Metabolomics in Atopic Eczema

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Atopic eczema (AE) is an inflammatory skin disorder affecting approximately 20% of children worldwide and early onset can lead to asthma and allergies. Metabolomics, the analysis of small molecules in the skin produced by the host and microbes, opens a window to observe the mechanisms of the disease which then may lead to new drug targets for AE treatment.

Keywords: atopic eczema ; atopic dermatitis ; dermatitis ; metabolomics ; lipidomics ; skin disease ; skin metabolome

1. Introduction

Atopic eczema (AE), also known as atopic dermatitis, is an inflammatory skin disorder that affects approximately 20% of children worldwide and is increasing in prevalence [1][2][3][4][5][6]. AE can naturally resolve prior to adulthood, but for approximately 2–4% of individuals, it is a life-long condition [7]. Additionally, AE onset is also not limited to children, and 26.1% of AE-afflicted adults developed the disease in adulthood [8]. Even though AE can go into remission past childhood, it can also begin a cascade of immune reactions later on in life (such as asthma and allergies) in a process termed the “atopic march” [9]. AE is also associated with an increased incidence of heart disease, and heart failure is 70% more common in people with severe AE [10]. One prevailing AE symptom is skin itchiness [11], which leads to scratching and, in most cases, mechanical skin barrier damage and the exacerbation of inflammation. This starts a vicious cycle of inflammation, further itching, further scratching, and continuous damage to the skin. This AE state also extends deeper than direct physical suffering, as patients have a significantly reduced quality of sleep and, consequently, often additionally suffer from depression and anxiety, leading to an overall reduced quality of life [11].

Despite the large breadth of the literature describing AE, the mechanisms are still unknown [12] and often disputed, especially in the case of whether the host or the environment is the initial or main driving stimulus of AE. People can be predisposed to AE by both their genetics and their environment [5][13]. Some of the genetic predisposition of AE is due to the mutation of skin barrier proteins such as filaggrin, loricrin, and involucrin [14][15][16][17], with filaggrin (FLG) mutation being more common relative to loricrin and involucrin [18]. In addition, heavy use of soap and exposure to pollution can both lead to AE development as both of them damage the microbial skin barrier [19][20][21][22][23]. Alongside the damage to the microbial skin barrier there is also overgrowth of known pathogen *Staphylococcus aureus* [24], where it is even a predictive factor for severity [25].

As AE is described as an inflammatory disease, naturally, the immune system also plays a role in the mechanism of AE and provides a connection between the host and the environment. Physiologically, AE-uninvolved, non-lesional skin has a thinner epidermis in comparison to healthy skin and those with other types of dermatitis [26], which allows easier exposure to the skin’s immune system. Stimulation, whether through allergens or irritants, makes keratinocytes release cytokines such as thymic stromal lymphopoietin (TSLP) to recruit dendritic cells, leading to the T helper cell 2 (Th2) response [27]. AE is characterized as a Th2-cell-dominated immune response [28][29]. Acute and chronic AE can be further stratified by their Th cells, where Th2, 17 and 22 are associated with acute AE and Th 1, 2, and 22 with chronic AE [30]. In addition, as hinted at by the process of atopic march, the allergy-related cytokine IgE is upregulated in the patients of AE [31][32]. IgE can activate mast cells, and mast cells are more abundant in AE lesions, but this accumulation can also occur independently of IgE presence [32]. While it can be debated whether the root cause of the disease is host-dependent or purely environmental, recent advances in the field shows it is likely a combination of factors—implicating both the host and the environment in the onset of AE.

Metabolomics can provide unique insight into the mechanisms of this disease by defining the low molecular weight compounds involved in the AE biological system. In essence, the metabolome provides a promising window into the mechanics of the body’s microbe–host interaction [33].

