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Genetic dysfunctions leading to the pathogenic cascade of atopic dermatitis

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Abstract
Atopic dermatitis is a skin disorder caused by the dysfunction of a multitude of genetic components. This paper reviewed three main genetic factors leading to the pathogenesis of atopic dermatitis including: the epidermal barrier, the body's immune system, and the filaggrin protein.

Running title: Genetic dysfunctions and atopic dermatitis

Keywords: atopic dermatitis, epidermal barrier, immune response, Th cells, filaggrin, filaggrin deficiency

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Introduction

Atopic dermatitis (AD) is an extremely common chronic inflammatory skin disease that causes irritation to the skin that will affect one in 10 people in their lifetime [1]. It is found in approximately 15% to 20% of children and 1% to 3% of adults worldwide [2]. If affected with this disease, one can experience uncomfortable dry and red patches of the skin, leading to the endless need to scratch and thus worsening of the symptoms. It is even associated with sleep disturbances in 47% to 80% of children and 33% to 90% of adults [3]. AD is caused by a multitude of pathophysiologic events such as genetic predisposition, epidermal barrier disruption, and dysregulation of the immune system [4]. AD is a "multi-gene disease" which means there are "many targets for regulation of expression of these genes which may contribute to the pathogenesis of AD" [5]. The main purpose of this manuscript is to explore the role of the genes in AD occurrences.

Epidermal barrier

The epidermal barrier is our bodies' first line of defence against the external environment and serves to prevent loss of water from the skin. If this important barrier is impaired, it may be the catalyst in AD and continue to cause skin inflammation and allergic sensitisation [4]. If crucial protein and lipid components of the stratum corneum, the outermost layer of the epidermis, are missing, dry skin with "abnormal barrier lipid structure and function" may be produced [6]. The protein components that provide the barrier with structural stability include corneocytes (which are differentiated and flattened keratinocytes) and corneodesmosomes (which are modified desmosomes). Together, the corneodesmosomes will hold the corneocytes together and form a barrier that can withstand tension and protect the internal environment from outside microbes [7]. An important process to note is the desquamation of the stratum corneum, which is the regular shedding of superficial corneocytes in order to maintain a consistent thickness of the barrier [8]. However, this process is highly regulated by the balance between proteases and protease inhibitors. If there is enhanced protease activity, either through a genetic mutation in protease/protease inhibitor encoding genes or through exogenous proteases such as those found in house mites and dust, corneocytes of the barrier will be broken down faster than they are replenished [9]. Another key component of the stratum corneum to consider in AD is the lipid lamellae layer. This layer is water resistant and surrounds the corneocytes in order to prevent water loss and strengthen the barrier's permeability while keeping the skin flexible. It is made up of "ceramides, cholesterol, fatty acids, and cholesterol esters" [7]. In abnormal barriers, it is found that levels of sphingomyelin deacylase, the enzyme that catalyses sphingomyelin into other products besides ceramides, are high [7]. This leads to a ceramide deficiency, and thus a lack of the crucial lipid layer needed for a healthy epidermal barrier. Once the physical structure of the barrier is impaired and inflammation worsens, the body will generate cytokines from keratinocytes in order to enhance the allergic immune response [10]. These cytokines are Th2-promoting cytokines, which include thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 [11]. When the immune response is initiated, regular cytokines like interleukins IL-4, IL-13, and IL-31 will stimulate sensory nerves directly and induce pruritus [12]. This will trigger further scratching of the skin and lead to greater skin barrier dysfunction.

