Abstracts

Symposium

„New concepts in dermatopharmacology“

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Gesellschaft für
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Symposium: New concepts in dermatopharmacology

Dermatopharmacological importance of H4-receptors

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Histamine is a multifunctional biological amine with diverse activities in the immune system. During inflammation, histamine is released from preformed stores in mast cells and basophils.

Histamine exerts its effects through four defined histamine receptor subtypes, namely H1R, H2R, H3R and H4R. All HxRs belong to the superfamily of G-protein-coupled receptors (GPCRs) that possess seven transmembrane domains. Each receptor is characterized by a distinct function: the H1R is mostly involved in acute allergic reactions, the H2R is responsible for gastric acid secretion and the H3R is primarily expressed in the brain and modulates neurotransmission. The H4R is the newest of the four histamine receptors identified and is expressed in tissues and cells of the immune system such as the spleen, thymus, bone marrow and preferentially in leukocytes.

The H4R was independently identified about 10 years ago by several groups and has already attracted substantial attention by the scientific community. A major reason for the exceptional interest in the H4R is the fact that this GPCR is expressed in cells of the immune system including mast cells, eosinophils, various T cell populations and antigen-presenting dendritic cells.

Several activities of the H4R on cells involved in inflammatory responses have been investigated so far. Chemotaxis of mast cells, eosinophils, monocyte-derived dendritic cells and natural killer cells have been noted via the H4R. In former studies we could show functional effects of H4R on cells involved in inflammatory and allergic diseases such as human monocytes and dendritic cells including Langerhans cells. Furthermore we showed that the H4R is up-regulated under Th2 conditions on human T-cells. The stimulation of Th2 cells via H4R leads to the activation of AP-1 and to an increase of IL-31 mRNA.

Based on this expression pattern and functions, it is assumed that the H4R plays a pro-inflammatory role in various diseases including bronchial asthma, chronic allergic dermatitis and pruritus [4-7]. Accordingly, substantial efforts have been made towards the development of potent and selective H4R antagonists and first clinical studies have been performed or are planned with these new substances.

Symposium: New concepts in dermatopharmacology

New concepts in dermatopharmacology of vitamin D

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The beneficial aspects of vitamin D in bone health are well established. However, in the last several years there has been considerable interest in the biomedical research community regarding the link between vitamin D metabolism and the risk of a variety of infectious, inflammatory, and autoimmune diseases.

Pre-vitamin D is synthesized in the skin upon exposure to UVB and is modified, mostly in the liver, to 25D, then converted, mostly in the kidney by the 25-hydroxyvitamin D-1α-hydroxylase, to the bioactive form, 1,25D. Clinical measurement of circulating 25D is used to identify vitamin D insufficiency, given that 1,25D levels aregenerally maintained by parathyroid feedback, except in cases of more severe vitamin D deficiency. Intriguingly, deficiency of 25D, rather than 1,25D, is associated with immune dysfunction in vivo and recent investigations have identified mechanisms by which 25D regulates immune responses in vitro. In human macrophages the autocrine function of the 25-hydroxyvitamin D-1α-hydroxylase and the vitamin D-24-hydroxylase, which converts vitamin D into inactive metabolites, is regulated by both Toll-like receptor and T cell cytokine signals. These findings provide insight into how the intracellular vitamin D metabolism regulates human immune responses and contributes to the pathogenesis of human disease.

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Mechanism driven approach to the prevention and treatment of basal cell carcinomas

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BASAL CELL CARCINOMAS (BCCs) are the most common type of human malignancy in the United States; more than one million Americans are diagnosed with BCCs each year. BCC risk directly correlates with exposure to environmental solar ultraviolet (UV) radiation. BCCs manifest sonic hedgehog (Shh) activation and Shh is among the most fundamental signal transduction pathways in embryonic development. Shh pathway activation occurs in both human and UVB-induced murine BCCs, and aberrant Shh signaling, due to inactivating germline mutations in Ptch, the repressor of this pathway, is associated with the rare, dominantly inherited disorder known as Nevoid Basal Cell Carcinoma or Gorlin syndrome. These patients develop large numbers of BCCs, in addition to developing various extracutaneous tumors such as medulloblastomas and rhabdomyosarcomas. Knowledge of the importance of Shh signaling in driving BCC pathogenesis, has led to the identification of small molecules that target different components of this pathway, including smoothened (Smo), Shh, and Gli-1. However, because the Shh signaling pathway is indispensable for development and tissue homeostasis, the safety of Shh inhibitors is an essential consideration for human use. Moreover, preclinical studies indicate that simply targeting the Shh pathway may not totally block the proliferation of BCC cells, suggesting that additional pathway(s) may contribute to drive BCC pathogenesis. Our approach has been to use murine models of BCCs to verify efficacious suppression of the growth of UVB-induced tumors by simultaneously inhibiting the Shh and Akt1 and mTOR pathways thereby implicating Akt1-mTOR signaling in BCCs development. Furthermore, we have shown that the Shh pathway directly regulates mTOR expression and that mTOR is a direct transcriptional target of SOX9, a transcription factor regulated by Gli-1. We have also shown that mTOR inhibition by rapamycin is only partially effective in reducing the growth of UVB-induced BCCs indicating the involvement of Akt1-dependent, but mTOR- independent, pathways that drive the growth of BCCs. Our goal is to develop mechanism-driven innovative approaches to the prevention and treatment of BCCs, the most common type of human malignancy. Indeed we are currently conducting clinical trials in patients with Gorlin syndrome using this approach.