Preisverleihung 2016

STIFTUNG PROFESSOR DR. MAX CLOËTTA

Heft Nr. 44

Prof. Dr. Andreas Lüthi

«The Neuronal Circuitry of Fear and Anxiety»

Prof. Dr. Michel Gilliet

«Role of Innate Immunity in Driving Inflammation: Lessons Learned From the Skin»

STIFTUNG
PROFESSOR DR. MAX CLOËTTA

dreiundvierzigste Preisverleihung

4. November 2016
Basel

Heft Nr. 44 der Schriftenreihe

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VORWORT

Prof. Dr. med. Adriano Fontana

Mit **Prof. Dr. Andreas Lüthi** würdigt die Stiftung Professor Dr. Max Cloëtta einen Neurowissenschaftler, welcher durch seine Studien das Gebiet der Angstforschung auf neue Grundlagen gestellt hat. Insbesondere gelang es ihm, zu zeigen, dass definierte neuronale Netzwerke in der Amygdala im Temporallappen des Gehirns essenziell sind, um gelernte Erinnerungen an Ängste zu kontrollieren.

Der zweite Preisträger ist **Prof. Dr. Michel Gilliet,** der neue Mechanismen der Immunantwort in der Haut identifizierte, um diese in Zusammenhang mit dem Zustandekommen von Autoimmunkrankheiten wie der Psoriasis zu bringen.

Ausgezeichnet werden zwei Wissenschaftler, welche kraft ihres Scharfsinnes, Ideenreichtums und hervorragenden «Projektmanagements» erfolgreich neue Wege in der Krankheitsforschung eingeschlagen haben.

Fortschritte in der Krankheitsforschung basieren mitunter auf neuen technischen Errungenschaften wie beispielsweise den bildgebenden Verfahren der Positronen-Emissions-Tomographie (PET), der Magnetresonanz-Tomographie (MRT) oder den neuen molekularbiologischen Methoden zur Genanalyse. Technische Durchbrüche sind unerlässlich, um neue Wege in den Naturwissenschaften und in der Krankheitsforschung einzuschlagen. Und doch bleiben im Zentrum der Mensch, der/die Forscher/in und die naturwissenschaftliche Denkweise. Freudiges Beobachten und Experimentieren, Ordnen und Hinterfragen neuer Befunde bleiben die Grundlagen erfolgreicher Forschung.

Die mit dem Preis der Stiftung Professor Dr. Max Cloëtta ausgezeichneten Forscher profitieren von ihren akademischen Einrichtungen – das Friedrich Miescher Institut in Basel und das Universitätsspital Lausanne –, welche mit beträchtlichen finanziellen Mitteln die für die Forschung notwendigen Technologieplattformen aufbauen und den akademischen Betrieb steuern. So muss es ein vordringliches Ziel sein, auch in Zeiten finanzieller Knappheit den Forschungsstandort Schweiz weiter voranzutreiben.

Mit der Verleihung des Cloëtta-Preises werden die Leistungen von Prof. Dr. Andreas Lüthi und Prof. Dr. Michel Gilliet gewürdigt. Die Stiftung Prof. Dr. Max Cloëtta freut sich, die Preisträger am 4. November 2016 in Basel zu feiern.

Brigitt Küttel
Geschäftsführerin

Stiftungsrat

Die Errichtung der Stiftung Prof. Dr. Max Cloëtta wurde am 27. September 1973 öffentlich beurkundet und am 12. November des gleichen Jahres im Handelsregister des Kantons Zürich eingetragen. Der Stifter Antoine Cloëtta berief vier Personen in den ersten Stiftungsrat: Jean-Antoine Cramer, Bank Cramer & Cie. in Genf, Dr. Alfred Hartmann, Vizepräsident und Delegierter des Verwaltungsrates der F. Hoffmann-La Roche & Co. AG in Basel, Dr. Hans W. Kopp, Rechtsanwalt in Zürich, und Prof. Alexis Labhart, Professor für Pathologie, Endokrinologie und Stoffwechsel in Zürich. Erst vor Kurzem haben wir erfahren, dass mit Jean-Antoine Cramer, der von 1973 bis 2010 in der Stiftung aktiv war, am 23. Oktober 2014 auch das letzte der Gründungsmitglieder verstorben ist. Zu sagen, dass die Stiftung nun definitiv erwachsen geworden sei, wäre unangemessen. Aber wir werden den vier Herren, die sie geprägt haben, ein ehrendes Andenken bewahren.

Über die Jahre haben verschiedene Persönlichkeiten die Stiftung getragen und weiterentwickelt. 2016 dürfen wir Prof. Fritjof Helmchen vom Institut für Hirnforschung an der Universität Zürich und Träger des Cloëtta-Preises 2015 im Stiftungsrat begrüssen. Wir freuen uns auf die Zusammenarbeit!

Cloëtta-Preis

Auch dieses Jahr dürfen wir wieder zwei herausragende Forscher mit dem Cloëtta-Preis auszeichnen. Für Prof. Andreas Lüthi ist die Preisverleihung an der Universität Basel, wo wir nach 2013 zum zweiten Mal zu Gast sein dürfen, quasi ein Heimspiel. Prof. Michel Gilliet forscht in Lausanne. Unser herzlicher Dank gilt den Verantwortlichen der Universität Basel und ihrer Vertreterin in unserem Stiftungsrat, Prof. Dr. Daniela Finke, für ihre grosse Unterstützung.

Schriftenreihe als e-Papers

Seit ihrer Errichtung publiziert die Stiftung Prof. Dr. Max Cloëtta jedes Jahr anlässlich der Preisverleihung eine Broschüre mit Beiträgen der Preisträger. In mehr als 40 Jahren ist so eine spannende Sammlung von Forschungsberichten entstanden, die auch medizinhistorisch von Bedeutung ist. Seit 2015 stehen alle Ausgaben der Cloëtta-Schriftenreihe auf der Website einem breiteren Publikum zur Verfügung.

Forschungsstellen

Das Forschungsstellenprogramm der Stiftung Prof. Dr. Max Cloëtta ist für den akademischen Mittelbau in der Schweiz von grosser Bedeutung. Finanziert werden Stellen an schweizerischen Hochschulen, Kliniken oder Instituten für bereits ausgebildete und selbstständig arbeitende Forscherinnen und Forscher bis max. 40 Jahre. Mit diesem Programm will die Stiftung einem Mangel an Forschernachwuchs in der Schweiz entgegenwirken und den Stelleninhabern helfen, die manchmal nicht einfache Phase bis zur Berufung auf eine ordentliche Professur zu überbrücken. Die Stipendien werden alle zwei Jahre vergeben. 2016 sind 28 Gesuche eingetroffen, deren Evaluation bis Februar 2017 läuft.

2016 finanzierte die Stiftung Prof. Dr. Max Cloëtta folgende Forscher an Schweizer Universitäten mit fünfjährigen Grants:

Dr. Rajesh Jayachandran, 1977, Biozentrum der Universität Basel. Projekt: Role for Coronin 1 signaling in the development of autoimmunity and T cell mediated disorders. Unterstützungsdauer 1.7.2011–30.6.2016.

Dr. Mathias Hauri-Hohl, 1975, Universitäts-Kinderspital Zürich, Abteilung Stammzellentransplantation. Projekt: Improving T-Cell Reconstitution and Enhancing Central Tolerance Mechanism in Hematopoietic Stem Cell Transplantation. Unterstützungsdauer: 1.1.2016–31.12.2020

Dr. Alexandre Theocharides, 1975, Universitätsspital Zürich, Klinik für Hämatologie. Projekt: The Role of Cell-Extrinsic Factors in Hematopoietic Stem Cell Malignancies. Unterstützungsdauer: 1.6.2015–31.5.2020

Dr. Wei Lynn Wong, 1976, Universität Zürich, Institut für experimentelle Immunologie. Projekt: The Role of IAPs and RIPKs in Hematopoiesis and Disease, Specifically in Tumor Formation and Metastasis. Unterstützungsdauer: 1.1.2016–31.12.2020

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta in Zusammenarbeit mit der Uniscientia Stiftung, Vaduz, Stipendien «Klinische Medizin Plus». Medizinerinnen und Medizinern werden während oder unmittelbar nach Abschluss der Facharztausbildung Stipendien von drei bis maximal zwölf Monaten für die Absolvierung einer Spezialausbildung an einer renommierten, vornehmlich ausländischen Institution ausgerichtet. Die Uniscientia Stiftung finanziert das Programm, die Stiftung Prof. Dr. Max Cloëtta ist verantwortlich für den wissenschaftlichen Teil. Ende 2015 wurde der Vertrag über diese erfolgreiche Zusammenarbeit um weitere drei Jahre bis und mit 2018 verlängert.

2016 kommen folgende Medizinerinnen und Mediziner in den Genuss eines Stipendiums (Unterstützung läuft oder wurde 2016 zugesprochen):

Dr. med. Florence Hoogewoud, 1986, Resident in ophthalmology, Geneva University Hospital. Intensive training in the uveitis subspecialty and in medical retina. Guest Institution: Hôpital Cochin-Uvéites and Hôpital Lariboisière-Rétine, Paris, FR, 1.6.2015–31.5.2016

Dr. med. Christian Schürch, 1983, Resident, Institute of Pathology, University of Berne, Associate Postdoc, Tumour Immunology, Department of Clinical Research. 1) Special training in hematopathology and Research Project. Guest Institution: Eberhard-Karl's University, Institute of Pathology, Tübingen, DE, 1.8.2015–31.7.2016

Dr. med. Petra Sabine Zimmermann, 1982, Fellow in Paediatric Infectious Disease, University Children's Hospital Berne. Training in Paediatric Infectious Diseases. Guest Institution: Royal Children's Hospital Melbourne, AU, 1.9.2015–30.10.2016

Zusammen mit dem Team der Geschäftsstelle freue ich mich, die Stiftung Prof. Dr. Max Cloëtta auch weiterhin in eine aktive Zukunft für die Förderung der medizinischen Forschung in der Schweiz begleiten zu dürfen. Dem Stiftungsrat, der Uniscientia Stiftung, unseren Stipendiatinnen und Stipendiaten und den medizinischen Fakultäten danken wir herzlich für die jederzeit sehr angenehme Zusammenarbeit.

THE CLOËTTA PRIZE 2016
IS AWARDED TO

PROFESSOR

ANDREAS LÜTHI

BORN IN 1968 IN BASEL, SWITZERLAND
SENIOR GROUP LEADER AT THE FRIEDRICH MIESCHER INSTITUTE
FOR BIOMEDICAL RESEARCH AND
TITULAR PROFESSOR AT THE UNIVERSITY OF BASEL

FOR HIS OUTSTANDING FINDINGS ABOUT UNDERSTANDING
LEARNING PROCESSES IN THE BRAIN

Basel, 4th November 2016

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT | MEMBER | THE VICE PRESIDENT

Andreas Lüthi

BIOGRAPHY

Name:	Lüthi, Andreas
Date of Birth:	17th November 1968
Place of Birth:	Basel, Switzerland
Citizenship:	Swiss

Education

1988–1992 M.Sc. in Biology	University of Basel, Switzerland
1993–1996 Ph.D. in Neurobiology	University of Basel, Switzerland

Employment

1996–1998	Postdoctoral Fellow	Department of Anatomy, University of Bristol, UK
1998–2000	Postdoctoral Fellow	Brain Research Institute, University of Zurich, Switzerland
2000–2003	Assistant Professor	Department of Pharmacology/Neurobiology, Biozentrum, University of Basel, Switzerland
2003–2004	Junior Group Leader	Friedrich Miescher Institute, Basel, Switzerland
2004–	Group Leader	Friedrich Miescher Institute, Basel; Titular Professor, University of Basel, Switzerland

Andreas Lüthi has since 2003 been Group Leader at the Friedrich Miescher Institute for Biomedical Research in Basel and since 2006 Titular Professor at the University of Basel. Born in 1968 in Basel, he studied Biology in Basel and received his PhD in Neuroscience in 1996 working on the synaptic mechanisms of hippocampal long-term potentiation. After postdoctoral fellowships with Graham L. Collingridge at the University of Bristol, UK and Beat H. Gähwiler at the University of Zurich, Switzerland, he established his own group as a Junior PI, first at the University of Basel and then at the Friedrich Miescher Institute for Biomedical Research, where he currently is a Senior Group Leader. Andreas Lüthi received several awards including the Pfizer Research Prize 2006 (with Y. Humeau), the Betty and David Koetser Award for Brain Research in 2009 and most recently an ERC advanced grant. He is a member of EMBO and of the National Research Council of the Swiss National Science Foundation. His research is focusing on the cellular and circuit mechanisms underlying associative learning using a multi-disciplinary approach to study classical conditioning paradigms in mice.

