controls MHCII expression via the S–Y module was unraveled to a large extent by the study of a hereditary immunodeficiency disease called MHCII-deficiency or the Bare Lymphocyte Syndrome (reviewed in 1, 6–8). MHCII-deficiency is caused by a virtually complete absence of MHCII expression. The loss of MHCII expression leads to defective $CD4^+$ T-cell development in the thymus, the inability to present antigens to $CD4^+$ T-cells in the periphery, and thus to dramatically impaired immune responses (1, 7, 8). Patients consequently exhibit a severe susceptibility to infections, primarily of the respiratory and gastrointestinal tracts, by a wide range of infectious agents, including viruses, bacteria, fungi and parasites (1, 7, 8). These infections generally lead to failure to thrive and death in early childhood.

MHCII-deficiency is due to mutations in regulatory genes required for MHCII expression (reviewed in 1, 6–8). Patients have been classified into four complementation groups corresponding to defects in four regulatory genes. Our past work contributed directly or indirectly to identification of the genes affected in the four MHCII-deficiency com-

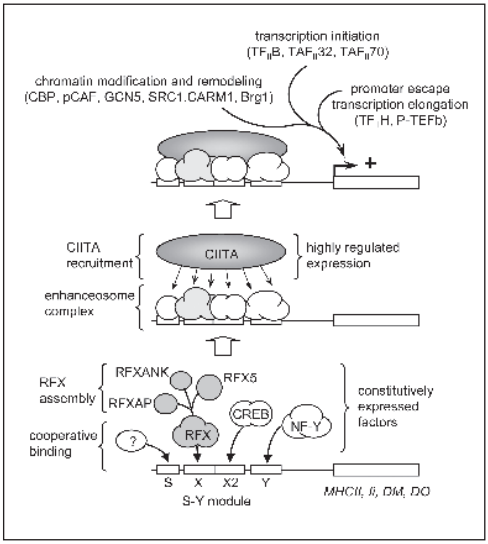

Figure 2. *Overview of MHCII gene regulation. The ubiquitously expressed factors RFX, CREB, and NF-Y bind cooperatively to generate a highly stable enhanceosome complex on the S-Y modules found in the promoters of MHCII, Ii, DO and DM genes (bottom). This enhanceosome complex serves as a platform to which the highly regulated non-DNA-binding coactivator CIITA is recruited (middle) by means of multiple protein-protein interactions (arrows). Mutations in the genes coding for the shaded factors (CIITA, RFX5, RFXANK and RFXAP) give rise to the MHCII-deficiency disease. The enhanceosome complex and CIITA collaborate in promoting chromatin remodeling by recruiting histone acetyltransferases, histone methyltransferases and nucleosome remodeling factors (top). They are also implicated in the recruitment of components of the general transcription initiation machinery, and factors involved in promoter clearance and transcription elongation (top). Abbreviations: Brg1, Brahma-related gene 1; CARM1 coactivator-associated arginine methyltransferase 1; CBP, CREB-binding protein; CREB, cAMP response element-binding protein; GCN5, general control of amino acid synthesis 5; NF-Y, nuclear factor Y; pCAF, p300/CBP-associated factor; P-TEFb, positive transcription elongation factor b; SRC1, steroid receptor coactivator 1; TAF, TBP-associated factor; TBP, TATA-box-binding protein; $TF_{II}B$ and $TF_{II}H$, general transcription factors for RNA Polymerase II.*

plementation groups (9–12). Isolation of these genes led to the identification of two critical MHCII-specific transcription factors called Regulatory Factor X (RFX) and the Class II Transactivator (CIITA). RFX is a DNA-binding transcription factor that binds to the X box of the S–Y module and consists of three essential subunits called RFX5, RFXAP and RFXANK (also called RFX-B [6]) (**Figure 2**). CIITA is a non-DNA-binding transcriptional coactivator that is recruited to MHCII promoters via protein-protein interactions with RFX and other transcription factors (CREB, NF-Y) bound to the S-Y module (**Figure 2**) (1, 5–8).

To date all MHCII-deficiency patients can be accounted for by complete or partial loss-of-function mutations in the genes encoding RFX5, RFXAP, RFXANK or CIITA (1, 6–8). Both CIITA and RFX are therefore essential components of the molecular machinery that regulates the coordinate transcription of MHCII genes. The key role of CIITA and RFX in the regulation of MHCII expression was also confirmed by the generation of *CIIta*$^{-/-}$ and *Rfx5*$^{-/-}$ mice.

