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Sweat mechanisms and dysfunctions in atopic dermatitis

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ABSTRACT

Skin barrier dysfunction is inherent to atopic dermatitis (AD), causing dryness, irritation, and increased permeability to irritants, allergens and pathogens. Eccrine sweat functions as part of the skin's protective barrier. Variations in sweat responses have been observed in patients with AD, and altered sweat composition and dynamics are under-recognized as important factors in the disease cycle. This review discusses the role that sweat plays in the pathogenesis of AD, examines evidence on abnormal sweat composition, secretion, and neuro-immune responses to sweat in atopic skin, and highlights the value of sweat management.

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory dermatosis that involves a complex interplay between genetic, immunologic and environmental factors [1]. Barrier abnormalities play an important role in the pathogenesis of AD, as mutations in the gene for the structural protein filaggrin (*FLG*) result in increased epidermal permeability, decreased SC hydration and increased pH [2,3]. SC pH provides an acidic environment for optimal antimicrobial enzyme activity and surface microbiome diversity [4]. SC pH is determined by exogenous products applied to the skin, as well as endogenous factors such as sweat, sebum [5], and skin microbiota and their metabolism [4].

1.1. Functions of sweat

Sweat is a clear, odorless, hypotonic solution secreted by eccrine sweat glands. In addition to affecting SC pH through delivery of lactic acid and amino acids [6,7], sweat functions in thermoregulation, electrolyte balance, moisturization and immune defense. The mixing of sweat and sebum forms a protective hydrolipid film that limits evaporative water loss and supports skin's microenvironment [8]. Sweat excretion is elevated in response to increased core temperature, serving as a primary thermoregulatory mechanism [9]. Sweat also contributes to skin surface hydration by delivering natural moisturizing factors (NMF) including lactate, urea, and electrolytes [9]. Additionally, antimicrobial peptides and immunoglobulins contained in sweat perform immune defensive functions at the skin interface between our body and the environment [8].

1.2. Eccrine gland anatomy and mechanism of secretion

Eccrine glands are made up of a coiled tube structure in the dermis lined by two layers of secretory cells and surrounded by myoepithelial cells, with numerous capillaries around the gland and duct for reabsorption of ions as the duct extends toward the skin surface (Fig. 1) [8,10]. Sweating is induced by ambient heat, internal temperature change with exercise, and emotion, all of which activate peri-eccrine cholinergic sympathetic nerve fibers to stimulate sweat secretion (Fig. 1) [8]. Acetylcholine (ACh) is the main neurotransmitter that mediates sweating, and is inhibited by histamine [8,11], which blocks cholinergic signal transduction following ACh binding [12]. Cholinergic stimulation of sweat gland cells via muscarinic ACh receptors initiates a signaling cascade in which glycogen synthase kinase 3β (GSK3β) is phosphorylated

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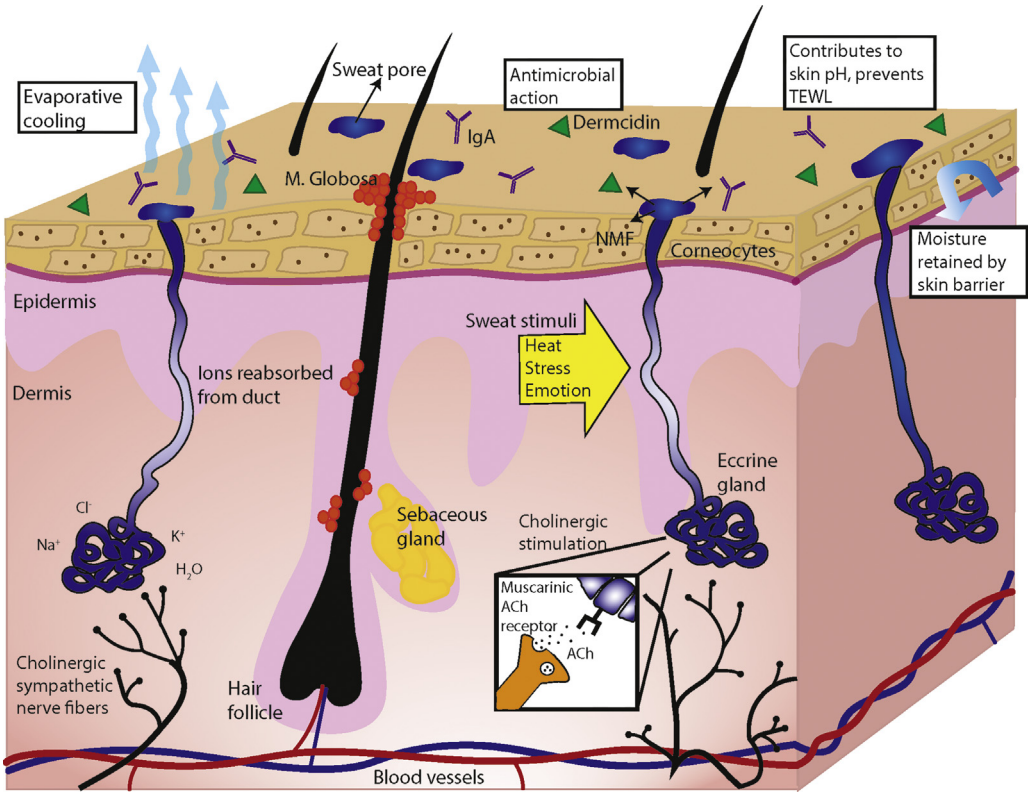