Honors and Fellowships

Swiss National Science Foundation/ EU Fellowship – 1996; EMBO Long-Term Fellowship – 1996; Borderline Personality Disorder Research Foundation, Junior Investigator Award – 2003; Swiss National Science Foundation, Professorship – 2003; Titular Professor, University of Basel – 2006; Pfizer Research Prize, Neuroscience – 2006; NARSAD Independent Investigator Award – 2008; Betty and David Koetser Award for Brain Research – 2009; Annual Meeting of the American Society for Neuroscience, Special Lecture – 2011; EMBO Member – 2012; ERC Advanced Grant – 2015; FENS Meeting Copenhagen, Plenary Lecture – 2016; Cloëtta Prize – 2016.

SELECTED PUBLICATIONS

1. Tovote P, Esposito MS, Botta P, Chaudun F, Fadok JP, Markovic M, Wolff SBE, Ramakrishnan C, Fenno L, Deisseroth K, Herry C, Arber S, Lüthi A (2016) Midbrain circuits for defensive behavior. ***Nature*** 534: 206–212.

2. Wolff SBE, Gründemann J, Tovote P, Krabbe S, Jacobson GA, Xu C, Müller C, Herry C, Ehrlich I, Friedrich RW, Letzkus JJ, Lüthi A. (2014) Amygdala interneuron subtypes control fear learning through disinhibition. ***Nature*** 509:453–458.

3. Senn V, Wolff SBE, Herry C, Grenier F, Ehrlich I, Gründemann J, Fadok JP, Müller C, Letzkus JJ, Lüthi A (2014) Long-range connectivity defines behavioral specificity of amygdala neurons. ***Neuron*** 81: 428–437.

4. Letzkus JJ, Wolff SBE, Meyer EMM, Tovote P, Courtin J, Herry C, Lüthi A (2011) A disinhibitory microcircuit for associative fear learning in auditory cortex. ***Nature*** 480: 331–335.

5. Ciocchi S, Herry C, Grenier F, Wolff SBE, Letzkus, JJ, Vlachos I, Ehrlich I, Sprengel R, Deisseroth K, Stadler M, Müller C, Lüthi A (2010) Encoding of conditioned fear in central amygdala inhibitory circuits. ***Nature*** 468: 277–282.

6. Herry C, Ciocchi S, Senn V, Demmou L, Müller C, Lüthi A (2008) Switching on and off fear by distinct neuronal circuits. ***Nature*** 454:600–606.

7. Humeau Y, Shaban H, Bissière S, Lüthi A (2003) Presynaptic induction of heterosynaptic associative LTP in the mammalian brain. ***Nature*** 426: 841–845.

8. Lüthi A, Schwyzer L, Mateos JM, Gähwiler BH, McKinney RA (2001) NMDA receptor activation limits the number of synaptic connections during hippocampal development. ***Nature*** Neurosci 4: 1102–1107.

9. Lüthi A, Chittajallu R, Duprat F, Palmer MJ, Benke TA, Kidd FL, Henley JM, Isaac JTR, Collingridge GL (1999) Hippocampal LTD expression involves a pool of AMPARs regulated by the NSF-GluR2 interaction. ***Neuron*** 24: 389–399.

10. Lüthi A, Laurent JP, Figurov A, Muller D, Schachner M (1994) Hippocampal long-term potentiation and neural cell adhesion molecules L1 and NCAM. ***Nature*** 372: 777–779.

THE NEURONAL CIRCUITRY OF FEAR AND ANXIETY

Andreas Lüthi

Summary

Mood and anxiety disorders are the greatest societal burdens in terms of impairment and disability. However, the neurobiological mechanisms underlying the etiology and pathophysiology of mental disorders is poorly understood. It emerges that maladaptive neuronal plasticity caused by environmental and genetic factors can give rise to pathological neuronal circuit function, and that this process is key for the progression and manifestation of mental diseases.

To investigate the basic underlying circuit mechanisms, we are using classical Pavlovian fear conditioning (FC), a simple and robust form of learning, in which an animal learns to associate an initially neutral stimulus with an aversive outcome. A large number of studies in animals and humans have identified the amygdala as a key structure embedded in a brain-wide neuronal network mediating fear conditioning. Using a multidisciplinary approach in mice, we investigate the anatomical and functional logic of amygdala circuits, and their interactions with other brain areas during the formation, expression and extinction of learned fear in animal models for physiological and pathological fear and anxiety.

Our research shows that functionally, anatomically and genetically defined types of amygdala neurons are precisely connected both within local and within larger-scale neuronal networks, and that they selectively contribute to specific aspects of fear learning, expression and extinction of conditioned fear responses. Understanding the neuronal circuitry and the plasticity mechanisms underlying these processes will be fundamental not only for an understanding of memory processes in the brain in general, but also to inform new therapeutic strategies for psychiatric disorders involving dysregulated emotional responses associated with amygdala hyper- or hyposensitivity such as anxiety disorders or major depression.

Introduction

Fear and anxiety are emotional states that are crucial for eliciting appropriate defensive reactions in order to avoid harm and to ensure survival in threatening situations. However, in humans, excessive fear or chronic anxiety are core symptoms associated with severe mental diseases. The World Health Organization (WHO) has calculated that mental disorders are the greatest societal burdens in terms of impairment and disability (Murray et al., 1996). In particular, anxiety disorders and major depression are the most costly diseases among people in the middle years of life. These diseases thus represent one of the greatest preventive and therapeutic challenges in medicine. To meet these challenges, there is an urgent need for a better understanding of the underlying neurobiology.

Over the past decades, research on humans and on animal models has revealed that the neurobiological basis of anxiety disorders, and other mental diseases such as major depression or addiction, is not primarily based on neuronal degeneration and death, but rather on maladaptive functional and structural changes in the underlying neuronal circuits, e.g. a form of pathological learning (Lüthi & Lüscher, 2015). Most of what we know about the basic neurobiological mechanisms governing physiological and pathological forms of learning in the context of fear and anxiety originates from studies on classical fear conditioning (FC), a simple and robust form of associative learning, in which a human subject or an animal learns that an initially neutral sensory stimulus, the so-called conditioned stimulus (CS), predicts an unpleasant or aversive stimulus, the unconditioned stimulus (US).

Over the past decades, a large number of studies in animals and humans have identified the amygdala, a complex of multiple subcortical nuclei located in the temporal lobe, as a key structure embedded in a brain-wide neuronal network mediating fear conditioning (LeDoux, 2000; Davis, 2000; Fanselow and Poulos, 2005). Information about the CS and the US converge in the lateral nucleus of the amygdala (LA), which together with the basal (BA) and basomedial (BMA) nuclei, comprises the basolateral complex (BLA). Information then generally flows from the LA to the BA, which is strongly interconnected with other forebrain areas, including the medial prefrontal cortex (mPFC), the hippocampus (HC) and the

nucleus accumbens (NAc). The central nucleus of the amygdala (CEA) integrates information from the BLA and cortex to generate a complex fear response via its projections to downstream targets in the brainstem and hypothalamus. At the mechanistic level, an essential first step during the formation of CS-US associations involves activity-dependent synaptic plasticity. There is strong evidence supporting a role for NMDA receptor-dependent long-term potentiation (LTP) at glutamatergic sensory afferents to LA principal neurons (PNs)(LeDoux, 2000; Paré and Pape, 2010).

However, in contrast to the well-understood contributions of different brain areas to Pavlovian fear conditioning, and detailed knowledge on the basic mechanisms of synaptic plasticity in these brain areas, there is a big gap in our understanding of how these events relate to processing at the level of defined neuronal circuits during learning and memory.

A key feature of neuronal circuits is that they are composed of a multitude of excitatory and inhibitory neuron types. While the most of insights into the mechanisms and consequences of classical fear conditioning have been obtained from excitatory projection neurons, much less is known about the contribution of inhibitory interneurons to the processing of sensory information and to plasticity in amygdala circuits.

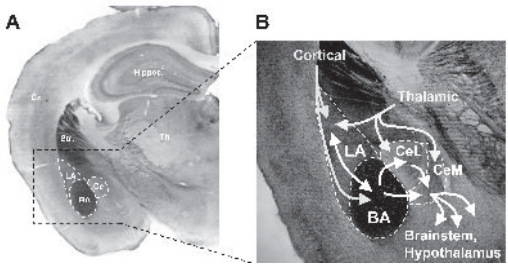

Fig. 1: Basic neuronal circuitry of the amygdala. A. *Coronal slice of a mouse brain stained for acetylcholinesterase illustrating location of the amygdala.* ***B.*** *The neural circuitry underlying classical auditory fear conditioning. Acoustic and somatosensory stimuli reach the lateral nucleus (LA) via thalamic and cortical afferents. Thalamic afferents also project to the central nucleus (CeL, CeM). By projections to brainstem and hypothalamus, the CeM initiates behavioral responses. Abbr.: LA: lateral amygdala; BA: basal amygdala; CeL: central lateral amygdala; CeM: central medial amygdala; Cx: Cortex; Str: Striatum.*

Neuronal mechanisms of fear learning: a role for inhibitory interneurons

The BLA is a cortex-like structure that contains glutamatergic principal (projection) neurons and local circuit GABAergic interneurons. Principal neurons account for the majority of the BLA neuronal population, their morphological features resemble cortical pyramidal neurons (Sah et al., 2003). As in the neocortex, a broad diversity of local GABAergic interneurons has been identified in the BLA. They can be subdivided based on molecular markers, electrophysiological properties, morphology and postsynaptic innervation pattern (McDonald & Mascagni, 2001). Interneurons constitute only about 20 % of the neuronal population, but tightly control pyramidal cell activity by releasing GABA onto principal neurons in a temporally and spatially distinct manner, thereby preventing neurons from firing to irrelevant stimuli (Klausberger & Somogyi, 2008; Ehrlich et al., 2009; Bienvenu et al., 2012). However, how each individual subtype of BLA interneurons contributes to sensory processing and fear learning is just beginning to be elucidated.

In our early work on the mechanisms of synaptic plasticity in the LA, we have addressed the impact of inhibitory transmission on the induction and specificity of LTP at thalamic and cortical inputs onto LA projection neurons. We could show that the synapses made by thalamic and cortical afferents are morphologically and functionally very different, even though they contact the same postsynaptic dendrites (Humeau et al., 2003, 2005). In particular, we found that thalamic and cortical afferent synapses exhibit input specific LTP mediated by distinct mechanisms. Whereas LTP at cortical afferents is mediated by presynaptic mechanisms involving the activation of presynaptic NMDA receptors (Humeau et al., 2003), the cAMP/PKA pathway, and the presynaptic active zone protein RIM1α (Fourcaudot et al., 2006), LTP at thalamic afferents is induced postsynaptically and requires activation of R-type voltage-dependent Ca^{2+} channels (R-VDCCs)(Humeau et al., 2005). Importantly, these pre- and postsynaptic forms of LTP at thalamic and cortical afferents to the LA are tightly controlled by local inhibition. Neuromodulators that are released in the amygdala upon stress gate induction of plasticity by transiently suppressing pre- or postsynaptic inhibition (Bissière et al., 2003; Lorétan et al., 2004; Shaban et al., 2006). Moreover, presynaptic inhibition in par-

ticular appears to play a major role to prevent generalization of amygdala LTP and conditioned fear, one of the hallmarks of anxiety disorders.

More recently, we have used a multidisciplinary analysis to identify key circuit elements underlying fear learning *in vivo.* We have obtained converging evidence that dis-inhibitory mechanisms play an important role in fear learning in multiple brain areas including the BLA and auditory cortex (Letzkus et al., 2011; Wolff et al., 2014).