2. Factors Influencing the Skin Metabolome

The skin as a whole serves as the barrier to the outside environment and, because of its high degree of interaction with the environment, several external factors must be taken into account for direct-skin metabolomics. The skin's metabolome can be affected directly through the skin barrier, like in the case of cosmetics [34], pollution [35], and UV light [36], but also through gut-to-skin interaction, e.g., in the case of caffeine consumption [37]. In addition, intrinsic host factors play a role in the skin metabolome. One such factor is age. Along with the loss of firm collagen filaments and coenzyme Q10 in older skin, other metabolites previously thought to be unrelated can be affected [38]. Another potentially confounding host factor is biological sex, but this confoundment appears to depend on the skin matrix used, where different sexes have distinct metabolomes in sweat [39] but not in surface-stratum corneum sampling [40]. These environmental and host influences on the skin metabolome can sometimes benefit the medical community by providing explanations for disease development, treatment effectiveness and side effects. Small molecules such as glucose can be used as potential biomarkers for disease or elucidate deeper mechanisms present in skin disease [41][42]. Additionally, the skin metabolome does not change only in skin diseases but can even reflect changes from Parkinson's disease [43][44], cancer [45], and many other disorders, as summarized in [46]. There have also been cases where skin metabolomics was used for drug monitoring [47] [48]. All of the environmental and innate effects of skin immunity on metabolism display the high interconnectivity of the skin, and the potential use of the skin as a highway for non-invasive medical screening.

3. Understanding in the Metabolomics of Atopic Eczema

Constructing a universal picture of AE for all affected individuals is difficult due to the variety of endotypes involved in AE [31]. As hinted at by the process of atopic march, allergy-related cytokine IgE is upregulated in patients with AE [31][32]. Many have supposed that the atopic state is due to the lack of childhood stimuli to create an IgE-tolerant or allergen-tolerant phenotype because of the disease's origin early in the patient's life [49]. This was first termed the hygiene hypothesis [50], later renamed the "microbial exposure hypothesis" [51]. It has since been confirmed that early-life stimulation in less polluted yet "dirtier" rural environments decreases the incidence of AE [52]. The IgE phenotype is not universal across all individuals and is suggested to be one endotype of AE. Immunologically speaking, there are two endotypes: IgE-mediated (extrinsic) or non-mediated (intrinsic) [12][31], and biological race. Within the biological race endotype, the differences include a higher Th17 response in Asian AE sufferers that is completely absent in African AE and only slightly present in European AE [31]. In addition to immunologically characterized endotypes, there are also FLG-deficient or -present endotypes and *S. aureus*-influenced or -independent [31] endotypes. Because of the various endotypes of AE, there is a need for further metabolic profiling, because small molecules are often the signals between immune, genetic, and bacterial systems. Many scientists have attempted to illuminate the mechanisms of AE to allow for the more precise diagnosis, understanding, and treatment of patients through metabolomic profiling.

3.1. Findings within the Skin

A large portion of AE metabolomics research is focused on lipids, summarized from the epidermal lipid perspective in Bhattacharya et al., 2019 [53] and with a greater focus on the cornified layer in van Smeden and Bouwstra 2016 [54]. Seeing that AE is described as a skin disease, it is highly relevant to determine the metabolite presence directly at the location of the disease. Among those changed, on the lipidomic side, there are acylcarnitines and glycerophospholipids, and on the non-lipid side, there are amino acids and their derivatives [55]. Because of the typical locations of these metabolites within the skin, it suggests that the skin as a whole is modified in AE, instead of in one particular subcompartment. Metabolomics profiles can change according to the sampling location for healthy skin [56]. This is also the case for ceramides in non-lesional AE skin, where the forehead, the cubital fossa, and the proximal lower forearm have unique profiles [57]. Although the location of skin sampling can influence the metabolome, AE is a disease that affects the entire body, so metabolites that truly reflect the disease should be consistent regardless of location.

Starting with the filaggrin endotype, there is no initial correlation between the lipidome and filaggrin (FLG) mutation [57], and the FLG genotype does not alter the stratum corneum lipid structure [58]. Granted, the lipidome studied in [57] did not cover the correlation of long-chain ceramides with FLG but instead only the short-chain ceramides, free fatty acids, and cholesterols. This potential lack of association should be confirmed in an untargeted lipidomics study. Heterozygous FLG ($FLG^{+/-}$) mutation in AE does result in an increase in arachidonic acid due to the increased breakdown of linoleic acid and breakdown of phospholipids from IL-1β-induced PLA_2 activity [58]. The increase in arachidonic acid is not seen in wild-type ($FLG^{+/+}$) AE individuals; therefore, FLG might play a role in controlling arachidonic acid levels. Because arachidonic acid promotes inflammation, FLG ($FLG^{+/-}$) mutation may play a role in the inflammation of non-lesional AE skin through the production of arachidonic acid [58]. This adds a potential mechanism that may explain the FLG endotype, where FLG or its

products are inhibitors of arachidonic acid production. Aside from the lipids, and in spite of FLG being metabolized to form amino acids, currently there are no skin studies stratifying the amino acid changes in AE [55] to the FLG endotype.