Immune response and inflammatory processes

In patients with AD, regulation of innate and adaptive immune responses as well as inflammatory processes is not functioning normally. The initial and acute phase of AD in the immune system is dominated by Th2 and Th22 which are T-helper cells. As mentioned earlier, in cases of AD, a dysfunctional epidermal barrier is observed. Due to this, the body is more susceptible to external agents and harmful pathogens. Once these enter the body, keratinocytes in the skin are damaged and produce "epidermal alarmins" like IL-33, IL-25, and TSLP which in turn, will activate eosinophils and Th2 cells [13]. As a result of these high concentrations of Th2 cells in the acute phase, acute AD is thought of as a "predominantly Th2-driven disease process" [13]. As for Th22 cells, they produce IL-22 which inhibits keratinocyte differentiation and further damages the epidermal barrier [13]. As it develops into the chronic phase, Th1 and Th17 are present [12]. Th17 is recruited as they can promote the removal of extracellular bacteria and activate neutrophil granulocytes in order to fight infection [14]. As mentioned earlier, innate immune cells will release cytokines in response to inflammation which will only worsen the effect of AD. Most notable of the cytokines are IL-4 and IL-13. IL-13 is secreted by Th2 cells and will "down-regulate the levels of filaggrin (FLG), loricrin (LOR), and involucrin (INV) in keratinocytes" which will

intensify epidermal barrier inflammation and impairment [12]. IL-4 and IL-13 inhibit filaggrin through activation of a signal transducer and activator of transcription called STAT6 and STAT3 [15]. Since the skin is already destabilised in patients with AD, the further loss of integral barrier proteins like filaggrin will only worsen the condition. The importance of filaggrin will be described further in this paper. In cases of AD, IL-13 is "over-expressed locally" and as a result, will recruit more inflammatory cells which will prolong the inflammation and promote itching [16]. The over-expression of IL-4 will promote bacterial skin infection and induce IgE production [17]. This happens because IL-4 promotes the differentiation of naive T cells into Th2 cells and, similar to IL-13, will alter keratinocyte protein differentiation and thus inhibit filaggrin. It has been proven that IL-4 and IL-13 drive AD pathogenesis and itching through their receptor expression on sensory neurones [18]. These cytokines will create a cycle of itching and amplification of inflammation in the skin, worsening the patient's condition.

Filaggrin deficiency

Filaggrin (filament aggregating protein, or FLG) is a protein that is found in the epidermis that is essential for helping skin retain moisture. Filaggrin begins as the precursor profilaggrin which is encoded by the FLG gene. Then, it is dephosphorylated and cleaved by endoproteases into filaggrin monomers. The newly synthesised filaggrin will bind to keratin fibres in cells, forming tight bundles which strengthen the epidermal barrier. It does this by aggregating the keratin filaments and collapsing them into a "flattened squam" [19]. This flattened shape helps to strengthen the skin barrier. After aggregation, FLG is degraded into amino acid metabolites by caspase-14, calpain 1, and bleomycin hydrolases [20]. These end products are crucial for stratum corneum hydration, and thus FLG is also responsible for the production of water-retaining molecules [21]. If a patient lacks FLG due to mutations in the FLG gene, this may predispose them to AD as it "renders skin equivalents more sensitive to the detrimental effects of IL-4 and IL-13 compared to skin equivalents with normal FLG expression" [12]. Some mutations of the FLG gene are a complete loss of function, meaning there is a complete loss of the protein [19]. Without filaggrin, the epidermal barrier is much weaker which means it is more susceptible to exogenous molecules, allowing them to enter the body [21]. With this consistent entry of external pathogens, the Th2-mediated immune response will continue to be stimulated, producing more Th2 cytokines like IL-4 and IL-13 [22]. However, it is important to note that even if there are no mutations of the FLG gene, the Th2 immune response characteristic of acute AD will still cause down-regulation of filaggrin (as described earlier). This means all patients with AD will still show lower levels of filaggrin [19]. It is clear that without FLG, the skin barrier will be weaker and more dry, thus creating the perfect setting for AD pathogenesis.

Conclusions

Atopic dermatitis is a multi-gene disease and therefore one must consider a multitude of components when exploring its pathogenesis. This article describes three main factors contributing to the prevalence of AD: the structure of the epidermal barrier, the body's immune responses and subsequent inflammation, and the role of filaggrin and the effects of its deficiency. If even one factor is dysfunctional, it may cause an unrelenting cascade of bodily reactions leading to AD pathogenesis.

Ethical approval

The study was a descriptive one. No human or animals were a subject of examinations.

Acknowledgments

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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