Using a combination of *in vivo* single unit recordings and optogenetic manipulations, we found that in the BLA, parvalbumin (PV) and somatostatin (SOM) expressing interneurons bidirectionally control the acquisition of fear conditioning through two distinct disinhibitory mechanisms (Wolff et al., 2014). During the auditory CS, PV^+ interneurons are excited and indirectly disinhibit the dendrites of BLA principal neurons via SOM^+ interneurons, thereby enhancing auditory responses and promoting CS-US associations. During the aversive US, however, both PV^+ and SOM^+ interneurons are inhibited, which boosts postsynaptic US responses and gates plasticity and learning. These findings demonstrate that associative learning is dynamically regulated by the stimulus-specific activation of distinct disinhibitory microcircuits through precise interactions between different subtypes of local interneurons.

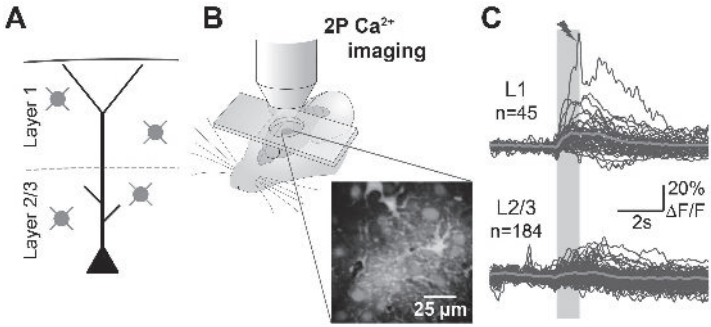

Fig. 2: Somatosensory responses in auditory cortex L1 interneurons A: *Cytoarchitecture of upper layers of auditory cortex (interneurons grey, pyramidal neuron black).* ***B:*** *2-photon calcium imaging in anesthetized mice using the membrane permeant dye OGB-1 AM (green). Glial cells were counterstained with sulforhodamine 101 (red).* ***C:*** *Responses in L1 and L2/3 to hindpaw stimulation in single neurons. Layer 1 interneurons display much stronger activation than layer 2/3 neurons.*

Disinhibition emerges as a general mechanism of aversive learning that is not limited to the BLA. Recordings in auditory cortex revealed that US stimulation elicits strong, time-locked firing in layer 1 interneurons. This response was mediated by rapid acetylcholine release from basal forebrain afferents activating nicotinic receptors on these interneurons. Firing of layer 1 interneurons in turn caused an inhibition of fast-spiking PV+ basket cells in layer 2/3 leading to disinhibition of layer2/3 pyramidal neurons and to a marked increase in the neuronal responses to concomitantly presented auditory CSs (Letzkus et al., 2011). Optogenetic interference with these processes led to a strong deficit in fear learning, indicating that disinhibition in auditory cortex is required for fear learning possibly by gating plasticity at afferent synapses or in downstream areas such as the BLA.

Circuit mechanisms underlying the expression and selection of fear behavior

In addition to acquisition, disinhibition also plays an important role in fear memory expression. One example is the control of fear expression by the central amygdala, a striatum-like nucleus composed mainly of GABAergic neurons. It can be subdivided into a lateral (CEl) and medial (CEm) part (McDonald, 1982), the latter being one of the main output pathways of the amygdala to downstream areas involved in fear responses (Ehrlich et al., 2009). Neurons in CEl project to CEm (Ehrlich et al., 2009), suggesting that amygdala output is under tight inhibitory control from CEl. In line with this scenario, we found that pharmacological inactivation of CEl causes unconditioned freezing (Ciocchi et al., 2010), as did pharmacogenetic inhibition of a population of CEl neurons expressing PKC delta (Haubensak et al., 2010). Conversely, optogenetic activation of CEm neurons causes unconditioned freezing (Ciocchi et al. 2010). While the central amygdala was previously thought to be mainly involved in the behavioral expression of fear memory residing in the BLA, several lines of evidence suggest that the central amygdala is also a critical site for plastic changes during fear learning (Ciocchi et al., 2010). First, activity in CEl was required for fear memory acquisition, whereas memory expression was selectively impaired by CEm inactivation. Moreover, fear conditioning caused plastic changes in CS respons-

es of different central amygdala neurons. In the CEl, one population of neurons acquired an excitatory response (CEl_{on} neurons), whereas an equal number of cells displayed inhibitory responses to the conditioned tone (CEl_{off} neurons) **(Fig. 3)**. CEl_{off} neurons correspond to $PKC\delta^{+}$ positive cells (Haubensak et al., 2010), and their inhibitory response to the conditioned tone likely mediates dis-inhibition of CEm output neurons, which in turn elicits conditioned freezing.

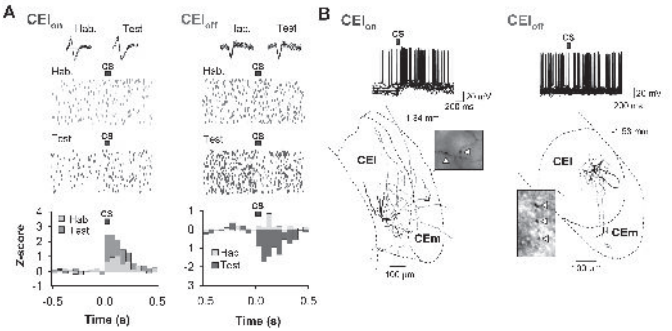

Fig. 3. Fear conditioning induces cell type specific plasticity in CEl circuits. A: *Extracellular single unit recordings in the central amygdala of behaving mice reveals two distinct sub-populations of CEl units showing an increase (CEl_{on} neurons) or a decrease (CEl_{off} neurons) in CS-evoked firing after fear conditioning.* ***B:*** *Intracellular recordings from CEl on and CEl_{off} neurons in anaesthetized mice. Anatomical reconstructions of recorded neurons demonstrates that both CEl_{on} and CEl_{off} neurons send axon collaterals to CEm, the output nucleus of the amygdala. Modified from Ciocchi et al., 2010.*

Generalization of conditioned fear responses can be desirable if expressed under the appropriate circumstances. Understanding these processes is critical not only for the identification of neuronal processes that specifically relate to associative fear learning, but also for gaining insights into the transition of emotional states from normal fear to pathological anxiety exhibited in affective disorders, PTSD or generalized anxiety. These disorders may be viewed as instances of overgeneralization. However, we know little about the neural mechanisms mediating appropriate generalization during fear learning.

$PKC\delta^{+}$ neurons not only gate acute fear responses through a dis-inhibitory mechanism, but also show increased spontaneous activity in animals exhibiting fear generalization. Fear generalization is often associated with

states of anxiety and has been described in PTSD patients. The neuronal mechanisms underlying such maladaptive behavioral changes are, however, poorly understood. We recently found that acute stress regulates the excitability of PKCδ^{+} neurons through α5GABA$_A$ receptor-mediated extrasynaptic inhibition, thereby controlling anxiety behavior and fear generalization (Botta et al., 2015). Our findings demonstrate that the neuronal circuitries of fear and anxiety overlap at the level of defined populations of CEA neurons and indicate that persistent changes in cellular excitability within CEA circuitry underlies concerted changes in conditioned fear and unconditioned anxiety.

Our work over the past years mainly focused on amygdala circuit plasticity underlying learning and expression of conditioned freezing, one particular behavior that can be part of a conditioned fear response. In a recent project, we have addressed how the amygdala taps into downstream circuits in the midbrain, which drive specific behavioral aspects of conditioned fear including passive and active defensive behaviors (Tovote et al., 2016). Understanding the neuronal circuitry underlying the selection and regulation of distinct behavioral coping strategies will provide new insight into evolutionary conserved survival mechanisms. An imbalance between active and passive coping strategies is observed in highly prevalent psychiatric conditions.

The midbrain periaqueductal grey (PAG) has been implicated in generating active and passive defensive behaviors evoked by threatening situations, but the identity and function of forebrain inputs to the PAG, local microcircuits and outputs underlying specific defensive behaviors is not known. We used circuit-based optogenetic, in vivo and in vitro recording, and neuroanatomical tracing methods to characterize PAG circuits for specific defensive behaviors (Tovote et al., 2016). We identified an inhibitory pathway from the central nucleus of the amygdala (CEA) to the PAG that produces freezing by disinhibition of ventrolateral PAG excitatory outputs to pre-motor targets in the magnocellular nucleus of the medulla. In addition, we found that this freezing pathway functionally interacts with long-range and local circuits mediating flight. Our findings define the neuronal circuitry underlying important components of a conditioned fear response and indicate that PAG circuitry plays a key role in the selection and execution of appropriate behavioral defensive programs.

Mechanisms of fear extinction

While tremendous progress has been made in identifying the mechanisms underlying fear learning, much less is known about inhibition of conditioned fear, although this question is attracting increasing interest because of its clinical importance. Inhibition of conditioned fear can be obtained if the conditioned stimulus is repeatedly presented alone, a phenomenon called fear extinction. Behavioral studies in animals demonstrate that fear extinction is not simply the forgetting of previously learned fear, but rather an active learning process (Myers and Davis, 2006). Fear extinction requires exposure to the CS in the absence of the US as opposed to the simple forgetting of CS-induced fear behavior over time. Moreover, fear extinction is generally not permanent, that is the original CS-evoked fear behavior can spontaneously recover over time, or can be recovered by exposing animals to a novel context, or to simple US presentations (Myers and Davis, 2006).

The amygdala is thought to play a central role for the acquisition of fear extinction. Studies using the fear-potentiated startle paradigm demonstrate that local infusion of an NMDA receptor antagonist or a blocker of the ERK/MAPK pathway prevents extinction (Falls et al., 1992; Lu et al., 2003). However, because using the fear-potentiated startle paradigm it is not possible to discriminate between acquisition and retention, the precise role of the amygdala during fear extinction remained unclear. Recently, we and others have used classical fear conditioning to show that intra-amygdala application of NMDA receptor antagonists and ERK/MAPK pathway blockers interfere with the acquisition of fear extinction (Herry et al., 2006). Single unit studies in the LA demonstrate that fear extinction decreases CS-evoked unit activity (Quirk et al., 1997) in a context-specific manner (Hobin et al., 2003). However, there might be different neuronal subpopulations, one of which appears resistant to extinction training (Repa et al., 2001). Together, these experiments establish a strong case for synaptic plasticity in the amygdala during the initial phase of fear extinction.

The formation of a context-specific long-term memory for fear extinction is believed to involve a more distributed neuronal network comprising the medial prefrontal cortex (mPFC)(Quirk et al., 2006) and the hip-

pocampus (Bouton et al., 2006), both of which are strongly interconnected with the amygdala (Ottersen, 1982; Pitkanen et al., 2000). Although the neuronal circuitry underlying amygdala-mPFC and amygdala-hippocampus interactions are still poorly understood, it has been proposed that the role of the mPFC and the hippocampus in fear extinction is ultimately mediated by controlling amygdala activity (Quirk et al., 2006). In analogy to animal experiments, functional imaging studies in human are consistent with the concept that fear extinction is mediated by an amygdala-hippocampus-mPFC network (Phelps et al., 2004; Kalisch et al., 2006). Moreover, pathological amygdala hypersensitivity in patients with anxiety disorders has been repeatedly associated with poor prefrontal control (Phelps and LeDoux, 2005).

Recently, we identified two functionally distinct classes of neurons in the basal nucleus of the amygdala (BA), so-called fear and extinction cells (Herry et al., 2008). While fear neurons were not responsive to tone presentations in unconditioned animals, they showed increased firing rates when the tone was presented during and after fear conditioning (**Fig. 4**). Repeated tone presentations in turn, caused a loss of CS evoked firing. Contrary to fear neurons, extinction neurons became tone responsive only during extinction learning, when the CS was presented repeatedly without being paired with a foot shock (**Fig. 4**).

