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Special Focus Review

Sebaceous gland receptors

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Receptors are proteins, embedded in a cell or cytoplasmic membrane, to which a mobile signaling molecule may attach. Receptor ligands may be peptides (such as neurotransmitters), hormones, pharmaceutical drugs and/or a toxins, whereas "binding" ordinarily initiates a cellular response. Human sebocytes are biologically and metabolically very active cells and consequently express numerous receptors. Three of four groups of peptide/neurotransmitter receptors, the so-called serpentine receptor group are present (corticotropin-releasing hormone receptors 1 and 2, melanocortin-1 and 5 receptors, μ-opiate receptors, VPAC receptors, cannabinoid receptors 1 and 2, vascular endothelial growth factor receptor and histamine 1 receptor). The single-transmembrane domain receptors are represented by the insulin-like growth factor-I receptor and the third group, which does not possess intrinsic tyrosine kinase activity, by the growth factor receptor. Nuclear receptors expressed in sebocytes are grouped into two major subtypes. From the steroid receptor family, the androgen receptor and the progesterone receptor are expressed. The thyroid receptor family includes the estrogen receptors (α and β isotypes), the retinoic acid receptors (isotypes α and γ) and retinoid X receptors (isotypes α, β, γ), the vitamin D receptor, the peroxisome proliferator-activated receptors (isotypes α, δ and γ) and the liver X receptors (α and β isotypes). The vanilloid receptor belongs to the transient ion channels and is expressed in differentiating human sebocytes. Further sebocyte receptors, which may influence their function are fibroblast growth factor receptor 2, epidermal growth factor receptor, c-MET, CD14, Toll-like receptor 2, Toll-like receptor 4 and Toll-like receptor 6. Receptor-ligand interactions control sebocyte proliferation, differentiation and lipid synthesis. However, not every ligand that binds to a sebocyte receptor also activates it, such ligands are receptor antagonists and inverse agonists.

Introduction

Sebocytes, also called sebaceous gland cells, form the sebaceous gland, a holocrine gland of the skin composed of acini attached to a common excretory duct.[1] These glands are found throughout the skin except on the palms and soles. They are highly hormone-sensitive and account for the vast majority of hormone metabolism in the skin.

Sebocytes are epithelial cells that originate from a basal cell layer at the periphery of the gland. Differentiation and maturation of sebocytes is accompanied by the accumulation of increasing amounts of a unique mixture of lipids (sebum). Approximately 25% of human sebaceous lipids are wax esters that are not synthesized by other cells in the body. With respect to lipogenesis sebocyte differentiation may follow a similar program of differentiation as that observed in adipocytes.[2] These lipid-laden cells then migrate towards the central excretory duct. Eventually, the cells disintegrate and release their lipid content in a holocrine manner. Most of the lipids of the skin surface (approx. 90%) originate from sebaceous glands secretions.

Many studies on human sebocytes have been performed with SZ95 cells, an immortalized human sebaceous gland cell line that shows the morphologic, phenotypic and functional characteristics of normal human sebocytes.[3,4] Makrantonaki and Zouboulis[5] have described the expression profile of human SZ95 sebocytes that are differentially expressed in an age-related manner.

Human sebocytes express, among others, receptors for peptide hormones, neurotransmitters, which are mostly arranged on the cell surface, and for steroid and thyroid hormones, which are found in the cytoplasm or nuclear compartment.[4,6]

Sebocyte Receptors

Peptide hormone and neurotransmitter receptors. (Table 1) Three of four groups of peptide hormone and neurotransmitter receptors are represented in human sebocytes. To the first so-called serpentine or "seven transmembrane domain" receptor group belong

• Corticotropin-releasing hormone (CRH) recepror (CRH-R)1 and 2, whereas CRH-R1 is more abundant and seems to regulate CRH activity.[7,8] Through binding to CRH-R1, CRH and urocortin reduce sebocyte proliferation. CRH upregulates Δ^{5-4} 3β-hyroxysteroid dehydrogenase expression, synthesis of neutral lipids and interleukin(IL)6 and IL8 release;

• Melanocortin (α-melanocyte stimulating hormone, α-melan ocortin, α-melanotropin, melanotropin)-1 and 5 receptors (MC-1R and MC-5R), which bind α-melanocyte stimulating hormone and are located at the cellular surface of sebocytes. MC-1R regulates inflammation in SZ95 sebocytes[9] and exhibits a stronger expression in acne-involved sebaceous glands.[10] The expression of MC-5R is

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Table 1 **Sebaceous gland receptors and their functions on human sebocytes**

