The Trinity of Skin: A Neuro–Endocrine–Immune Organ

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For a long time, skin was thought to be no more than the barrier of human's body. However, in the last few decades, studies into the idea of skin as an independent functional organ have gradually deepened people's understanding of skin and its functions.

Keywords: skin ; neuro–endocrine–immune

1. Introduction

The skin is the largest organ of the human body, protecting internal homeostasis from the external environment. However, skin is not only a simple barrier, but also involved in maintaining internal homeostasis through bidirectional communications between the central nervous, endocrine and immune systems. As far back as 1998, the idea of a neuro–immune–cutaneous–endocrine network was developed and initialized as “NICE” [1], although the endocrine aspect was not elucidated in these early articles. Shifting the focus to the present day, emerging evidence has gradually verified that the skin shares and provides the same bioactive molecules as the body, especially the evidence of cutaneous production and action of neuropeptides, hormones and cytokines. This suggests the existence of cross-talk between the skin and the system, and gives the skin a new identity of a neuro–endocrine–immune organ.

2. Neuro Function of Skin

The term “neurogenic inflammation” suggests the critical role of the cutaneous nervous system in immune response and homeostasis. Chronic inflammatory skin diseases such as atopic dermatitis (AD) and psoriasis can be aggravated by stress [2][3][4][5][6], which is a good example of neurogenic inflammation.

2.1. Anatomic Foundation of Cutaneous Nervous System

Skin is derived from ectoderm, like the nervous system, which makes it easier to understand the diverse nervous function of skin. Skin is innervated with mostly sensory nerves, classified into A-β, A-δ and C fibers according to their diameter, myelinization, and velocity of conduction [7]. A-β fibers are highly myelinated, rapid conducting fibers and innervating specialized mechanosensory end organs that include Meissner’s corpuscles, Pacinian corpuscles, Merkel cells, and Ruffini corpuscles [8][9]. A-δ fibers are less myelinated fibers with slower conduction velocity that give sensation to mechanical, heat nociception and non-noxious cold thermal stimuli. C fibers are unmyelinated fibers with the lowest conducting speed, precept thermal and chemical and mechanical stimuli [10][11][12]. Along these fibers lies immune cells such as mast cells [13][14], dendritic cells [15][16], macrophages [17], innate lymphoid cells [18] and γδT cells [19], forming neuroimmune cell units (NICUs) that orchestrate skin homeostasis [20][21].

2.2. Neuroimmune Interactions of Skin

The cutaneous nervous system and immune system have a responsibility in common: sensing. Whether recognizing pathogens through immune cells or precepting noxious stimuli via sensory nerves, these two “sensing” systems of the skin work synergistically against environmental challenges.

Upon sensing stimuli, especially noxious ones, the cutaneous nervous system tends to communicate with the immune system via neurotrophins (NTs) and neuropeptides (NPs), causing subsequent cascading effects known as “neuroimmune interactions” [22][23][24][25]. NTs belong to a family of growth factors that control the development, maintenance, and apoptosis of neurons and regulate skin homeostasis; for example, the stimulation of mast cell degranulation and cytokine release [26]. NPs, such as substance P (SP), calcitonin gene-related protein (CGRP) and hundreds of other types, are secreted by cutaneous nerves [27]. SP induces mast cell degranulation and the release of histamine and vascular

endothelial growth factor (VEGF), subsequently causing proinflammatory effects, hypervascularization and infiltration of inflammatory cells [28][29]. CGRP is involved in vasodilation and neurogenic inflammation [30].

However, neuroimmune reaction of the skin is bidirectional. The cutaneous nervous system also takes orders from the immune system through cytokines. Immune cells sense pathogenic events though a set of receptors, recognizing pathogen-associated molecular patterns (PAMPs) such as LPS and CpG, and damage-associated molecular patterns (DAMPs); for instance, HMGB1, S100 proteins and heat-shock proteins [31][32][33]. Such pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs) and IL-1R, after binding with PAMPs and DAMPs, lead to inflammatory and immune responses through signaling to nuclear factor kB (NF-kB) [34], inducing the expression of proinflammatory cytokines such as IL-1, -6, -31, IFN-I and TNF-α [35][36]. With cytokine serving as ligands and activators of sensory nerves [37], downstream neuro effects take place. For example, IL-6 induces the expression of nerve growth factor (NGF) and NT-3, 4, and 5 [38][39], while IL-31 exerts its pruritic effects [40].

2.3. Skin-CNS Connection

The cutaneous nervous system, as part of the peripheral nervous system, sends and receives messages from the central nervous system (CNS), which can be elucidated using the model of pruritus. Itch receptors on neuropeptide-containing free nerve endings can be directly set off by histamine and other pruritogens, or indirectly by cytokine-induced histamine release [41]. Once an action potential is set off, it travels through the dorsal root ganglia onto the spinal cord, eventually to the somatosensory cortex in the brain. Conversely, CNS also participate in the modulation and inhibition of peripheral pruritis via periaqueductal grey matter (PAG) of the mid-brain [42][43]. Additionally, psychological stress can aggravate pruritus [44][45], which is another solid evidence of skin–CNS connection.