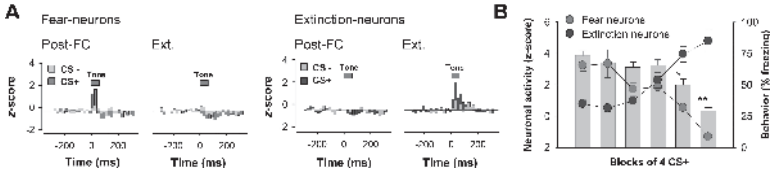

Fig. 4. Fear neurons and extinction neurons in basal amygdala. A: *Fear-neurons exhibited selective CS$^+$-responses after fear conditioning, which were fully reversed upon extinction. In contrast, CS$^+$-evoked firing of extinction-neurons was selectively increased after extinction.* ***B:*** *Averaged time courses of freezing behavior (grey bars) and neuronal activity (z-scores) of BA fear-neurons (red circles) and extinction neurons (blue circles) during extinction training. Modified from Herry et al., 2008.*

Fear and extinction cells are largely overlapping with projection neurons targeting the prelimbic (PL) or infralimbic (IL) subdivision of the medial prefrontal cortex, respectively. Based on our previous findings that the

BA contains functionally distinct neurons selectively activated by either fear conditioned or extinguished CSs (Herry et al., 2008), we recently used a combined anatomical and optogenetic approach to test the hypothesis whether BA fear and extinction neurons might differ with regard to their long-range projection targets (Senn et al., submitted). Using the immediate early gene cFOS as an activity marker, we found that BA neurons projecting to the PL were preferentially activated when the animal was in a state of high fear, whereas BA neurons projecting to the IL were active when animals exhibited low fear levels (i.e. after extinction; Fig. 4). Consistent with this finding, when recording from optogenetically identified PL- or IL-projecting BA neurons, we were able to show that this was also the case in awake behaving animals, and that optogenetic manipulations of the BA→PL and BA→IL pathways had opposite behavioral effects on the formation of long-term extinction memories (Fig. 4). Together, these findings indicate that extinction learning is driven by the switch of activity between two distinct neuronal pathways from the BA to separate subdivisions of the mPFC.

One possible mechanism that could underlie this switch in the balance of activity between distinct output pathways may involve local inhibitory circuits in the BA. We recently found that retrograde endocannabinoid signaling and CB1R-mediated regulation of inhibitory synaptic transmission of CCK-expressing interneurons onto BA PNs strongly depend on PN projection target (Vogel et al., 2016). It is conceivable that such cell-type specific short-term synaptic plasticity may transform uniform recruitment of CCK-lNs into asymmetric inhibitory input onto PL and IL projection-specific subpopulations of PNs during fear extinction. More generally, projection-specific shifts in the balance between inhibition and disinhibition may enhance contrast in activity between distinct amygdala output pathways thereby inducing rapid behavioral adaptations.

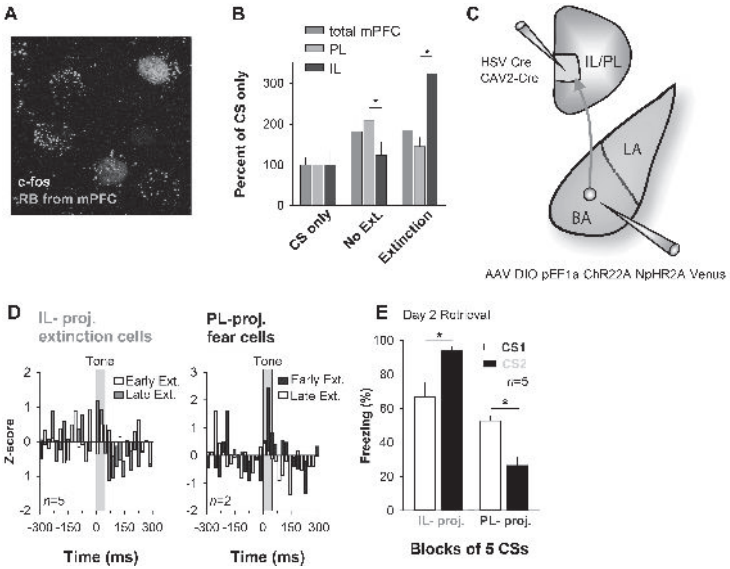

Fig. 5. Fear and extinction neurons target PL and IL subdivisions of mPFC. A: *Immediate early gene expression in anatomically defined neuronal subpopulations. Combining retrograde labeling (red fluorescent beads) with Fos immunostaining (green) reveals Fos expression in subsets of mPFC-projecting neurons.* ***B:*** *Neurons projecting to the infralimbic division (IL) of the mPFC exhibit extinction-specific changes in Fos expression, whereas neurons projecting to the prelimbic division (PL) show increased Fos expression 2 hrs after fear conditioning or upon CS exposure 2 days after consolidation.* ***D:*** *Intersectional viral strategy targeting specific subpopulations of BA output neurons.* ***D:*** *Optogenetically identified IL- or PL-projecting neurons specifically respond to extinguished or fear conditioned CSs.* ***E:*** *Optogenetic manipulation of IL-projecting or PL-projecting BA neuron activity oppositely affects long-term extinction memory acquisition.*

Conclusions and outlook

Together with research from other laboratories, our work over the past years revealed that functionally, anatomically and genetically defined types of amygdala neurons are precisely connected both within local and within larger-scale neuronal networks, and that they selectively contribute to specific aspects of fear learning and extinction. For instance, the activity of distinct sets of amygdala projection neurons can mediate rap-

id, switch-like changes in fear behavior. Moreover, we have identified specific subpopulations of inhibitory interneurons that gate and regulate circuit plasticity and behavior. Finally, we have started to address how the amygdala taps into downstream midbrain and brain stem circuits, which drive specific behavioral aspects of conditioned fear responses, including passive and active coping strategies.

During the last decade, systems neuroscience has witnessed a revolution in terms of novel technologies allowing for imaging and manipulating the activity of defined neuronal circuits *in vivo.* The advent of two-photon microscopy along with optogenetics and molecular genetic tools has allowed to address questions and causalities at a hitherto unprecedented level. These developments have had great impact also on our understanding of the neuronal circuit mechanisms underlying pathological fear and anxiety. Novel deep brain imaging approaches (Gosh et al., 2011) will even further accelerate progress in this field. One of the key challenges will be to integrate across different levels of analysis, from genetics and molecular mechanisms to cellular and synaptic physiology up to circuit function and behavior. Ultimately, this approach will enable us to selectively target and treat pathological circuit states underlying psychiatric conditions caused by maladaptive plasticity within fear and anxiety circuits.

Acknowledgements

I feel deeply honored and I am very thankful to the Professor Max Cloëtta Foundation for recognizing our work with this award. I would like to thank past and present members of my research group at the Friedrich Miescher Institute – students, postdocs and technicians for their excellent work. It has been a great pleasure to work with you!

I am very grateful to my scientific mentors Edilio Borroni, Jean-Paul Laurent, Graham L. Collingridge and Beat H. Gähwiler for sparking my interest in neuroscience and to Denis Monard, Susan Gasser and my colleagues at FMI for making this a special place. Our research would not have been possible without the generous support of the Swiss National Science Foundation, the ERC, the Friedrich Miescher Institute for Biomedical Research, and the Novartis Institutes for Biomedical Research.

My final thanks go to my family for their invaluable support during all these years.

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UNIVERSITY OF LAUSANNE

FOR HIS FUNDAMENTAL DISCOVERIES ON THE LINK
BETWEEN INNATE IMMUNE ANSWERS AND AUTOIMMUNE AND
INFLAMMATORY DISEASES, NOTABLY OF THE SKIN

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2015–2018	Fonds Nationale Suisse Role of IL-26 in skin inflammation
2015–2018	Oncosuisse STING activation in the tumor microenvironment of melanoma
2016	Von Sick Foundation Novel vaccines combined with PD-1 targeting for melanoma patients
2016 –17	The Ludwig Foundation
2016	Acerta Pharma Evaluation of BTK inhibitor for the treatment of psoriasis

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2013–2015	Oncosuisse Targeting intracellular nucleic acid receptors for melanoma immunotherapy
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2012–2015	Berthe Samelli Foundation Role of antimicrobial peptides in the pathogenesis of psoriasis
2012–2015	FBM Lausanne
2009–2014	SPORE in Melanoma P50CA093459, (NIH) Treatment of melanoma patients with intratumoral LL37
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2007–2010	The Dana Foundation. Antimicrobial peptides in inflammation and autoimmunity of the skin
2008–2010	The Goodwin Foundation Converting tumor cells into virus-like particles
2006–2010	The Gillson-Longenbaugh Foundation Role of dendritic cells in cancer metastases

2009–2010	MDACC SPORE Ovarian Cancer Project (NIH), Role of pDC in the generation an of T regulatory cells in ovarian cancer
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2003–2004	Swiss National Science Foundation. Role of pDC and type I IFNs in the pathogenesis of psoriasis

Issued patents

International Patent number: WO/2006/037247
Issue date: 13.04.2006 Inventors: M. Gilliet & F. Nestle
Title: Type I interferon-blocking agents for prevention and treatment of Psoriasis.

International Patent number: WO/2008/076981
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International Patent number: WO/2016/50494
Issue date: 13.07.2016 Inventors: S. Meller & J. Di Domizio & M. Gilliet
Title: IL-26 Inhibitors

10 SELECTED PUBLICATIONS:

1. Meller S, Di Domizio J, Voo KS, Friedrich HC, Chamilos G, Ganguly D, Conrad C, Gregorio J, Le Roy D, Roger T, Ladbury JE, Homey B, Watowich S, Modlin RL, Kontoyiannis DP, Liu YJ, Arold ST, *Gilliet M.* T(H)17 cells promote microbial killing and innate immune sensing of DNA via interleukin 26. **Nat Immunol** (9):970-9. (2015)

2. Lande R, Chamilos G, Ganguly D, Demaria O, Frasca L, Durr S, Conrad C, Schröder J, *Gilliet M.* Cationic antimicrobial peptides in psoriatic skin cooperate to break innate tolerance to self-DNA. **Eur J Immunol.** (1):203-13. (2015)

3. Chamilos G, Gregorio J, Meller S, Lande R, Kontoyiannis D, Modlin RL, *Gilliet M.* Cytosolic sensing of extracellular self-DNA transported into monocytes by the antimicrobial peptide LL37. **Blood** 120:3699 (2012)

4. Lande R, Ganguly D, Facchinetti V, Frasca L, Conrad C, Gregorio J, Meller S, Chamilos G, Sebasigari R, Riccieri V, Bassett R, Amuro H, Fukuhara S, Ito T, Liu YJ, *Gilliet M.* Neutrophils Activate Plasmacytoid Dendritic Cells by Releasing Self-DNA-Peptide Complexes in Systemic Lupus Erythematosus. **Sci Transl Med.** 3:73 (2011).

5. Gregorio J, Meller S, Conrad C, Di Nardo A, Homey B, Lauerma A, Arai N, Gallo RL, Digiovanni J, *Gilliet M.* Plasmacytoid dendritic cells sense skin injury and promote wound healing through type I interferons. **J Exp Med** 207:2921-30 (2010).

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8. Ito T, Yang M, Wang YH, Lande R, Gregorio J, Perng O, Qin XF, Liu YJ, *Gilliet M.* Plasmacytoid dendritic cells prime IL-10-producing T regulatory cells by ICOS-ligand. **J Exp Med.** 204:105. (2007).

9. Urosevic M, Dummer R, Conrad C, Beyeler M, Laine E, Burg G, *Gilliet M.* Disease-independent skin recruitment and activation of plasmacytoid predendritic cells following imiquimod treatment. **J Natl Cancer Inst** 97:1143. (2005)

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ROLE OF INNATE IMMUNITY IN DRIVING INFLAMMATION: LESSONS LEARNED FROM THE SKIN

Prof. Dr. Michel Gilliet

Introduction

Traditionally, immunologists focused on T cells and B cells, the key drivers of adaptive immunity, T cells and B cells have receptors that are generated by cutting and rearranging pieces of genes and stitching them together in a random order. These receptors are therefore capable of adapting and recognizing any molecule (antigen). However, in the early 90s it became clear that in order to activate T cells and B cells, a second signal is required in addition to the antigenic stimulus. This second signal involves the activation of innate immune cells with production of pro-inflammatory cytokines and the maturation of antigen-presenting cells (APC), which turned out to be essential for the generation of T or B cell responses.

In 1992, Charles Janeway predicted that this second signal is linked to infections and recognition of particular molecular patterns shared by a variety of microbes but normally not present in mammalian organisms (*1*). Janeway's prediction was subsequently validated by 2 seminal discoveries. In 1996, Jules Hoffman identified Toll receptors in fruit flies and demonstrated their ability to recognize fungal infections and elicit an innate immune response (*2*). In 1998, Bruce Beutler found that a human homologue of Toll (called Toll-like receptor, TLR) recognized lipopolysaccharides present in the cell wall of gram-negative bacteria but not present in mammalian organisms (*3*). For these discoveries Hoffman and Beutler received the 2013 Nobel prize for Medicine.