Given their pivotal roles as regulators of MHCII gene transcription, our work has for many years concentrated on elucidating the structure, function, mode of action and specificity of RFX and CIITA, and on studying how these factors regulate the complex cell-type-specific and inducible pattern of MHCII expression (4, 7, 13). Furthermore, we have exploited the knowledge gained by these studies to generate transgenic and knockout mouse models that have been invaluable for deciphering the role of MHCII expression by specific cell types *in vivo* in the context of an intact immune system (4, 13).

Structure, function and mode of action of RFX and CIITA

RFX5, the largest subunit of the RFX complex, derives its name from the fact that it was the 5th identified mammalian member of the RFX family of transcription factors (10, 14). RFX factors serve a diverse range of functions in species ranging from yeast to man (14). They all bind to X box related sequences via a conserved DNA-binding domain. Establishment of the structure of the DNA-binding domain of RFX1 demonstrated that it is related to the winged-helix subfamily of helix-turn-helix domains (15). Structure-function analysis demonstrated that the DNA-binding-domain region of RFX5 is sufficient for its association with RFXAP and RFXANK, and thus for the assembly of a functional RFX complex capable of activating MHCII expression (16).

An animal model for MHCII-deficiency has been generated by gene targeting of the mouse *Rfx5* gene (17). *Rfx5*$^{-/-}$ mice reproduce all major phenotypical and immunological features of the human disease, including the loss of MHCII expression, impaired positive selection of

$CD4^+$ T-cells, decreased peripheral $CD4^+$ T-cell counts and a deficiency in $CD4^+$ T-cell dependent immune responses (17).

All mammalian RFX factors can bind to the X box of MHCII promoters *in vitro*. However, only RFX5 is required for MHCII expression *in vivo*. The other family members have very different functions. The generation of *Rfx3*$^{-/-}$ mice has for instance allowed us to demonstrate that RFX3 is required for the formation and function of cilia on various cell types (18, 19), and for the development and function of pancreatic endocrine cells (19).

RFXAP (RFX associated protein), the second subunit of RFX, derives its name from the fact that it associates with RFX5 but does not contain the characteristic DNA-binding domain of the RFX family (11). RFXAP exhibits no homology to any other human proteins. Structure-function analysis demonstrated that a glutamine-rich C-terminal region of RFXAP is essential and sufficient for its association with RFX5 and RFXANK, assembly of the RFX complex and activation of MHCII genes (20). We also defined a domain that is required for optimal expression of HLA-DP and HLA-DQ but dispensable for HLA-DR (20).

RFXANK, the smallest subunit of RFX, derives its name from the fact that it contains a domain consisting of four tandemly repeated «ankyrin» motifs (12, 21). Ankyrin repeat domains (ARD) are well-known protein-protein interaction domains found in numerous different proteins. Structure-function analysis has demonstrated that the ARD of RFXANK is essential and sufficient for assembly of the RFX complex and for activation of MHCII genes (21). Critical sub-domains mapping to four distinct surfaces of the three-dimensional structure of the ARD were defined by a series of single and clustered point mutations (21). Three of these surfaces mediate protein-protein contacts with RFXAP and RFX5. The fourth serves an unknown function required for MHCII promoter occupation by RFX and CIITA *in vivo*.

The trimeric RFX complex binds to the X box cooperatively with the X2-box-binding factor CREB and the Y-box-binding factor NF-Y (6, 7). This generates a stable multi-protein complex called the MHCII

«enhanceosome» (**Figure 2**) (22). An as yet unidentified S-box-binding factor also assembles into the enhanceosome complex (23). The well-defined architecture of the S-Y module reflects spatial constraints imposed by assembly of the enhanceosome. The enhanceosome constitutes a landing pad to which CIITA is recruited (5–7, 22). In RFX-deficient cells, enhanceosome assembly and CIITA recruitment are abolished, such that MHCII promoters remain completely unoccupied *in vivo* (7).

