ABSTRACTS FROM NEUROBIOLOGY OF THE SKIN SYMPOSIUM

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Neurogenic mechanisms in the pathogenesis of mast cell-driven skin conditions
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In many inflammatory and pruritic skin conditions, mast cells (MCs) have been identified to be major contributors to the pathology. In others, for example psoriasis or prurigo nodularis, the contribution of MCs is less clear. There is increasing evidence, however, that the interaction of MCs and sensory nerves may be relevant to some extent in all of these diseases. We have known for some time that there is a close relation of skin MCs and cutaneous sensory nerves. This is exemplified by the role of neuropeptides and their interaction with MCs in clearly defined MC-driven diseases such as urticaria as well as diseases in which the contribution of MCs is largely unknown, for example prurigo nodularis.

Taken together, our observations and recently published data show that MCs and SNs can work as functional units in the induction and termination of pruritic inflammatory skin reactions. The bidirectional interaction of MCs and SNs in the induction and control of pruritus and cutaneous inflammation may provide novel therapeutic targets for the treatment of various chronic inflammatory and pruritic skin diseases.

Emerging role of alternative splicing in the skin neuroendocrinology
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Skin is constantly subjected to external and internal stressors, thus it is not surprising that it possesses local and fully functional neuroendocrine system. The skin is respond to the stimuli by local expression of multiple neuropeptides, cytokines and hormone, which act autocrine, paracrine and at least in some cases endocrine fashion. Those regulatory molecules may act on target cells thought the interaction with membrane-bound or nuclear receptors and regulate their proliferation, activity and immune properties.

The majority of the genes including those for receptors code several protein variants contributing to the generic variability. Moreover, recent studies suggest that alternative splicing of mRNA is an additional level of regulation of the receptor activity. The corticotrophin-releasing factor (CRF) and its receptor (CRF1 and CRF2) are the principal elements of hypothalamic-pituitary-adrenal axis (HPA) – the main central mechanism of stress response. Both CRF receptors were found to be expressed in various numbers of isoforms in the human and rodent skin. As shown for CRF1 the pattern of the isoforms changed in the skin and is regulated by environmental factors. Moreover, presence of alternative isoforms influences trafficking, localization and activity of main isoform - CRF1a, as shown for keratinocytes (HaCaT) model co-expression various CRF1 isoforms. The possible mechanism include dimerization, decrease of affinity to ligand, modulation of interaction with G-proteins, fast mRNA decay and decay receptor. Because, alternative splicing of mRNA is common feature of majority of membrane-bound and nuclear receptors this model may be extended and form additional level of regulation of their activity.

Moreover, neuropeptides and hormones are implicated in the pathogenesis of several human skin diseases suggesting potential role of alternative splicing in their development and could represent an additional target for drug design.

Recent advances in neurotrophin receptor functions in keratinocytes
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Keratinocytes express the low-affinity p75 neurotrophin receptor (p75NTR) which binds all neurotrophins (NTs), alone or in combination with the high-affinity, tyrosine kinases receptors, TRKA, TRKB or a truncated form of TRKC. p75NTR is expressed in the basal keratinocyte layer and confined to the terminal arborizing (TA) cells. Calcium treatment of subcutaneous keratinocytes induced the up-regulation of p75NTR co-expressed with the expression of the differentiation markers, while TRKA was downregulated. p75NTRposes keratinocytes, freshly isolated from TA cells, expressed more survivin and CX15, while displayed less CK10 and TRA than p75NTRneg TA. p75NTR retroviral infection of stem cells induced a more differentiated phenotype with the same features of like TA cells. On the other hand, when p75NTR was silenced, calcium treatment failed to induce differentiation in subcutaneous keratinocytes. Moreover, p75NTR, a ligand for p75NTR, induced apoptosis in human keratinocytes only in p75NTR expressing keratinocytes. BDNF or NT-4, which signal through p75NTR, determined a higher rate of apoptosis in HaCaT cells overexpressing p75NTR. On the other hand, NT-4 induced cell death in p75NTRRNA transfected HaCaT cells. Because p75NTR is characterized by a dysregulation of epidermal homeostasis, namely alteration of differentiation and resistance to apoptosis, we evaluated the expression and function of p75NTR in this disease. p75NTR was absent in lesional psoriatic skin and p75NTR levels were significantly lower in psoriatic than in normal TA keratinocytes. The rate of apoptosis in psoriatic TA cells was significantly lower, as compared to normal TA cells. p75NTR retroviral infection restored apoptosis in psoriatic keratinocytes. These results suggest that 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.