Subsequently, several TLRs and their microbial ligands were identified (**Figure 1**). TLRs were found to be well-conserved type I transmembrane proteins that trigger activation of nuclear factor κB leading to the production of pro-inflammatory cytokines and the maturation of dendritic cells. One group of TLRs, which includes TLR1, 2, 4, 5, and 6, are expressed

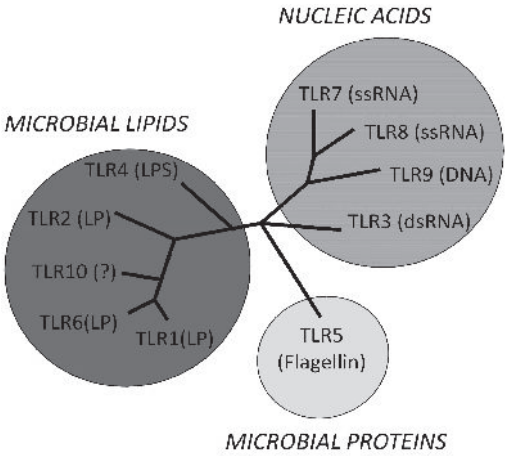

Figure 1. Human Toll-like Receptors (TLR). *Surface TLRs recognizing lipids (blue) and proteins (yellow) of microbial origin, as well as endosomal TLRs (red) with the capacity to recognize both microbial and host-derived (self) nucleic acids provided that they access endosomal compartments*

on the surface of APC. TLR2 forms a complex with TLR1 or TLR6 allowing recognition of lipoproteins and peptidoglycans present specifically in the wall of gram-positive bacteria. TLR4 recognizes bacterial lipopolysaccharides (LPS), and TLR5 bacterial flagellin. The second group of TLRs includes TLR3, 7, 8, and 9 and is characterized by the exclusive expression in endosomal compartments of cells. These endosomal TLRs recognize microbial nucleic acids (DNA and RNA) that are brought into cells during the process of infection. TLR3 binds viral double-stranded RNA *(4),* TLR9 is activated by unmethylated cytosine guanine oligodeoxynucleotide (CpG) motifs common to both bacterial and viral DNA *(5),* and TLR7 and TLR8 are required for recognition of the viral single-stranded RNA (*6–8*). In recent years it has however become clear that the ability of these endosomally-expressed TLRs to recognize microbial nucleic acids and distinguish them from mammalian (host or self) nucleic acids is not based on chemical differences between the two. In fact, unmethylated CpG motifs which are key ligands for TLR9, are abundant in microbial DNA, but also exist in self-DNA. Furthermore, the phosphate-rich sugar backbone of DNA itself, present in both microbial and

self-DNA, is a direct TLR9 ligand (*9*). Enforced internalization of self-DNA by lipofection can lead to potent TLR9 activation indicating that rather than the chemical composition of nucleic acids, the discrimination between microbial and self DNA is guaranteed by the endosomal localization of TLR9. This localization allows sensing of viral DNA that enters cells during infection but not self-DNA released into the extracellular environment by dying cells. Extracellular DNA fails to enter endosomal compartments because it is rapidly degraded by DNases in the extracellular environment.

In 1994, Polly Matzinger suggested a competing theory, called the "danger theory". According to the danger theory, innate immune responses are not due exclusively to the presence of foreign molecular patterns but can also be triggered by "danger signals," released by the body's own cells (*10*). For example, cellular stress, necrotic cell death with the release of heat shock proteins (HSP), interferon-α, interleukin-1β, uric acid, etc., have been suggested to function as "danger" signals. Although this theory explains the existence of "sterile inflammation" and the close association between immune responses and tissue damage, the exact identification of "danger" signals and the receptors involved has remained difficult.

Our research has focused on the identification of such triggers using psoriasis as a model of "sterile" skin inflammation mediated by autoimmune T cells. We identified a unique innate immune pathway required for the activation autoimmune T cells in psoriasis. This pathway is based on the activation of plasmacytoid dendritic cells (pDC), a subset of dendritic cells characterized by the unique expression of endosomal nucleic acid receptors TLR7 and TLR9. We found that cationic antimicrobial peptides produced by host cells allow otherwise non-stimulatory extracellular self-DNA and self-RNA to access endosomal compartments of pDC and trigger TLR7 and TLR9 activation. As a result, pDC are activated to produce very large amounts of type I IFN, which unleash the autoimmune T cell response in psoriasis. Our finding reconcile the apparently discordant theories of Janeway and Matzinger, by showing that danger–associated host–derived molecules can break a safety mechanism and activate pattern recognition molecules that are normally designed for microbial recognition.

Psoriasis as a model for "sterile" skin inflammation

Psoriasis is a common chronic inflammatory skin disease that affects 2 to 3 % of the worldwide population (*11, 12*). In its most prevalent form, plaque psoriasis manifests as scaly erythematous plaques that may cover large body areas (**Figure 2**). Over the past years it has become clear that plaque psoriasis is mediated by T cells producing high levels of Th17 cytokines (*13*). The pathogenic Th17 cells are stimulated in the dermis by aberrantly activated conventional dendritic cells producing TNF-α and IL-23 and subsequently migrate into the epidermis where they recognize a yet unknown auto-antigen. As a consequence, pathogenic Th17 cells produce IL-17 and IL-22, which are directly responsible for stimulating keratinocyte hyperproliferation leading to the development of the psoriasis plaque. IL-17 and IL-22 also activate keratinocytes to produce chemokines that recruit neutrophils and other immune cells. Furthermore, IL-17 and IL-22 stimulate keratinocytes to produce high levels of antimicrobial peptides, which protect the skin from microbial infection, thus classifying it as "sterile" inflammation. The pathogenic role of the Th17 cells in psoriasis is now validated by mouse models of psoriasis (*14*), the efficacy of targeting IL-23 or IL-17 (*15*), and the discovery of genetic polymorphism in the IL-23A and IL-23R genes associated with the development of psoriasis (*16, 17*).

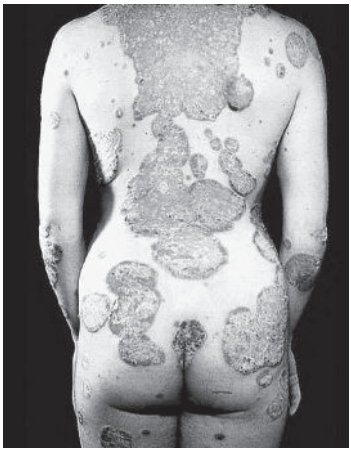

Figure 2. Clinical manifestations of psoriasis. *Chronic plaque-type psoriasis.*

Plasmacytoid dendritic cells accumulate in psoriasis skin lesions

The role of innate events initiating the pathogenic Th17 cell cascade in the psoriatic skin has been poorly investigated. In 2003 we made an interesting clinical observation in a patient treated topically with the TLR7 agonist imiquimod (Aldara™) for what was thought to be a bowenoid keratosis. After 10 weeks of treatment, the patient showed an enlargement of the lesion along with surrounding satellite lesions consistent with the development of a psoriasis plaque (*18*). Toll-like receptor 7 (TLR7)

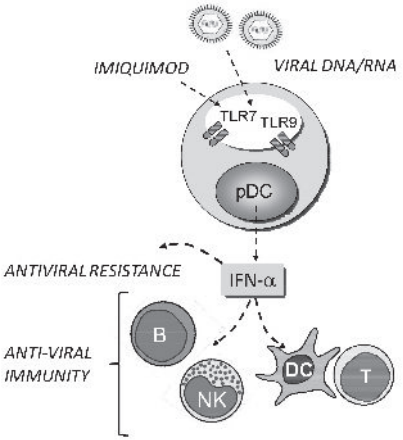

Figure 3. Plasmacytoid dendritic cell function in anti-viral immunity

is an endosomal receptor for viral single-stranded RNA that is specifically expressed by a subset of human dendritic cells called plasmacytoid dendritic cells (pDC) (*19*). pDCs are key effectors in antiviral immunity because they express TLR7 along with TLR9, a specific receptor for viral DNA (**Figure 3**). Upon viral infection, pDC expressing TLR7 and TLR9 sense viral RNA and DNA when brought into the endosomal compartment during the process of infection (*19*). In response to TLR7 and TLR9 activation, pDCs produce large amounts of type I IFN (mainly IFN-α, approximately 100 fold more than any other cell type of the human body). Type I IFN produced by pDC provide cell resistance to viral infection but also critically shape antiviral immune responses by matur-

ing conventional dendritic cells expanding memory T cells and activating cytotoxic NK cells (**Figure 3**). Whereas pDC are absent in healthy skin under homeostatic conditions, large numbers of pDC infiltrating the dermis were found in imiquimod treated skin (*18*) and in developing psoriatic skin lesions (*20*) (**Figure 4**).

PDC activation and production of ifn initiates the formation of psoriatic skin lesions

Not only were these pDC accumulating in developing psoriatic skin lesions, but they were also found to produce large amount of type-I IFN (*20*). The role of pDC and type I IFN in the pathogenesis of psoriasis was assessed in a xenotransplant model of human psoriasis that is based on transplantation of un-involved skin of a psoriatic patient on an immunosuppressed (AGR 129) mouse. In this model, the engrafted human skin develops spontaneously into a fully-fledged psoriatic plaque within 35 days upon transplantation, a process mediated by resident Th17 cells and characterized by early type I IFN expression (**Figure 4**). Injection of ei-

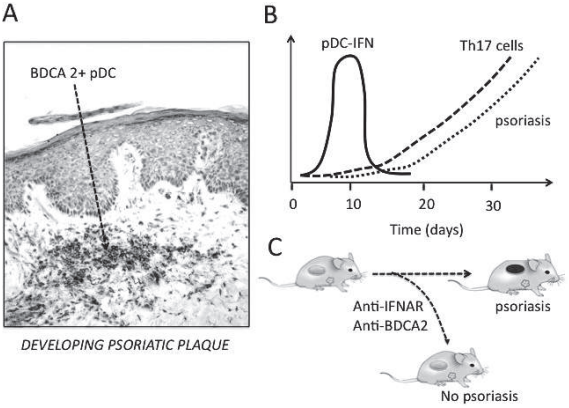

Figure 4. Plasmacytoid dendritic cell accumulation and activation in psoriatic lesions early during development. A. *BDCA2+ human pDC in the dermis of a developing psoriatic plaque.* ***B.*** *Early type I IFN production preceding T cell activation in the AGR xenotranplantation model of psoriasis. This model is based on the engraftment of non lesional skin of a psoriasis patient onto an AGR mouse, which leads to a spontaneous conversion of the graft into a fully-fledged psoriatic plaque within 35 days.* ***C.*** *Antibody-mediated inhibition of type I IFN signaling (anti6IFNAR) or pDC function (anti6BDCA62) abrogates the development of human psoriasis in the AGR xenotransplantation model.*

ther neutralizing anti-IFNAR (type I IFN receptor) antibodies or an anti-BDCA2 antibody, which targets specifically human pDC and blocks their ability to produce type I IFN, completely inhibited the Th17 cell-dependent development of psoriasis (*20*), indicating that pDC and their activation to produce type I IFN is an upstream event in the immunopathogenesis of psoriasis.

A role of pDC in the development of psoriasis has also been demonstrated in the STAT3C and JUN-B mouse models of psoriasis by showing that pDC depletion abrogates the formation of psoriasiform skin lesions (*21*). Furthermore, repetitive topical application of imiquimod cream leads to a psoriasiform skin phenotype, although the role of pDC as TLR7 sensor in this model is still debated (*22*).

