Neurobiology of the Skin
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Abstracts

Merkel Cells
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Merkel cells (MCs) are neuroendocrine cells which are located in the basal layer of the epidermis. Their origin is still discussed but new arguments are in favour of an epidermal origin rather than a neural-crest origin. MCs are in close contact with nerve endings and their role was limited to an involvement in mechanosensory function until recently. New data indicate that they can be considered as mechanoreceptors by themselves. Because they are dendritic cells and produce neurotransmitters, a very important role as a mediator between epidermal cells and the nervous system has been suggested. Nowadays, it is confirmed that MCs are regulatory cells in the neuro-endocrino-immuno-cutaneous system (NEICS). Due to new possibilities to isolate and culture them, knowledge about MCs is more numerous. The interest about these cells is renewed since the role of a new polymavirus in the genesis of Merkel cell carcinoma (MCC) has been discovered. Merkel cell polyomavirus (MCPyV) is present in most MCC and is very important in this cancer. This is a new very stimulating field of research.

The Effect of Neuropeptides on CLA+ T Cells in Atopic Dermatitis
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Pruritus in atopic dermatitis (AD) can be treated with immunosuppressants or corticosteroids indicating the involvement of T-cell dependent mechanisms in this relevant symptom of AD. On the contrary, CLA+ T-cells constitute a very relevant T cell subset involved in AD. This skin-homing subset of memory T cells are found in AD lesions, preferentially responds to cutaneous allergens, bear Staphylococcus aureus responsive TCRVβ segments, and produce Th2 or Th1 cytokines depending on AD stage. In addition, these lymphocytes express an array of adhesion molecules and chemokine receptors (CCR10 and CCR4) that direct them from blood to inflamed skin lesion, source of their specific ligands. Mental stress increases the frequency of circulating CLA+ T cells in comparison to healthy individuals. CLA+ T cells are also producers of IL-31 whose receptor is present in dorsal root ganglia and that, when overexpressed in the mouse induces pruritus. During AD CLA+ T cells recirculate between skin lesion and blood, since during anti-LFA-1 treatment increases in circulating CLA+ T cells in comparison to healthy individuals. CLA+ T cells are also more numerous. The interest about these cells is renewed since the role of a new polymavirus in the genesis of Merkel cell carcinoma (MCC) has been discovered. Merkel cell polyomavirus (MCPyV) is present in most MCC and is very important in this cancer. This is a new very stimulating field of research.

Molecular and Cellular Mechanisms Regulating Neurogenic Inflammation and Pruritus
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Sensory nerves in the skin regulate a variety of functions such as touch, body defense or thermoregulation, for example. Under pathophysiological conditions, nerves are implicated in inflammatory responses and immune defense, and transmit pruritus and pain. The cellular and molecular mechanisms involved in the regulation of the different neuronal processes are poorly understood. Sensory nerves release neuropeptides that may be beneficial for immune mediated responses in resident target cells or transient immune cells in the skin. Neuropeptides include peptides such as substance P, calcitonin gene-related peptide (CGRP) or PACAP, for example. While some neuropeptides mediate proinflammatory effects and recruit leukocytes to the site of inflammation, others are capable of downregulating proinflammatory cytokines or chemokines. Proteinsases such as trypsin or neutral endopeptidase, for example, inactivate neuropeptides in the extracellular space or at the cell surface thereby terminating neuropeptide-induced inflammatory or immune responses. Proteinase-activated receptors (PARs) or transient receptor potential ion channels of the vanilloid subtype (capsaicin receptors) are recently described receptors which may have a high impact in regulating cutaneous neurogenic inflammation. Upon stimulation by exogenous (temperature changes, irritation, microbes) or endogenous ("stress", hormones, mediators) factors, sensory nerves become activated thereby transmitting the stimulus via afferent fibers to the central nervous system. The interaction between the neuronal mediators and their receptors is tightly regulated and includes mechanisms of receptor inactivation and desensitization as well as degradation. For example, endothelin-converting enzyme-1 (ECE-1) regulates neuropeptide receptor internalization and intracellular cell signaling of MAP kinases by degrading the neuropeptide/neuropeptide receptor complex in lysosomes. Thus, a close multidirectional interaction between neuropeptides, high-affinity receptors and regulatory proteases on nerves, cutaneous cells and immune cells guarantees to restore and maintain tissue integrity and terminates inflammatory responses in the skin. Thus, understanding the molecular pathways of neuro-immune communication represents an important basis for the development of therapies in diseases like atopic dermatitis, and of symptoms such as pruritus or pain.