Serotonergic mechanisms in atopic dermatitis
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Atopic dermatitis is a severely itching chronic inflammatory disease. Patients with atopic dermatitis have been suggested to have a changed personality and being pharoe to have increased stress susceptibility and anxiety. Serotonin (5-hydroxytryptamin; 5-HT) is an important neuromediator being involved in anxiety and stress susceptibility.

In the present study 28 patients with atopic dermatitis have been characterized regarding extent of the disease (SCORAD), pruritus, depression, chronic stress, and personality traits, being correlated with expression of serotonergic markers, 5-HT and its receptor mRNAs, 5-HT1A, 5-HT2A and 5-HT2C, and serotonin transporter protein (SERT), in involved and non-involved (lower) skin, by immunohistochemistry. Expression of 5-HT1AR was found in the upper part of the epidermis, as well as on melanocytes and dermal inflammatory cells. The number of such dermal inflammatory cells in the involved skin correlated with SCORAD values. 5-HT2AR expression was found in the epidermis, on the basal membrane and vessel walls. In the non-involved skin the vessel expression of 5-HT2AR correlated with SCORAD. SERT was expressed in dendritic cells in the epidermis and the dermis and also in the basal layer of the epidermis. The stronger the basal epidermal immunoreactivity of SERT in the involved skin the less degree of stress susceptibility and chronic stress. These results indicate that serotonergic mechanisms are involved in atopic dermatitis.

Itch and pain: Psychophysiological mechanisms and therapeutic strategies
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The complex mechanisms of acute and chronic pain, for example due to sensitization of nociceptors, have been studied extensively. In contrast, research on itch has received far less attention, while itch shares common neurophysiological and psychophysiological processes with pain. In this lecture, recent evidence on the similarities and differences between itch and pain will be discussed on a psychophysiological level, with a focus on both mechanisms and therapeutic strategies. Specifically, an overview about recent psychophysiological studies will be given, including sensory, cognitive, behavioral and affective factors, demonstrating both common and distinctive psychophysiological mechanisms and therapeutic strategies for chronic itch and pain. Implications for possible common therapeutic strategies will be discussed.

The influence of disease on Major Life Changing Decisions
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Skin disease can have a great impact on current quality of life, but it can also have a profound long-term impact on the course of a patient’s life. Everyone takes a number of Major Life Changing Decisions (MLCD) concerning for example which career to follow, or whether to have children. If these are influenced by having a skin disease, this influence will echo down that person’s life: such influences are not confined to skin disease but occur across all aspects of medicine. We have undertaken a detailed literature review of MLCDs and have suggested that MLCDs are integral to cumulative life course impairment.

In order to understand the range of MLCDs influenced by disease of skin or other organs we interviewed dermatology patients (n=51), and patients with chronic disease from the rheumatology, diabetes, cardiology, pulmonary and renal clinics completed questionnaires (n=310). NVivo8 software was used to assist the qualitative analysis.

Career choice (66%) and job (58%) were the most commonly reported MLCDs influenced by skin disease. In the other patients, the most frequently reported concerned early retirement (47%), impact on job (29%), having children (25%), career choice (22%) and relationships (16%). Affected MLCDs were identified and grouped into 15 categories. Amongst the dermatology patients the mean number of affected MLCDs was 5.5. Amongst the other specialties, the mean number was highest in patients with cystic fibrosis and lowest in nephrology patients.

A definition of “MLCD” was proposed based on this analysis, and a MLCD Profile is being created and validated based on the findings of the study. There is a large impact of skin and other diseases on MLCDs. This has important clinical implications: timely proactive counselling of patients may potentially assist patients to take appropriate MLCDs, and hence reduce the long-term burden of chronic disease.