Host-derived antimicrobial peptides trigger the pDC-IFN inflammation pathway in psoriatic skin lesions

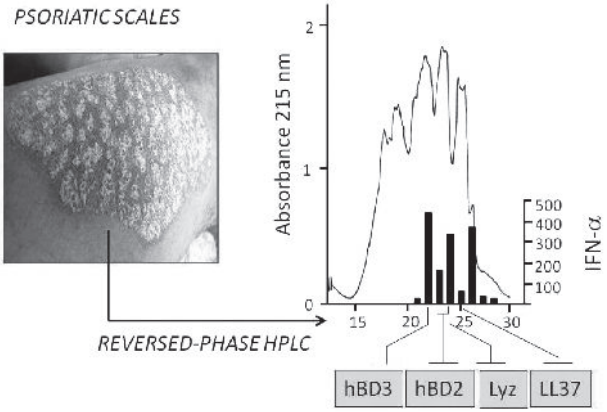

Figure 5. Identification of the IFN-inducing factors in psoriatic scales. *Psoriatic scales were collected from multiple patients. Samples were pooled and protein extracts fractionated by reversed-phase HPLC. Fractions eluting at the indicated time (min) were then tested on purified blood pDC for their ability to induce IFN-α. IFN-inducing HPLC fraction were analyzed by ESI-MS to identify peptides according to mass, and subsequently confirmed by sequencing.*

But how are pDC activated to produce type I IFN in psoriasis, a chronic inflammatory disease not linked to viral infection? To address this question we used fractions derived from HPLC of psoriatic scales to activate pDCs isolated from peripheral blood. These experiments, followed by extensive biochemical characterization of the IFN-a inducing fractions using mass spectrometry and sequencing, allowed us to identify first lL-37 (*23*), and then human β-defensin 3, human β-defensin 2 and lysozyme (*24*) as pDC activators (**Figure 5**). These factors are all antimicrobial peptides, which belong to an important evolutionarily conserved defense mechanism of host cells against bacterial and fungal infections. There are several classes of antimicrobial peptides: LL37 is the only human member of the cathelicidin family of alpha-helical peptides expressed by keratinocytes and neutrophils; hBD2 and hBD3 are inducible b-defensins with beta-sheet structure produced by keratinocytes. Cathelicidins, defensins and lysozyme belong to different gene families but share common structural feature: they are highly cationic and possess an amphiphatic structure. These unique feature allows antimicrobial peptides to associate with negatively charged phospholipids in bacterial membranes leading to the formation of pores and the killing of microbes (*25*). Antimicrobial peptides Agents. Antimicrobial peptides are normally not expressed in healthy skin but can be rapidly induced in keratinocytes and released by neutrophils upon skin injury in order to protect wounds from microbial invasion. In psoriasis, LL37, hBD2 and hBD3, as well as lysozyme are overexpressed throughout all epidermal layers but some staining can be found in the dermal compartment, where pDC are located (*23, 24*), suggesting their role in the activation of pDC and in the triggering of psoriasis.

Antimicrobial peptides break innate tolerance to extracellular DNA by transporting them into endosomal compartments of pDC

But how can antimicrobial peptides activate pDC? pDC are activated by viral RNA and DNA brought into TLR7 and TLR9 containing endosomal compartments during the infection to activate pDCs because these nucleic acids are rapidly degraded in the extracellular environment and therefore fail to be internalized by pDC. We found that, via their positive charges, antimicrobial peptides can form complexes with extracellular

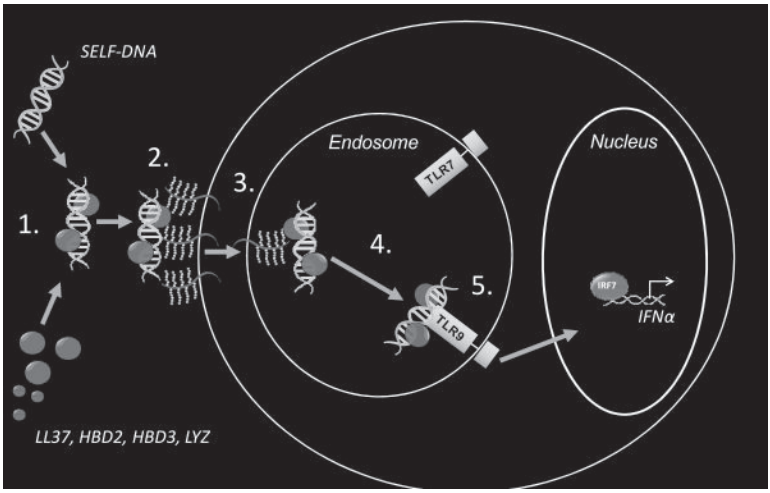

Figure 6. Antimicrobial peptides break innate tolerance to extracellular self-DNA. (1.) *Charge-driven complex formation inducing DNA condensation and aggregation, thus protection from DNase mediated degradation of DNA fragments in the extracellular environment.* ***(2.)*** *The peptide-DNA complex becomes slightly positively charged allowing attachment to heparan-sulfate proteoglycans in the cell membrane of pDC, followed by clathrin-independent (receptor independent) endocytosis of the DNA complexes* ***(3.)****.* ***(4.)*** *The peptide-DNA complexes are retained in early endosomal compartments and escape autophagy through yet undefined mechanisms. This leads to prolonged persistence of complexes in TLR9-containing endosomal compartments. Together with the specific DNA spacing induced by the peptide complex which allows interdigitation of TLR9* ***(5.)*** *this leads to high levels of IFN-α induction in pDC.*

self-DNA fragments and protect them from DNase-mediated extracellular degradation by inducing condensation and aggregation (*23, 26*). These aggregated complexes acquire net positive charges, which allow them to associate with anionic heparan-sulfate proteoglycans (HSPG) in the membrane of pDC. As a consequence the nucleic acid complexes are endocytosed in a clathrin-independent manner (thus independent on specific receptor) reaching intracellular TLR9 compartments, where they trigger the production of type I IFN. Key elements for the induction of high levels of type I IFN is the retention of complexes in early endosomal structures and the escape from autophagic recognition (*23*). Thus, cationic antimicrobial peptides IL37, hBD2, hBD3, and lysozyme can break innate

tolerance to self-DNA by protecting it from extracellular degradation and transporting it across membranes into TLR9 containing compartment and thereby leading to innate immune activation of pDC (**Figure 6**).

Antimicrobial peptide-complexed DNA interdigitates TLR9.

Because DNA complexed with LL37 is protected and internalized upon condensation and because the later is induced by the cationic charges of the peptide, we asked whether all cationic molecules can break innate tolerance to DNA and trigger TLR9 activation. Indeed, we found that a broad range of antimicrobial peptides and other cationic molecules can induce DNA condensation, leading to protection from extracellular degradation and allowing DNA entry into TLR9 containing endosomal compartments. However, only a portion of the tested cationic compounds were able to induce strong IFN production (*27*). This phenomenon was related to the ability of the peptide to space DNA molecules at regular intervals in a grill-like arrangement that interlock with multiple TLR9 like a zipper (*27*). This leads to multivalent electrostatic interactions that drastically amplify binding TLR9 and thereby the immune response. Although the exact structure of the cationic peptide needs still to be determined, it appears that these peptides are also amphiphatic leading to multimerization of the peptides. Thus, in addition to controlling DNA degradation and internalization, antimicrobial peptide also control TLR9 activation by spacing the DNA at optimal distances for receptor interdigitation.

Antimicrobial peptides form complexes with RNA and activate TLR7 and 8 in pDC and conventional DC

Because AMPs are abundantly expressed in psoriatic skin, we sought to visualize the extracellular DNA-AMP complexes in the tissue. Interestingly, we found complexes that stained for DNA, but many more that stained for Ribogreen (a dye that stains both DNA and RNA) *(28).* In fact, we found that dying cells release both DNA and RNA that can be efficiently bound by AMPs. LL37 can bind extracellular self-RNA, protect it from extracellular degradation, and transport it into endosomal compartments. In pDC, self-RNA–LL37 complexes activate TLR7 and, like self-DNA–LL37 complexes, trigger the secretion of IFN-alpha. In

contrast to self-DNA–LL37 complexes, self-RNA–LL37 complexes also trigger the activation of classical myeloid DCs (mDCs). This occurs through TLR8 and leads to the production of TNF-alpha and IL-6, and the differentiation of mDCs into mature DCs *(28)*. In fact self-RNA–LL37 in psoriatic skin lesions was associated with the presence of mature mDCs in vivo *(28)*.

Psoriasis is driven by an overexpression of antimicrobial peptides

In healthy individuals, skin injury is linked to a transient expression of antimicrobial peptides that protect the wound from microbial invasion (*29*). In psoriasis patients, skin injury (called the Koebner phenomenon) leads to a persistent AMP expression that drives exaggerated pDC acti-

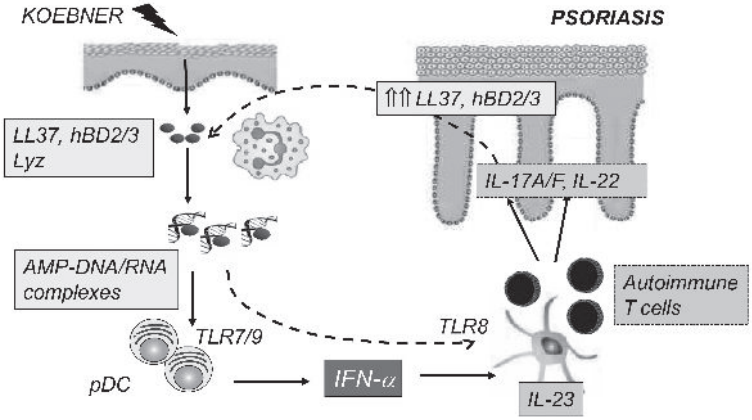

Figure 7. The pDC-IFN pathway in the pathogenesis of psoriasis. *Mechanical stress to the skin (Koebner phenomenon) leads to the expression of LL37 and defensins (hBD2 and hBD3) by keratinocytes as well as infiltration of neutrophils that release LL37 and Lysozyme. This leads to the formation of peptide-nucleic acid complexes that trigger initial TLR7/9 activation of pDC to produce IFN-α. PDC-derived IFN-α promotes maturation of conventional DCs. This is promoted by the concomitant direct activation of conventional DC via TLR8. Maturing conventional DC stimulate autoimmune T cells to migrate into the epidermis and to produce Th17 cytokines. Th17 cytokines IL-17 and IL22 stimulate keratinocyte hyperproliferation giving rise to the epidermal phenotype in psoriasis. Th17 cytokines also activate keratinocytes to produce elevated levels of antimicrobial peptides providing a feedback loop that sustains the formation of immunogenic DNA/RNA complexes that trigger innate activation of DC subsets.*

vation. This leads to chronic inflammation with the development of autoimmunity, which ultimately drives epidermal hyperproliferation and development of the psoriatic plaque (*23*). But what drives the constant overexpression of antimicrobial peptides in psoriasis? One important factor is the high levels of Th17 cytokines in the plaque, which contribute to the constant activation of keratinocytes to produce antimicrobial peptides. Indeed, both IL-17 and IL-22 alone or in combination have been shown to trigger expression of antimicrobial peptides in keratinocytes (*30, 31*) (**Figure 7**). Genetic evidence for an enhanced Th17 response in psoriasis comes from the identification of disease associations with SNP in IL-23 and IL-23R genes. In fact, IL-23 is an essential cytokine driving the development of Th17 cells. Another interesting element is the identification of human β-defensin copy number polymorphism associated with the development of psoriasis, providing a genetic basis for the AMP overexpression in psoriasis (*32*).