3. Endocrine Function of Skin

3.1. Skin as Endocrine End Organ

Skin is the target of several hormones and expresses a number of endocrine receptors. For example, glucocorticoids (GCs) and mineralocorticoids (MCs) interfere with the epidermal development and homeostasis through GC receptor (GR/NR3C1) and mineralocorticoid receptor (MR/NR3C2), both of which are members of the nuclear receptor (NR) subclass NR3C and are present in all skin compartments [46]. Like GCs and MCs, thyroid hormones (THs) also participate in epidermal development and homeostasis via nuclear thyroid hormone receptors (TRs) TRα and TRβ, expressed in epidermal and dermal cells [47]. Androgen receptors in sebaceous glands and hair follicles regulate sebum secretion and hair growth [48]; insulin receptor and insulin-like growth factor 1 (IGF-1) receptor in keratinocytes (KCs) modify cutaneous development and metabolism [49]. In conclusion, various kinds of hormones bring their biological effects into skin through binding with cutaneous endocrine receptors. Therefore, when the systemic endocrine function is compromised, cutaneous homeostasis will also be influenced. There are abundant supporting clinical findings such as the correlation between acanthosis nigricans, acrochordon and metabolic syndrome in patients with lichen planus [50]; the connection between alopecia areata, vitiligo and autoimmune thyroid disease [51]; and the relationship between acne, hypertrichosis and insulin resistance [52].

3.2. Skin as Endocrine Initiating Organ

Hormones are synthesized in skin mainly through two ways: activation of circulating hormone precursors and de novo synthesis. Examples of the former way include the activation of cortisol and corticosterone through local 11β-hydroxysteroid dehydrogenase (11β-HSD) [53] and the intracellular T4 conversion into T3 via iodothyronine deiodinase enzymes D1 and D2 [47]. Both GCs and THs are essential for skin homeostasis, GCs downregulate inflammation [54] while THs enhance skin susceptibility to inflammation [55]. Another well-known example of hormone activation is the conversion of dehydroepiandrosterone (DHEA) to androstenedione, then to testosterone through isotypes of 17β-hydroxysteroid dehydrogenase (17β-HSD) in skin. Further conversion of testosterone into its most potent form, 5α-dihydrotestosterone (5α-DHT), is completed by 5α-reductase in skin [56].

Other than in traditional endocrine organs, de novo synthesis of hormones also takes place in skin. The most studied example is the equivalent of hypothalamic-pituitary-adrenal (HPA) axis in skin. The traditional adaptive responses to systemic stress are regulated by the HPA axis. Activation of the traditional HPA axis begins with the pituitary production of the corticotropin-releasing hormone (CRH) following stimulation by corticotrophin-releasing factor (CRF) secreted from the hypothalamus. Then, CRH receptor type 1 in the anterior pituitary is activated and induces the cleavage of proopiomelanocortin (POMC) into the adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH)

and β-endorphin (β-END) [57]. ACTH stimulates the adrenal cortex to secret GCs, which responds to stressors and suppresses the HPA axis through negative feedback [57].

When stressors come to the skin, KCs produce hormonal products, similar to that produced in systemic stressful events such as CRH, POMC, β-END, ACTH and α-MSH [58]. Moreover, enzymes of corticosteroid synthesis such as CYP11A1, 3β-HSD, CPY17A1, CYP21A2 and CYP11B1 are expressed in KCs and thus produce corticosterone and cortisol [59][60], which further proves the existence of the skin HPA axis. In an IMQ-treated mouse model whose KC-derived CYP11B1 was knocked out, local homeostasis was impaired and psoriasiform inflammation was exacerbated. Furthermore, even non-IMQ-treated mice presented psoriasiform inflammation after CYP11B1 knock out, showing the homeostasis stabilizing effect of KC-derived GC and the importance of the whole skin equivalent of the HPA axis [54].

Apart from the well-known GCs, vitamin D and its analogs are known as secosteroids, which is synthesized from the skin. In KCs of the basal layer of epidermis, 7-dehydrocholesterol (7-DHC) is converted to vitamin D3 under UVB light, then released into system to further undergo biological activation in the hepatocytes and kidneys [61]. Numerous skin functions are regulated by vitamin D and its receptor, including coregulation in epidermal proliferation and differentiation [62], regulation of the hair follicle cycle [63], promotion of innate immunity [64], and suppression of tumor formation and inflammation [65]. Vitamin D disturbance is often seen in skin diseases, such as low vitamin D status in psoriasis [66] and chronic urticaria patients [67], and elevated vitamin D level in rosacea patients [68].

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