CIITA is a non-DNA-binding transcriptional coactivator that is recruited to the MHCII enhanceosome by means of multiple protein-protein interactions (**Figure 2**) (5–7, 22). Protein-protein contacts have been defined between CIITA and various enhanceosome components, including two subunits of RFX (RFXANK, RFX5), two subunits of NF-Y (NF-YB, NF-YC), CREB and the S-box-binding factor (5–7). These multiple contacts are believed to function synergistically to promote stable recruitment of CIITA to the MHCII enhanceosome complex.

The enhanceosome and CIITA collaborate to activate transcription of MHCII genes by promoting the establishment of histone modifications, inducing chromatin remodeling, facilitating recruitment of the general transcription machinery (GTM), activating promoter clearance by RNA polymerase II (Pol II) and stimulating transcription elongation (**Figure 2**) (5–7, 24). Most studies have suggested that these effector mechanisms are mediated mainly by CIITA. CIITA has been proposed to activate transcription by recruiting the coactivator OBF1, histone acetyltransferases (CBP, pCAF, GCN5, SRC1), histone methyltransferases (CARM1), nucleosome remodeling factors (Brg1), components of the GTM ($TF_{II}B$, $TF_{II}D$) and transcription elongation factors ($TF_{II}H$, P-TEFb) (5–7, 24). CIITA may also harbor an intrinsic acetyltransferase domain (5–7, 24). The relative importance of these different activities of CIITA remains unclear.

In contrast to CIITA, a more passive role limited to the formation of a docking surface for CIITA has generally been attributed to the enhanceosome complex. However, there is growing evidence that the functional importance of CIITA has been overemphasized whereas that of the

enhanceosome complex has been underestimated. We have now shown that several functions initially attributed to CIITA (such as the introduction of histone H3 acetylation and methylation) are in fact secondary consequences of ongoing transcription (25). We have also demonstrated that the enhanceosome makes critical CIITA-independent contributions to histone acetylation and to recruitment of the GTM and Pol II at certain MHCII promoters (*HLA-DPB and HLA-DMB*) (26). More recently, we have shown that the enhanceosome plays a critical role in inducing nucleosome eviction from MHCII promoters (27). This nucleosome eviction unmasks the transcription start site and thereby ensures that transcription is initiated at the correct position (27). Finally, RFX and the enhanceosome complex protect MHCII promoters against the establishment of epigenetic silencing by DNA methylation (28), thereby ensuring that MHCII genes remain accessible and inducible in all cell types, even in MHCII-negative cells lacking CIITA.

In addition to acting locally at MHCII promoters, the enhanceosome and CIITA also function at distant S–Y (S'–Y') modules scattered throughout the MHCII locus (29, 30). Binding of the enhanceosome and CIITA to these S'–Y' enhancers induces long-distance chromatin remodeling as evidenced by a global increase in histone acetylation (29, 30). It also induces the synthesis of intergenic transcripts of unknown function (29, 30). Both features are typical of locus control regions (LCR), which are regulatory regions exerting long-distance control over gene expression. Unpublished results have indicated that the distal S'–Y' modules engage in long-distance chromatin interactions with each other, with MHCII promoters, and/or with other regulatory sequences. Collectively, these findings suggest that the regulation of MHCII promoters by RFX and CIITA may be superimposed by global control mechanisms exerted over all or large segments of the MHCII locus by distant regulatory elements.

Target gene specificity of RFX and CIITA

The phenotype of MHCII-deficiency patients had initially suggested that CIITA and RFX are highly specific for MHCII genes. It was sub-

sequently demonstrated that these factors also regulate the expression of accessory genes required for MHCII-mediated antigen presentation, namely the Ii gene and the genes coding for the non-classical MHCII molecules HLA-DO (H-2O) and HLA-DM (H-2M) (5–7). Additional studies revealed that these factors also contribute, albeit to a lesser degree, to the expression of MHC class I (MHCI) genes (5–7). For many years, these genes remained the only well-documented targets of CIITA and RFX, and these factors were therefore believed to be highly dedicated for genes implicated in antigen presentation.