Fig. 1. Normal Sweat Gland Structure and Function.

and inactivated. Conversely, histamine signaling through H1 receptors causes dephosphorylation and activation of GSK3β, which prevents cholinergic stimulation of sweat glands [12]. ACh signaling pathway leads to Ca^{2+} release from the endoplasmic reticulum, causing efflux of water and Na^+ and Cl^- ions into the lumen [8,10]. The ionic content of sweat is further modified by channels in the apical surface of sweat duct epithelial cells, including cystic fibrosis transmembrane conductance regulator (CFTR) and epithelial sodium channel (ENaC). These channels allow for reabsorption of Na^+ and Cl^- to minimize salt loss in sweat [10].

1.3. Normal sweat composition

In addition to water and electrolytes, additional substances have been isolated that contribute to the multiple functions of sweat. Dermcidin (DCD) is an antimicrobial peptide (AMP) produced in eccrine glands and secreted onto the skin surface to fight against surface pathogens such as *Staphylococcus aureus (S. aureus)* and *Escherichia coli (E. coli)* [13] and maintain a balanced skin microbiome [13].

All classes of immunoglobulin have been isolated from sweat, further indicating a role of sweat in immune defense [14]. Sweat modulates skin surface immune milieu through the release of inflammatory mediators including prostaglandins [15] and IL-1α, IL-1β, and IL-31 [16]. These sweat immune mediators activate keratinocytes to produce additional pro-inflammatory mediators. For example, when sweat comes into contact with keratinocytes through a compromised skin barrier, IL-1 and IL-31 function as danger signals, inducing keratinocytes to mount an inflammatory response [16].

Sweat contains NMFs which contribute to barrier integrity by retaining water in the SC. NMFs are made of lactate, urea, free amino acids (AAs), and pyrrolidone carboxylic acid (PCA). The hygroscopic nature of these small molecules attracts water to enhance skin hydration [17] and counteract environmental drying effects. Filaggrin is a major barrier protein that is incorporated into the lipid envelope of corneocytes. It is also a major source of NMFs, as it undergoes degradative processing during corneocyte maturation to release free AAs such as serine, glycine, and alanine, which are found in eccrine secretions [17–19].

While the effects of sweat in healthy skin have been previously characterized, studies on derangements in sweat content and responses in AD patients have yielded conflicting reports. Sweat has largely been considered an exacerbating factor in the disease cycle, but developments in the study of sweat and its effects in AD have shed light on a new emerging perspective. A clearer understanding of the relationship between sweat as a natural homeostatic response and the AD disease process is both warranted and applicable. The purpose of this review is to summarize the current understanding of the role that sweat plays in the pathogenesis of AD, to outline alterations in sweat composition and response, and to discuss the role of sweat management in AD patients.

2. Sweat-associated dysfunctions in atopic dermatitis

2.1. Altered sweat composition in AD

Conflicting evidence exists on whether altered sweat composition is a cause or result of AD. Liebke et al. compared the sweat sodium concentration in 56 children with AD with 60 age-matched healthy controls [20]. Median sodium concentration in sweat of AD children was significantly higher than that of healthy children (21.4 mmol/L versus 12.3 mmol/L, $p < 0.001$). Sugawara et al. investigated how sweat-derived NMF components in AD patients compare to healthy patients and found contrasting results [21]. Patients with mild AD had significantly reduced levels of sodium,

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