Receptor	Ligand	Proliferation	Differentiation/ Apoptosis	Lipid synthesis	Cytokine synthesis
Peptide Hormone Receptors					
CRHR1	CRH, urocortin	↓		↑	↑
CRHR2					
MC-1R	α-MSH	↓			
MC-5R	α-MSH		↑		
OPR	β-endorphin			↑	
VPAC	VIP, NY, CGRP				↑
CBR1			↑		
CBR2	Endocannabinoids		↓		
Histamine-1R	Histamine, antihistaminics			↓ (squalene)	
IGF-IR	IGF-I, insulin			↑	
GHR	GH			↑	
Nuclear Receptors					
AR	Androgens	↑		↔	
PR	Progesterone				
ER-α	Estrogens				
ER-β	Estrogens			↑ (polar lipids)	
RARα	Tretinoin	↓			
RARγ	Tretinoin	↓			
RXRα	Retinoids	↑	↑		
RXRβ					
RXRγ					
VDR	Vit. D	↑	↓	↓	
PPARα	LTB4			↓	↑
PPARγ	Linoleic acid, 15d-PGJ2, thioglitazones, WY 14643			↑	
LXR-α	22(R)-hydroxycholesterol, TO901317	↓		↑	
LXR-β					
VR	Capsaicin	↓			
Other Receptors					
FGFR2b					
EGF	HGF				
c-MET					
CD14					↑
TLR-2	LPS				↑
TLR-4	LTA				↑
TLR-6					↑

weaker than that of MC1-R but has been shown to be a marker of human sebocyte differentiation, since it is expressed in differentiated, lipid-containing sebocytres, only.[11]

• μ-opiate receptors (OPR), which bind β-endorphin. β-Endorphin stimulates lipogenesis and specifically increases the amount of C16:0, C16:1, C18:0, C18:1 and C18:2 fatty acids to an extent similar to linoleic acid in sebocytes.[12]

• VPAC receptors, which bind vasoactive intestinal popypeptide (VIP), neuropeptide Y (NY) and calcitonin gene-related peptide (CGRP).[13] NY activates cytokine synthesis. CGRP is often co-localized with substance P.[14]

• Cannabinoid receptors (CBR) 1 and 2 are expressed in SZ95 sebocytes and sebaceous glands.[14,15] CBR1 was found in the differentiated sebocytes and CBR2 in the undifferentiated cells, whereas endocannabinoids influence sebocyte differentiation via CBR2.

• Histamine 1 receptor, which is bound by histamine and regulates squalene synthesis.[16] Antihistaminics, ligands of histamine 1 receptor reduced squalene synthesis in SZ95 sebocytes.

The insulin-like growth factor (IGF)-I receptor belongs to the second group, the single-transmembrane domain receptors, that harbor intrinsic tyrosine kinase activity, is expressed on SZ95 sebocyte cell surface and can be activated by IGF-I and high concentrations of insulin.[17] IGF-I amplifies lipid accumulation in SZ95 sebocytes in a dose dependent manner. The activation of the IGF-I receptor induced lipogenesis in SEB-1 sebocytes by sterol response

element-binding protein-dependent and independent pathways.[18] IGF-I also stimulates proliferation and differentiation of rat preputial gland cells, which resemble sebocytes, especially in combination with growth hormone (GH).[19]

The third group, which is functionally similar to the second group, does not possess intrinsic tyrosine kinase activity but appear to function through interaction with soluble transducer molecules which do possess such activity. In human sebocytes, they are represented by the GH receptor,[8] whose regulation by GH upregulates sebocyte differentiation and augments the effect of 5α-dihydrotestosterone (DHT) on sebum synthesis.[19]

Nuclear receptors. The nuclear receptors are soluble molecules and employ transcriptional regulation as a means of promoting their biological effects. Thus, though some receptors are compartmentalized in the cytoplasm while others are defined to the nucleus, they all operate within the nuclear chromatin where they bind a hormone-specific "hormone response element". These receptors are expressed in human sebocytes and can be grouped into two major subtypes based on shared structural and functional properties.

From the first group, the steroid receptor family, the androgen receptor (AR) and the progesterone receptor (PR) are present in human sebocytes, in basal and early differentiated ones.[6,20,21]

• AR is stabilized und upregulated by ligand binding, its downregulation reduces sebocyte proliferation.[22] Five intracellular enzymes—all of them expressed in sebocytes[20]—are involved in activation—before binding to AR—and inactivation of androgens. DHEA-sulfate is metabolized by the stearoyl CoA desaturase to DHEA. DHEA and androstosterone are converted to testosterone and later to DHT by 5α-reductase.[20,23] Sebocyte studies of Akamatsu et al. and Zouboulis et al. showed a dose dependent induction of sebocyte proliferation by testosterone treatment[24] and no effect on lipid stimulation.[3] Investigations by Rosenfield et al. and Makrantonaki et al. proved that the expected effect of androgens on sebaceous lipids is mediated by peroxisome proliferators-activated receptor (PPAR) ligands.[25,26]