The high specificity of CIITA for genes involved in antigen presentation has been challenged by several studies suggesting that it regulates numerous other genes within and outside of the immune system, including the IL-4, FasL, Collagen α2(I), thymidine kinase, cyclin D1 and plexin A1 genes, as well as numerous genes revealed by microarray experiments performed with CIITA-deficient B-cells (reviewed in 4, 13). However, the regulation of these genes by CIITA has in most cases turned out to be indirect, relatively minor, mediated by unknown mechanisms, or controversial (4, 13). Using CIITA transgenic and knockout mice (31), as well as genome-wide bioinformatic and ChIP-chip (chromatin immunoprecipitation coupled to microarray) screens (30, 32, 33), we have notably been unable to confirm for most of the proposed target genes that they are indeed regulated directly by CIITA.

To settle the controversial issue of the target-gene specificity of CIITA we developed two genome-wide approaches designed to identify *bona-fide* new CIITA-regulated genes. First, we developed a computational approach to search the genome for the presence of new S–Y modules (30, 32). Second, we performed genome-wide ChIP-chip experiments to identify new target genes of CIITA in human B-cells and DC (33). These combined approaches demonstrated that CIITA is remarkably dedicated for the regulation of genes implicated in MHCII and MHCI mediated antigen presentation. Only very few novel target genes were identified, several of which could be implicated directly or indirectly in antigen presentation (32, 33). We have concentrated on studying the regulation of two of these genes, *RAB4B* and *BTN2A2*.

RAB4B (*Rab4b* in mice) encodes a member of the Rab family of small GTPases, which regulate intracellular vesicular-transport processes. The biological function of RAB4B/Rab4b is unknown. However, the closely related Rab4a functions in early endosome sorting and endosome recycling. Expression of a dominant negative variant of Rab4a in B-cells was found to interfere with receptor-mediated antigen-processing and MHCII-mediated antigen presentation. We have confirmed that *RAB4B* expression is indeed regulated by both RFX and CIITA in human B- cells, DC and IFNγ-induced cells (32).

The *BTN2A2* gene (*Btn2a2* in mice) encodes a member of a family of cell-surface proteins sharing homology to butyrophilin (BTN). BTN is required for regulated secretion of milk-lipid droplets. The functions of BTN-like proteins remain largely unknown. However, they are homologous to the B7 family of immunoregulatory proteins, and there is growing evidence that they have key functions in the immune system. We have discovered that the *BTN2A2/Btn2* gene is tightly coregulated with MHCII genes by RFX and CIITA in human and mouse B-cells, DC, IFNγ-induced cells and TEC (unpublished data), raising the exciting possibility that BTN2A2/Btn2a2 may serve a key immunoregulatory function associated with MHCII-mediated antigen presentation.

Regulation of CIITA expression

Whereas RFX and the other enhanceosome factors exhibit widespread expression in most cell types, the expression of CIITA is tightly regulated in a cell-type specific and inducible manner (4–7, 13). It is therefore the expression pattern of the gene encoding CIITA that determines the cell-type specificity and level of MHCII expression. We have made major contributions to our current understanding of this pivotal function of CIITA as the master regulator of MHCII genes.

Expression of the human *CIITA* gene is directed by four independent promoters – called pI, pII, pIII, and pIV – which precede four alternative first exons (**Figure 3**) (4-7, 13). Three of these promoters – pI, pIII and pIV – are conserved in the mouse *CIIta* gene (**Figure 3**) (4–7, 13).

The three conserved *CIITA/CIIta* promoters differ in their cell type specificity and response to IFNγ (4–7, 13). It is thus the differential activity of the *CIITA/CIIta* promoters that ultimately determines the cell type specificity and inducibility of MHCII gene expression (4–7, 13).

The functions of the *CIITA/CIIta* promoters have been defined by examining their usage in cell lines and key primary human and mouse cell types, by mapping regulatory elements using *in vivo* footprint experiments, transcription factor binding studies and functional assays, and by generating knockout mice in which the promoters were excised singly or in combination (4–7, 13). We notably constructed mice lacking pI (pI$^{-/-}$ mice, unpublished data), pIV (pIV$^{-/-}$ mice) (34, 35), and both pIII and pIV (pIII+IV$^{-/-}$ mice) (36). Collectively, these and other studies have generated a precise picture of the function and specificity of the three *CIITA/CIIta* promoters (**Figure 3**) (4–7, 13).