Neurotrophin Receptors in Healthy and Psoriatic Epidermis
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p75 neurotrophin receptor (p75NTR) belongs to the TNF-receptor superfamily and signals apoptosis in many cell settings. We evaluated the expression and function of p75NTR in human keratinocytes. p75NTR was only expressed in the basal keratinocyte layer and confined to transit amplifying cells (TA). Moreover, in vitro, calcium treatment failed to induce differentiation in subconfluent keratinocytes. Moreover, β-amyloid, a ligand for p75NTR, induced apoptosis in human keratinocytes only in p75NTR expressing keratinocytes, as shown by caspase-3 activation. Brain-derived neurotrophic factor (BDNF) or neurotrophin-4 (NT-4), which signal through p75NTR, stimulated the synthesis of neutral (sebaceous) lipids and of IL6 and IL8 in human keratinocytes, while only p75NTR has a dual role: it acts as a “switch on-off” in differentiation and/or as a pro-apoptotic receptor. Thus, p75NTR is essential for maintaining epidermal homeostasis.

Sebaceous Gland – the Brain of the Skin
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Current evidence suggests that, in addition to the central nervous system, at least some neuropeptides and their receptors are released/expressed in peripheral tissues. In the skin, this important endocrine function has been designated to the sebaceous glands, which also produce androgens, estrogens, all-trans retinoic acid, cortisol, vitamin D3 and eicosanoids. Synthesis of corticotropin-releasing hormone (CRH) in sebocytes indicates that endocrine stress responses can also occur outside of the classical hypothalamus-pituitary-adrenal axis. CRH-binding protein and CRH receptors (CRHR-1 and -2) have also been shown to be expressed in human sebaceous glands. CRH directly upregulates β3-α5-4-hydroxysteroid dehydrogenase, the enzyme that converts dehydroepiandrosterone to testosterone. Moreover, CRH stimulates the synthesis of neutral (sebaceous) lipids and of IL6 and IL8 in human sebocytes. Intracutaneous CRH expression is increased in acne-involved sebaceous glands, it activates and degranulates mast cells and releases histamine and several neuropeptides, such as substance-P. p75NTR expressing keratinocytes are in close contact with sebocytes. Interestingly, genes expressed in signalling pathways operative in age-associated neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, dentatorubral-pallidoluysian atrophy, and amyotrophic lateral sclerosis, have also been identified in hormonally aged human sebocytes. These data demonstrate that the skin, and especially its “brain” the sebaceous gland, represents an adequate model for neurobiological and aging research.

Pruritus in atopic dermatitis (AD) can be treated with immunosuppressants or corticosteroids indicating the involvement of T-cell dependent mechanisms in this relevant symptom of AD. Sensory nerve endings release neuromediators that activate specific receptors of the epidermis. Their origin is still discussed but new arguments are in favour of an epidermal origin rather than a neural-crest origin. MCs are in close contact with nerve endings and their role was limited to an involvement in mechanosensory function until recently. New data indicate that they can be considered as mechanoreceptors by themselves. Because they are dendritic cells and produce neurotransmitters, a very important role as a mediator between epidermal cells and the nervous system has been suggested. Nowadays, it is confirmed that MCs are regulatory cells in the neuro-endocrino-immuno-cutaneous system (NEICS). Due to new possibilities to isolate and culture them, knowledge about MCs is more numerous. The interest about these cells is renewed since the role of a new polymavirus in the genesis of Merkel cell carcinoma (MCC) has been discovered. Merkel cell polyomavirus (MCPyV) is present in most MCC and is very important in this cancer. This is a new very stimulating field of research.