The antimicrobial peptide LL37 is also auto-antigens recognized by psoriatic T-cells

Because antimicrobial peptides are taken up by dendritic cell subsets we asked ourselves whether these antimicrobial peptides could serve as auto-antigens and are presented to auto-immune T-cells in the psoriatic plaque. To address this question we used peripheral blood mononuclear cells from 52 psoriatic patients and stimulated them with either LL37 or a scrambled form of the LL37 peptide. We found in approximately 40% of the patients that LL37 induced a T-cell proliferation which was not present in control populations including healthy donors, scleroderma patients, erysipelas patients and atopic dermatitis patients (*33*). LL37 reactive T-cells did not only proliferate, but did also produce IFN-γ, and Th17 cytokines, IL-17 and IL-22 (*33*). LL37 reactive T-cells were both of CD4 and CD8 phenotype. Several CD4 and CD8 T-cell lines and clones were obtained and MHC restriction was demonstrated. Interestingly, HLA-Cw6, that is found in 50% of psoriasis patients and is highly associated with the development of psoriatic disease, was found to be an excellent binder of LL37. We also generated tetramers, which were able to detect LL37-specific T-cells in the circulation of psoriasis patients (*33*). A significant correlation between the presence of circulating IL37 specific

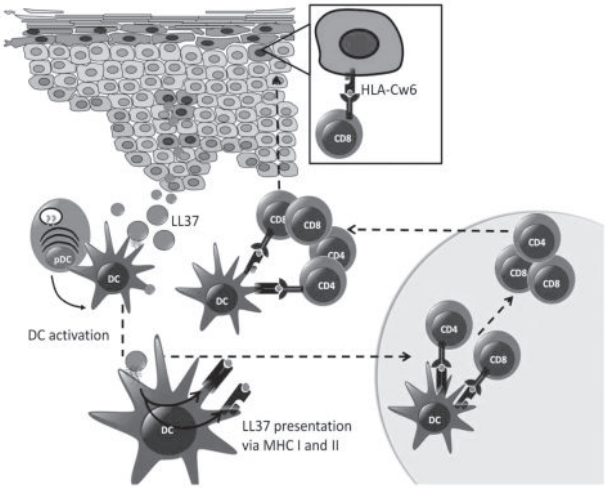

Figure 8. LL37 represents an autoantigen recognized by psoriatic T cells. *The antimicrobial peptide LL37 is presented to CD4 and CD8 T cells via both MHC class I and class II. Upon reactivation of LL37-specific T cells by maturing dermal DC, they migrate into the epidermis where they recognize LL37 expressed by keratinocyte and release their Th17 effector cytokines.*

T-cells and the disease activity was observed. In addition, about 80 % of patients with severe psoriasis (PASI >10) displayed circulating IL37 specific T cells. These findings alone with the fact that LL37 specific T-cells produce pathogenic Th17 cytokines and are present in skin lesions suggests that LL37 specific T cells may be pathogenic T-cells in psoriasis (**Figure 8**). Accordingly, patients undergoing disease remission during anti-TNF treatment displayed decreased proliferative activity and tetramer staining of their LL37-specific T cells. Furthermore, LL37-specific T cells lost skin homing receptors CCR10, CLA, CCR6, and their ability to produce IL-17 and IL-22 (*33*). More recent in vivo mouse studies, based on the repetitive injection of antimicrobial peptides into mouse skin, demonstrated a direct pathogenic role of AMP-specific T-cells. The injection of AMP induced the expansion of AMP-specific T cells in the skin and the development of a psoriatic phenotype, which was entirely T cell dependent (unpublished data).

Neutrophil extracellular traps contain antimicrobial peptide-DNA complexes that activate pDC

In recent years a novel form of neutrophil cell death has been identified. This form of cell death is associated with the active extrusion of nuclear and mitochondrial DNA into the extracellular space in the form of web-like DNA structures (the NETs) (*34*). NET-DNA, which is typically released in the context of infections or inflammation, is covered with granule-derived cationic antimicrobial peptides such as LL37 and HNPs. NETs are believed to play an important role in the fight against extracellular bacteria through their ability to entrap (via the web-like DNA structures) and kill these microbes (via the associated antimicrobial peptides) (*34*). Because NET-DNA is in complex with AMPs we asked whether it could activate TLR9 in pDC. Indeed, NETs strongly activated pDCs to produce IFN-α via TLR9 (*35, 36*). This process required the presence of the antimicrobial peptide LL37 in the NET (*35*). There are 3 reasons why NETs are highly immunogenic and potent activators of TLR9. First, during NET formation NET-DNA is mixed with the granular content of neutrophil which allows formation of LL37-DNA complexes that are extruded in the context of NETosis (*35*). Second, NETosis requires ROS formation, which oxidizes the DNA and renders it immunogenic (*37*). Finally, physiological NET formation appears to preferentially involve mitochondrial DNA rather than nuclear DNA (*38*). Mitochondrial DNA is unmethylated like bacterial DNA and more potent in the activation of TLR9.

Systemic lupus erythematosus is triggered by NETs that activate the pDC-IFN inflammation pathway

Systemic lupus erythematosus (SLE) is the second most common human autoimmune disease and is characterized by the presence of autoreactive B cells that produce autoantibodies against self-DNA and RNA and associated proteins. Upon binding of the autoantibody to extracellular self-DNA and RNA, these immune complexes are deposited in different parts of the body, leading to TLR7/9 activation of plasmacytoid dendritic cells (pDCs) to secrete type I interferons (IFNs) *(39).* The high levels of type I IFNs induce an unabated differentiation of monocytes into dendritic

cells *(40),* and lower the activation threshold of autoreactive B cells *(41),* thereby promoting autoimmunity in SLE. One intriguing observation is the association of type I IFN genes in SLE blood with the expression of neutrophil genes *(42)* suggesting a link between neutrophils and the chronic pDC activation in SLE. In fact, biochemical characterization of pDC-activating DNA complexes isolated from the circulation of SLE patients revealed the presence of neutrophil-derived antimicrobial peptides LL37 and HNP (human neutrophil peptides) in complex with the DNA *(35),* suggesting that NETs represent the origin of these immune complexes. In fact, we found that circulating neutrophils of SLE patients have a greater propensity to undergo NETosis *(35, 36).* Furthermore, decreased clearance of NETs in SLE patients correlates with disease activity *(43).* Interestingly, SLE patients were found to develop circulating antibodies to NET structures including DNA and neutrophil-derived antimicrobial peptides LL37 *(35).* Thus, NET-derived DNA-LL37 complexes induce innate activation of TLR9 but also represent autoantigens in lupus. NET-derived DNA-LL37 complexes can activate autoreactive B cells to produce anti-LL37 antibodies via both TLR9 and BCR. This activation is promoted by concomitant activation of pDC. Importantly, anti-LL37 antibodies were found to further sustain neutrophil NETosis with the generation of more DNA-LL37 complexes providing a feedback loop that sustains pDC activation and autoimmunity (**Figure 10**).

NET-derived antimicrobial peptide-DNA complexes also trigger the pDC-IFN inflammation pathway in artheriosclerosis and type I diabetes

Arteriosclerosis is a chronic inflammatory disease of the arterial wall. Studies have shown that the blood and the plaques of arteriosclerosis patients contain high levels of NET-derived LL37-DNA complexes (*38, 44*). These complexes trigger TLR9 activation of pDCs and inflammation of the arteries (*44*), leading to the formation of atherosclerotic plaque lesions in apolipoprotein E-deficient mice (*38*). In a mouse model for type I diabetes (NOD mice), similar to lupus, autoantibodies activate neutrophils to undergo NETosis (*45*). NET-derived AMP-DNA complexes then activate pDC to produce IFN via TLR9 leading to a diabetogenic inflammation and type I diabetes development (*45*). Thus, the NETs-pDC-IFN

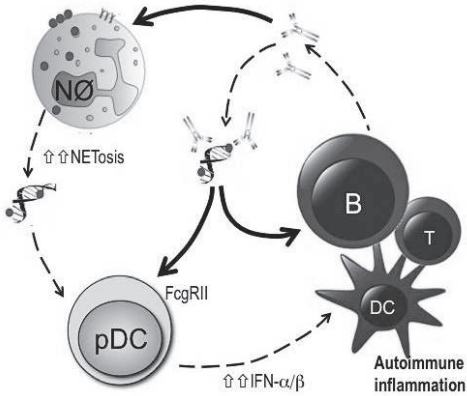

Figure 9. The pDC-IFN pathway in systemic lupus erythematosus. *Neutrophil extracellular traps induced by infection or injury activates pDC via LL37-DNA complexes. pDC-derived IFN plus the context of a genetically-determined increased reactivity of B cells leads to the activation of autoreactive B cells against NET antigens with production of anti-DNA and anti-LL37 antibodies. On one hand these autoantibodies bind NET-derived DNA-LL37 complexes to form immune complexes, which further activate pDC and autoreactive B cells (uptake via FcgRII). On the other hand, anti-LL37 antibodies trigger further NETosis providing a feedback loop that sustains pDC-IFN pathway and autoimmunity.*

responses appear to be a major pathogenic pathway in inflammatory diseases such as lupus, atherosclerosis and type I diabetes.

Antimicrobial peptide-nucleic acid complexes CAN activate cytosolic DNA and RNA sensors

LL37 also transports self-DNA into non-TLR9 expressing cells such as myeloid DC and monocytes (*46*). Stimulation of monocytes with LL37-DNA complexes leads to the production of type I IFNs in a TLR-independent manner (*46*). This type I IFN induction requires double-stranded B form of the DNA, but is independent on its sequence, CpG content, and its methylation status. IFN-induction in these cells involved signaling through the adaptor protein STING and TBK1 kinase, indicating a role of cytosolic DNA sensors (*46*). Thus, in non-TLR9 expressing cells, LL37 can shuttle the DNA into cytosolic compartments for type I IFN induction via cytosolic sensors. This type I IFN response appears to involve mainly IFN-beta, while pDC produce mainly IFN-α.

The role of the cytosolic nucleic acid sensing in inflammation is still unclear. We found that STING-dependent activation of cytosolic sensors in endothelial cells and the consequent induction of type I IFNs is an essential pathway in the spontaneous induction of anti-tumor immunity in melanoma (*47*). Although the mechanisms that allow DNA to enter cytosolic compartments of endothelial cells is still unknown, tumor cells themselves have the ability to release a number of cationic molecules that have the ability to shuttle DNA into cytosolic compartments for type I IFN induction. Another recent study found that the antimicrobial peptide LL37 can transport non-coding double stranded-RNA released from necrotic cells into cytosolic compartments of keratinocytes leading to IFN-beta production via activation of mitochondrial antiviral-signaling protein (MAVS) (*48*). Finally, in the MRL/lpr mouse model of lupus, the spontaneous NETosis by low-density granulocytes triggers STING-dependent type I IFN signaling (*37*). Thus, antimicrobial peptide-nucleic acid complexes can also activate cytosolic nucleic acid receptors and induce type I IFN expression (mainly IFN-β) in hematopoietic as well as non-hematopoietic cells.

IL-26 is a TH17-derived antimicrobial peptide that binds DNA and activates pDC to produce IFN

IL-26 is a 19-kDa α-helical protein that belongs to the IL-20 cytokine family and is expressed by Th17 cells. We became interested in IL-26 for two reasons. First, IL-26 appears to be strongly involved in tissue inflammation. In fact, IL26 is highly expressed in psoriasis (*49*), IBD (*50*) and rheumatoid arthritis (*51*) and strongly associated with the inflammatory activity. Furthermore, a risk locus containing IL26 and single-nucleotide polymorphisms within the IL26 gene region have been associated with inflammatory diseases such as multiple sclerosis (*52*), rheumatoid arthritis (*53*) and IBD (*54*). Another reason is that the inflammatory function of IL-26 is hardly explained by signaling through its receptor expressed exclusively by epithelial cells and leading to inhibition of proliferation and production of immunosuppressive IL-10. Strikingly, we found that IL-26 is a highly cationic with amphiphatic protein that forms multimeric structure (*55*). Based on this structure, we discovered that IL-26 has antimicrobial properties with the ability to directly kill extracellular bacteria through pore

formation (*55*). Furthermore, IL-26 was found to form complexes with extracellular DNA released by dying bacteria and host cells, leading to TLR9 activation of plasmacytoid dendritic cells (pDCs) (*55*). These findings provided novel insights into the potent inflammatory function of Th17 cells via the production of IL-26. Because IL-26 is produced by activated Th17 cells, these findings also provided an additional AMP-driven innate activation mechanism that is controlled by antigen.

Physiological role of the pDC-IFN inflammation pathway: the wound healing response

Having identified the pDC-IFN inflammatory pathway in diseases such as psoriasis, we asked whether there is a physiological role of this pathway. Because AMPs such as LL37 and hBD2/3 are induced upon injury we reasoned that the pDC-IFN pathway could be induced after mechanical injury to the skin. Indeed, mild injury to human or mouse skin by repetitive tape stripping induced a rapid and transient accumulation of pDC in the dermal compartment and their activation to produce type I IFNs (*29*). This occurred via TLR7 and TLR9, indicating sensing of nucleic acids. pDC-derived type I IFN production was essential in driving the inflammatory response and promoting the re-epithelialisation of the wound. In fact, either pDC depletion or inhibition of type I IFN-signaling abrogated the induction of a Th17 cytokines and significantly delayed wound healing (*29*).