Promoter pIV is essential for driving CIITA and MHCII expression in cTEC and in IFNγ induced cells of non-hematopoietic origin (**Figure 3**) (34, 35). Activation in cTEC is a pivotal function of pIV because MHCII expression by cTEC is essential for driving positive selection of CD4$^+$ thymocytes. Positive selection of CD4$^+$ thymocytes is completely abolished in pIV$^{-/-}$ mice (34, 35). The IFNγ-induced activity of pIV is targeted by several signals that inhibit the expression of MHCII genes (**Figure 3**) (4–7, 13). The repression of MHCII induction in trophoblasts is due to silencing of pIV. Anti-inflammatory cytokines capable of inhibiting IFNγ-induced MHCII expression – such as TGFβ, IL4 and IL10 – achieve this by inhibiting the activation of pIV.

pIII is the major promoter used in B-cells (**Figure 3**) (36). Silencing of pIII following B-cell-activation is responsible for the extinction of MHCII expression in plasma cells (**Figure 3**) (4-7, 13). pIII is also essential for driving CIITA and MHCII expression in a unique DC subtype called plasmacytoid DC (pDC) (**Figure 3**) (36). This recently allowed us to exploit our pIII+IV$^{-/-}$ mice to demonstrate that MHCII-mediated antigen presentation by pDC induces the development of Treg conferring protection against the development of experimental autoim-

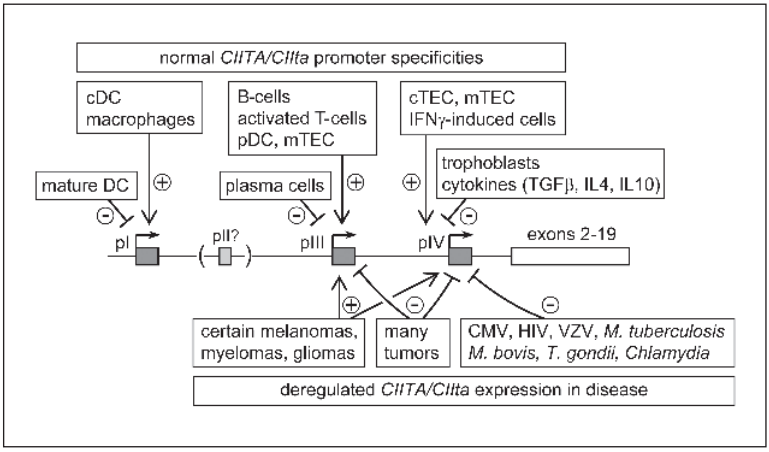

Figure 3. *Regulation of CIITA expression. Transcription of the human* ***CIITA*** *gene is controlled by four independent promoters (pI, pII, pIII, and pIV) preceding four alternative first exons (grey boxes). Three of these promoters (pI, pIII and pIV) are conserved in the mouse* ***CIIta*** *gene. The three conserved promoters exhibit well-defined cell-type specificities and responsiveness to IFNγ. The function of pII is not known. Promoter pI is active mainly in macrophages and conventional dendritic cells (cDC). Promoter pIII is active in B-cells, activated human T-cells, plasmacytoid dendritic cells (pDC) and medullar thymic epithelial cells (mTEC). Promoter pIV is active in both cortical and medullar thymic epithelial cells (cTEC, mTEC), and is induced by IFNγ in cells of non-hematopoietic origin. Promoters pI, pIII and pIV are silenced in mature DC, plasma cells, and trophobasts, respectively. Activation of pIV is inhibited by certain anti-inflammatory cytokines. Aberrant activation or silencing of pIII and pIV is observed in various tumors and infectious diseases.*

mune encephalomyelitis (EAE) (unpublished data), which is an autoimmune disease of the central nervous system (CNS) that is widely studied as an animal model for multiple sclerosis.

Promoter pI mediates CIITA and MHCII expression in macrophages and all conventional DC (cDC) subsets examined, including human monocyte-derived DC (MoDC), mouse bone-marrow-derived DC (BmDC), epidermal Langerhans cells, and splenic, lymph node and thymic cDC (**Figure 3**) (36). This has allowed us to exploit our $pI^{-/-}$ mice to demonstrate that the effector phase of EAE in the CNS is sup-

ported by collaboration between MHCII-mediated antigen presentation by blood-derived APC (cDC, macrophages) and CNS-derived APC (microglia, microglia-derived DC) (unpublished data).