• Progesterone receptor (PR) was found in nuclei of basal sebocytes of sebaceous glands.[21,27]

From the second group, the thyroid receptor family, the following receptors are expressed in human sebocytes:

• Estrogen receptors (ER; α- and β-isotypes).[27-29] ER-β is expressed in basal and partially differentiated sebocytes. ER-α is expressed in basal and early differentiated sebocytes. One of the natural estrogens, estradiol, is created by oxidative reduction of 4-androsten-3, 17-dion, like testosterone. Treatment of sebocytes with 17β-estradiol showed an effect on polar lipid production but no stimulating effect on neutral lipids.[30] Other previous in vitro data indicated that estrogens may have an influence on the biological activity of sebaceous glands.[31]

• Retinoic acid receptors (RAR; isotypes α and γ) and retinoid X receptors (RXR; isotypes α, β, γ).[32,33] RARα and γ and RXRα are the predominant retinoid receptors in human sebocytes, RAR regulate cell proliferation.[33] The natural ligands for RAR and RXR are atRA and 9-cis retinoic acid. 13-cis retinoic acid (13cRA) inhibits proliferation in SZ95 sebocytes, whereas 13cRA was found to be metabolized intracellularly to the RAR ligand atRA. RXR agonists are stimulating sebocyte differentiation and proliferation. The RXR agonists rexinoids in combination with the specific PPAR agonists, WY 14643, troglitazone and cabaprostacyclin affected differentiation and growth in cultured primary sebocyte-like rat preputial cells.[34]

• Vitamin D receptor (VDR).[35] SZ95 sebocytes also express vitamin D-25-hydroxylase (25OHase), 25-hydroxyvitamin D-1α-hydroxylase (1αOHase) and 1,25-dihydroxyvitamin D-24-hydroxylase (24OHase).[36] Vit. D_3 induces time- and dose-dependent modulation of cell proliferation, cell cycle regulation, lipid content and IL6 and IL8 secretion by cultured sebocytes. RNA expression of VDR and 24OHase was upregulated along with vit. D_3 treatment.

• Peroxisome proliferators-activated receptors (PPAR; α, δ and γ isotypes).[25,37,38] PPARα and γ are the predominant PPAR subtypes in human sebocytes. PPAR are present in mitochondria, peroxisomes and microsomes of sebocytes and regulate multiple lipid metabolic genes.

• Liver X receptors (LXR, α and β isotypes).[39,40] SZ95 sebocytes express both receptors at the mRNA and protein levels. The application of natural 22(R)-hydroxycholesterol or synthetic ligands significantly inhibited proliferation and increased lipogenesis. The expression of known LXR targets, such as fatty acid synthase and SREBP1, was induced by the synthetic LXR ligand TO901317, which also decreased the expression of cyclooxygenase 2 and inducible nitric oxide synthase that was induced by lipopolysaccharide treatment.[40]

The vanilloid receptor (VR) belongs to the transient ion channels and is expressed in differentiating sebocytes.[41] VR ligand capsaicin was shown to reduce SZ95 sebocyte proliferation.

Other receptors. Other receptors been identified in human sebocytes are

• The fibroblast growth factor receptors (FGFR) comprise a family of related but individually distinct tyrosine kinase receptors.[42] Four FGFRs designated FGFR1 to FGFR4 have been identified, two splice variants of FGFR2 are designated FGFR2b and FGFR2c. FGFR2b is localized mainly in the suprabasal spinous layer of the epidermis and sebocytes and plays a crucial role in controlling epithelial proliferation and differentiation. Increased fibroblast growth factor receptor-2 (FGFR2) signaling has been proposed to be involved in the pathogenesis of acne and explains acne in Apert syndrome and unilateral acneiform nevus associated with gain-of-function point mutations of FGFR2.[42]

• Epidermal growth factor (human milk growth factor, prostatic growth factor, β-urogastrone, urogastrone) receptor.[43]

• the proto-oncogene c-met product (c-MET), which is a receptor tyrosine kinase and functions as a receptor for hepatocyte growth factor (HGF; hepatocyte growth factor-scatter factor, fibroblast tumor cytotoxic factor, hepatopoietin A, scatter factor, tumor cytotoxic factor).[44]

• CD14 (endotoxin receptor, Leu M3, LPS-R, Mo2, MY4, myeloid cell-specific leucine-rich glycoprotein), Toll-like receptor (TLR)-2 (Toll-interleukin-1 receptor-like-4, lymphocyte antigen 105, CD282), TLR-4 (lymphocyte antigen 87, Rasl2-8, CD284) and TLR-6 (CD286), which indicate that human sebocytes are immunologically active cells capable of TLR- and CD14-mediated bacterial recognition and play an important role in initiating and perpetuating the activation of both innate and adaptive immune responses.[45,46]

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