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Pruritus In Mast Cell-Mediated Diseases
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Pruritic skin lesions are a hallmark feature of mast cell-driven diseases such as urticaria and mastocytosis. Mast cells are also involved in the pathogenesis of many other skin conditions including psoriasis, atopic dermatitis, and autoinflammatory syndromes that can come with pruritus. The release of histamine from activated skin mast cells and subsequent H1 receptor binding and activation is a key pathway, but not the only mechanism, in mast cell-mediated pruritus. Here, we will review classical and alternative pathways of how mast cells can induce, modulate and limit pruritus. Also, we will discuss the signals and cellular interactions involved in these processes and their potential as targets for future approaches to prevent and reduce pruritus. The development and introduction to routine clinical practice of novel antipruritic treatment options requires the generation, development and validation of better ways and instruments to measure pruritus and its impact on patients. We will review the instruments currently available to measure pruritus and its impact in clinical practice as well as clinical trials. Also, we will present some novel tools for assessing pruritus activity and impact on patients' quality of life and first results obtained from their use.

Brain Functional Magnetic Resonance Imaging (fMRI) in Dermatology
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Functional magnetic resonance imaging (fMRI) is a means of measuring brain blood flow by way of blood oxygen levels. The science of brain mapping has allowed a detailed insight of the relative processing functions of anatomic sites in this organ. We have used fMRI to dissect the neurocognitive mechanisms that mediate the adverse consequences of the social stigma associated with visible skin lesions of psoriasis, such as disgusted facial expressions of others. Disgust is known to activate the insular cortex. We investigated whether the social impact of psoriasis is associated with altered cognitive processing of disgust using a covert recognition of faces task conducted with fMRI. Psoriasis patients had significantly (p<0.005) smaller signal responses to disgusted faces in the bilateral insular cortex, compared with healthy controls. We hypothesise that patients develop a coping mechanism to protect them from stressful emotional responses by blocking the processing of disgusted facial expressions. Itch is the most prevalent symptom of allergic and inflammatory skin disease however, its pathophysiology and neurobiology are not well understood. Functional MRI investigation of histamine-induced itch demonstrated positive signal in regions including the supplementary motor cortex, premotor cortex and inferior parietal lobe, and multifocal negative signal in orbitofrontal, medial frontal and anterior cingulate cortices. Our novel time-series analysis approach demonstrated progressive activation of distinct regions of prefrontal cortex in itch perception. Improved understanding of both activated and deactivated regions may in the long-term facilitate development of more effective management strategies for treatment of itch. Overall, fMRI is proving a valuable tool for investigation of the “brain-skin” axis.

Back to Clinic – Coping Strategies in Chronic Skin Diseases
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Coping is regarded as a set of responses to stressful events by which the patient can modulate one's reactions to stressors and attenuate psychological outcomes. Coping strategies could be divided into active coping concentrated mainly on problem-solving, expression of emotions and social support seeking or passive coping including avoidance and denial. It was demonstrated that combined emotive coping strategies were associated with more disability, poorer mental health and worse health related quality of life (HRQL) in psoriatic patients. Of note in a one-year longitudinal study, psoriatic patients initially engaged in coping based on expression of emotions, seeking more social support and more distraction and less passive coping were prescribed a lower number of different therapies, were less anxious, less depressed and had a better physical health one year later. Of interest are three coping strategies which use was associated with great decrease in all HRQL domains namely telling others about psoriasis, covering the lesions and avoiding people. Chronic dermatology patients tend to employ less active coping strategies, planning , positive reinterpretation and humor comparing with controls. This observation seems to be in line with other chronic medical condition patients. It seems that teaching chronic dermatology patients abilities enabling them to implement most effective coping strategies could lead to augmentation of self-esteem, anxiety reduction, improvement in HRQL and better adherence to treatment.