Transcription of the *CIITA/CIIta* gene is silenced during the maturation of all cDC subsets studied (human MoDC, mouse BmDC, splenic DC) (**Figure 3**) (37). This silencing process is triggered by a wide range of stimuli, including lipopolysacharide (LPS), tumor necrosis factor α (TNFα, CD40 ligand (CD40L), interferon α (IFNα), bacterial and viral infections (37). Silencing is essentially complete within 1 hour, and is mediated by a global repression mechanism implicating histone deacetylation over a large domain spanning the entire regulatory region of the *CIITA* gene (unpublished data). We have recently performed a genome-wide ChIP-chip analysis of histone deacetylation induced in human MoDC by a brief 1 hour exposure to LPS. The results of this analysis suggest that the rapid epigenetic silencing mechanism we have documented for *CIITA* also impinges on numerous other genes in cDC, and is thus likely to have widespread importance for the cDC maturation process (unpublished data).

In contrast to cTEC, mTEC rely on both pIII and pIV for driving CIITA and MHCII expression (**Figure 3**) (38). This difference between cTEC and mTEC with respect to *CIIta* promoter usage has recently allowed us to exploit our pIII+IV$^{-/-}$ mice, in combination with a series of other transgenic and knockout mouse models, to demonstrate that MHCII expression by mTEC is required for the generation of mature mTEC (38). Briefly, we discovered that the development of wild type numbers of mature mTEC is dependent on TCR/MHCII-mediated interactions between thymocytes carrying autoreactive TCR and mTEC displaying the cognate self-antigens in the context of MHCII molecules (38). Mature mTEC play pivotal roles in the establishment and maintenance of T-cell tolerance because they are implicated in both the deletion of autoreactive thymocytes and the development of tolerizing Treg cells. The role of autoreactive CD4^{+} thymocytes and their interactions with MHCII-positive mTEC in the development and function of the thymic medulla are therefore being pursued actively.

Finally, it is becoming increasingly evident that deregulation of the *CIITA* promoters is associated with diseases (**Figure 3**) (reviewed in 4, 13). Both silencing and aberrant activation of promoters pIII and pIV have been associated with various types of tumors (4, 13). Furthermore, a variety of pathogens have developed the ability to inhibit IFNγ-induced activation of pIV expression – and thus MHCII expression – as a strategy to evade recognition by the immune system (4, 13). Notable examples include CMV, HIV, varicella-zoster virus, *Mycobacterium bovis, Mycobacterium tuberculosis, Toxoplasma gondii*, and *Chlamydia*. Finally, there is growing evidence that polymorphisms in the promoters of the *CIITA* gene could be associated with autoimmune and inflammatory diseases.

Conclusions and Perspectives

A great deal has been learned about the molecular machinery that regulates the expression of MHCII genes. However, this progress has also uncovered numerous unresolved issues and paved the way for challenging new avenues of research. The following are among the key questions that remain to be addressed by future work. Is the regulation of MHCII promoters by RFX and CIITA superimposed by global control mechanisms exerted over all or large segments of the MHCII locus? Do these global regulatory mechanisms involve a three-dimensional structure established by long-distance chromatin interactions? What is the nature and specificity of the regulatory mechanisms that impinge on the CIITA gene in key APC such as DC? Are the mechanisms that trigger rapid silencing of the *CIITA* gene in DC of more widespread importance for the maturation process, and what functions or pathways do these mechanisms regulate? Do the newly identified target genes of RFX and CIITA contribute to APC function and/or other functions in the immune system? How is the immune system perturbed by selective abrogation of CIITA expression in key cell types, such as mTEC? How does deregulated *CIITA* promoter function contribute to the development off disease? Addressing such questions will continue to be a major objective of our future work, because we hope that the information that will be gained will further our comprehension of the importance of

correctly regulated MHCII-expression for appropriate functioning of the immune system in healthy individuals, and will shed new light on the mechanisms and pathological consequences of deregulated MHCII expression during the course of diseases such as cancer, autoimmune pathologies and infectious diseases.

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Due to lack of space I have restricted myself mainly to citing suitable comprehensive reviews on the subject of MHC class II gene regulation, and key original research papers from my own laboratory. This by no means denotes a lack of acknowledgement on my part of the large number of significant contributions made by other research groups. I sincerely apologize for being unable to cite their work and encourage the reader to examine the original literature referred to in the review articles cited here.

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