Commensal bacteria are required for pDC-IFN inflammation pathway in skin wounds

The mechanisms underlying the recruitment and activation of pDC in injured skin are unknown. In the tape-stripping model of skin injury we found a very rapid and strong recruitment of neutrophils in injured skin preceding pDC infiltration. Skin infiltrating neutrophils acquired expression of Cxcl10 which acted as a chemokine as well as antimicrobial peptide that directly recruits and and activates pDC. In fact, depletion of neutrophils, which represent the major source of CXCL10 at early time points of skin injury or abrogation of CXCL10 expression largely abrogated recruitment and activation of pDC in injured skin. We found an essential

role of skin microbiota in this process. On one hand, skin microbiota induced Cxcl10 in skin-infiltrating neutrophils via TLR2. On the other hand, Cxcl10 killed skin bacteria and induced the formation of complexes with microbial DNA. Of note, complexes of microbial DNA and not host-derived DNA were required for TLR9 activation of pDC early during skin injury and subsequent inflammatory response. Interestingly, injury of human skin also induced high levels of type I IFN that was abrogated by local antibiotic treatment, which depleted the local skin microbiota. Thus, skin microbiota appears to play an important role in initiating inflammation in skin wounds by recruiting and activating pDC (**Figure 10**). These findings show that CXCL10 is not only a chemokine but is also an antimicrobial peptide that kills bacteria and binds DNA leading to activation of the pDC-IFN inflammatory pathway. It further shows that in the context of skin injury the induction of AMPs is dependent on microbiota and that AMPs preferentially kill and bind microbial DNA for induction of the pDC-IFN inflammatory pathway.

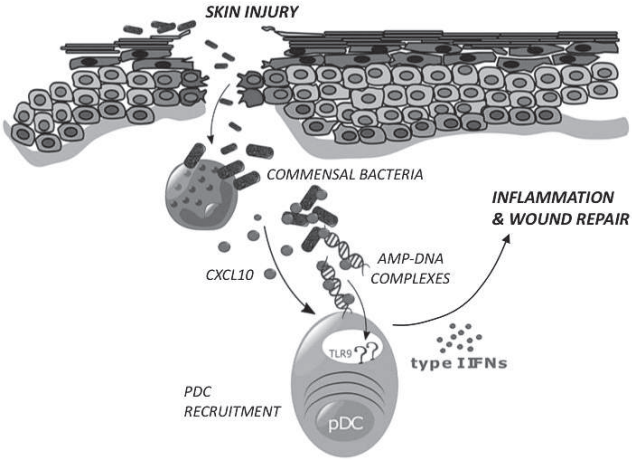

Figure 10. Commensal bacteria are required for the pDC-IFN inflammation pathway in skin wounds. Upon skin injury, neutrophils are recruited into the wound. *During this process the skin6resident microbiota stimulates them to express and release Cxcl10 via TLR2. Cxcl10 acts as chemokine that recruits plasmacytoid dendritic cells (pDC) to the skin via CXCR3. Cxcl10 also acts as an antimicrobial peptide that kills skin6resident bacteria. During bacterial lysis CXCL10 binds to the bacterial DNA and protects it from degradation. These CXCL106bacterial DNA complexes appear to be the principal triggers of TLR9*

Conclusions and perspectives

Our studies identified a unique inflammation pathway in the skin based on innate activation of pDC to produce type I IFN. This pathway is transiently active in skin wounds leading to controlled inflammatory responses and wound healing, whereas its over-activation in psoriasis leads to autoimmunity and disease development. By studying psoriasis, we also identify the mechanisms driving pDC activation, based on the expression of host-derived cationic antimicrobial peptide LL37. LL37 has the capacity to form complexes with extracellular self-nucleic acids, and to transport them into endosomal compartments to trigger activation of TLR7 and TLR9. The mechanism behind this appears to be protection from extracellular degradation, attachment to proteoglycans in cellular membranes of pDC and receptor-independent endocytosis, escape from autophagy, and spacing of DNA molecules for optimal TLR interdigitation. Our data provides a unique mechanism for how the host-derived factors such as antimicrobial peptides control the immunogenicity of extracellular self-DNA and self-RNA released in the context of cell death leading to the activation of pattern recognition receptors that are normally designed for microbial recognition. By showing that danger-associated host–derived molecules control the nature's safety mechanism that allows discrimination between self- and microbial nucleic acids, our finding reconciles two apparently discordant theories by Janeway and Matzinger.

Since the initial discovery of the ability of LL37 to break innate tolerance to self-DNA and trigger the pDC-IFN inflammatory pathway several other antimicrobial peptides with similar capacity have been identified. Some antimicrobial peptides are of epithelial origin (LL37, beta-defensin 2 and 3), others of neutrophil origin (LL37, lysozyme, CXCL10) and even of Th17 cell origin (IL-26). Furthermore, both endosomal (TLR7, 8 and 9) as well as cytosolic (STING and MAVS-dependent) nucleic acid receptors can be activated by nucleic acid complexes formed by these antimicrobial peptides (**Figure 11**). Antimicrobial peptide overproduction triggers an excessive activation of the pDC-IFN inflammation pathway, leading to autoimmunity in skin diseases such as psoriasis, but also other diseases such as lupus, type I diabetes, atherosclerosis, and potentially Crohn's disease, rheumatoid arthritis and multiple sclerosis (**Figure 12**).

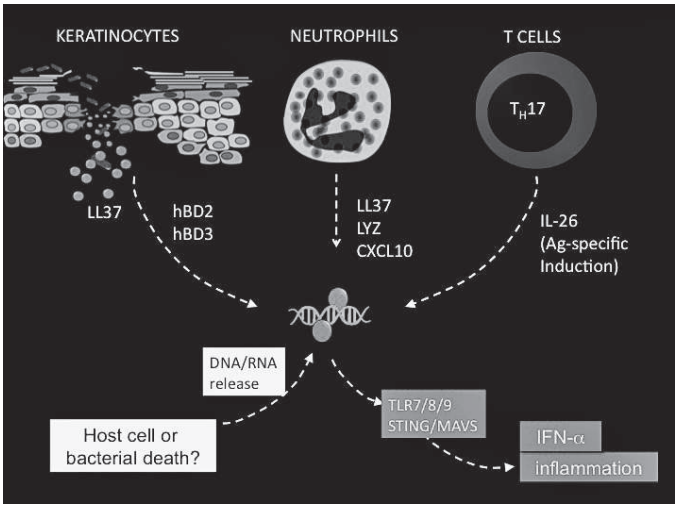

Figure 11. Antimicrobial peptides of different cellular origin break innate tolerance to extracellular nucleic acids and promote IFN-driven inflammation by allowing activation of endosomal and cytosolic nucleic acid receptors.

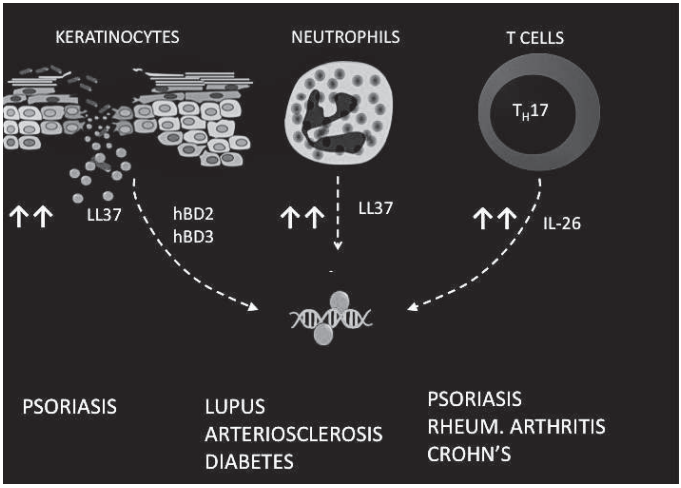

Figure 12. Association of antimicrobial peptide overexpression with inflammatory disease activity.

Interestingly, we found that in addition to being triggers of the pDC-IFN inflammation pathway, AMPs such as LL37 also functions as T and B cell autoantigens. In psoriasis, we found LL37-specific T cells are biased to produce Th17 cytokines, which further induce LL37 production by keratinocytes providing a self-sustaining inflammatory feedback-loop. In lupus, we found LL37-specific autoantibody production by autoreactive B cells. LL37-specific antibodies also provided a self-sustaining inflammatory feedback-loop by triggering additional NETosis of neutrophils.

The origin of the DNA in the complexes appears to be multifold, depending on the situation and disease. AMPs may form complexes with self-nucleic acids released into the extracellular environment by dying cells, but may also associate with NET-DNA released by neutrophils undergoing NETosis. AMP-DNA complexes in NETs appear to be particularly immunogenic as they are formed prior to extrusion in the DNase-rich extracellular environment and because NET-DNA is a better TLR9 activator being oxidized and of mitochondrial origin. NET-derived AMP-DNA complexes appear to play a predominant role in systemic inflammatory diseases such as lupus, type I diabetes and atherosclerosis. In skin wounds however, DNA appears to be of microbial origin, released upon AMP mediated killing of the skin microbiota. Whether microbiota also plays a role in chronic inflammatory skin diseases such as psoriasis or whether it is driven by the continuous release of self-DNA by dying cells or netting neutrophils will need to be determined

Based on our findings several therapeutic strategies to block the pDC-IFN inflammatory pathway are currently being developed and tested in clinical trials. Antibodies against pDCs (anti-BDCA2, Biogen Idec, anti-ILT7, Medimmune Inc) have entered phase I trials for lupus and dermatomyositis. Inhibitors of TLR9 (IMO-8400, Idera Pharmaceuticals) have completed phase II trials in psoriasis, anti-IFN-a (Sifalimumab, Medimmune) have been tested in phase II trials in psoriasis and lupus, anti-IFNAR antibodies (Anifrolumab, Medimmune) are being tested in lupus. Other strategies being considered are anti-IL-26 antibodies or antibodies against LL37-DNA complexes, which have shown efficacy in mouse models of atherosclerosis. In the near future we expect to gather additional evidence from these clinical trials for the importance of the described immune pathway in the elicitation of chronic inflammation of the skin and beyond.

Acknowledgments

I wish to thank the Cloëtta Foundation for distinguishing my research work with this award. I am extremely honored that the Foundation considers that this work merits such a fantastic recognition.

All of this could only be accomplished with the guidance of outstanding mentors, the contributions of highly dedicated collaborators, and the thoughtful insights of friends and colleagues.

I would like to thank Yong-Jun-Liu for his mentorship, invaluable support over the years and long-lasting friendship. He was my postdoc supervisor in Palo Alto (CA) and helped me start my career as a junior Faculty in Houston (TX). His geniality and approach to science taught me to think "out of the box".

I also would like to thank the current and past members of my laboratory team. In particular my thanks go to Jeremy Di Domizio, Roberto Lande, Olivier Demaria, Curdin Conrad, Dipyaman Ganguly, Stephan Meller, Loredana Frasca, Josh Gregorio, Cyrine Belkhodja, Sophie Dürr, Alessia Baldo, and Ana Joncic. Without their enthusiasm and dedication this work would not have been possible.

My sincere thanks also go to many outstanding collaborators and friends, who contributed substantially to my scientific work over the years with fruitful discussions and criticisms, especially Vassili Soumelis, Bernhard Homey, Robert Modlin, Jens Schroeder, Daniel Speiser, and Patrick Hwu.

I am also very grateful to my clinical mentors, Günter Burg and Ronald Rapini, who taught me clinical dermatology and provided the grounds for my career.

Special thanks go to my current faculty at the Department of Dermatology in Lausanne, Daniel Hohl, Curdin Conrad, Oliver Gaide, and Stéphanie Christen who share my vision of creating a strong clinical department with the environment necessary to pursue a productive research activity.

Finally, I thank my wife, Stefania, and my children Sélène, Nicole and Matthieu, who deserve much of the credit that I am getting today for their endless support and willingness to move to new places and to start their lives over again.

I would like to dedicate this award to the memory of my father, who was a dermatologist and instilled in me the passion for medicine and the drive for being inquisitive and creative.

This work was possible thanks to the continuous support from many funding agencies including the Swiss National Science Foundation, the Swiss Cancer League, the National Cancer Institute, and the American Cancer Foundation.

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Die Stiftung Prof. Dr. Max Cloëtta

Die Stiftung Prof. Dr. Max Cloëtta wurde am 27. September 1973 in Zürich von Dr. Antoine Cloëtta zu Ehren seines Vaters Prof. Dr. Max Cloëtta errichtet.

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