AE-afflicted individuals with the endotype of *S. aureus* colonization have a different lipidome as compared to *S. aureus*-absent individuals [59]. More specifically, AE skin has an increase in shorter-chain free fatty acids (SCFAs) [57], but this effect appears to be *S. aureus*-dependent. Saturated SCFAs are negatively correlated with Staphylococci [57], and their long-chain counterparts are decreased in *S. aureus*-colonized AE skin [59]. The connection with SCFA is further suggested through the inverse correlation of n-6 FA with disease severity [60], because it is known that *S. aureus* abundance can be a predictor of increasing AE severity [25]. The inverse correlation between *S. aureus* and SCFA may be due to the inherent effect that shorter fatty acids can more easily traverse the skin to acidify it, and *S. aureus* does not grow well in acidic healthy skin pH conditions. This means that a decrease in the level of long-chain free fatty acids (LCFA) may be due to cleavage to create shorter chains that allow for better mobility within the skin, and the cleavage is upregulated in AE skin to discourage *S. aureus* growth. This may also be due to direct inhibition, since SCFAs have been shown to inhibit the overgrowth of pathogenic S. aureus sub-strains [61]. The presence of ceramides also suggests inhibitory effects of *S. aureus* overgrowth in AE, where long-chain ceramides are downregulated in *S. aureus*-infected AE skin [59]. Although total ceramide levels are often reported as decreased in AE patients, this appears to be chain-length-dependent, and short-chain ceramide levels have been shown to be increased in AE patients [57][59], which may be indicative of future or current *S. aureus* presence, but further research is needed for confirmation. The relationship between ceramides and *S. aureus* may be an off-shoot of the original association between FFA and *S. aureus*. Since LCFA levels are decreased in *S. aureus*-colonized AE skin, they are no longer available for the de novo synthesis of ceramides by combination with sphinganine. This relationship between decreasing levels of long-chain ceramides [59] and AE could be modulated through dupilumab, a drug targeting IL-4 receptor alpha chain and known to decrease levels of *S. aureus* [62]. Dupilumab has been shown to alleviate the severity of AE and was shown to result in an increase in the level of C26 ceramide [63]. Unfortunately, this increase appears to be transient and more a factor of increasing stratum corneum hydration [63]. However, it does raise the question of the mechanism between dupilumab treatment and *S. aureus* reduction: could it be possible that C26 ceramide provides an inhibitory effect on *S. aureus*? Dupilumab could be simply reducing *S. aureus* abundance through skin hydration, but further non-targeted studies on dupilumab and *S. aureus* would be beneficial.

As of now, a large portion of direct skin AE studies focus on the changing ratio of the lipid components of the skin, due to its predominance in the structural integrity of the skin's barrier. Lipids are not the only metabolite present in the skin, and more studies are beginning to go beyond lipids to other molecules in order to explain the effects seen in AE. One such effect is the negative impact sweat has on AE. Contrary to skin measurements [64], sodium and salts were found to be similar between HE and AE individuals' sweat [42], and the presence of glucose within sweat positively correlated with AE severity [42]. This increase in glucose appeared to be specific to acute inflammation in comparison to chronic AE inflamed and non-inflamed skin [42], suggesting a role in early AE development. The increase in glucose did not correlate with an increase in the downstream fermentation product lactate, suggesting that it was not a cessation of the TCA cycle [42]. It is possible that this lactate does not come from human cells but is a product of microbial fermentation. This explanation would also support the decrease in pyruvate seen, where the TCA cycle may be downregulated, resulting in less pyruvate [42]. If true, this increase in glucose would signify a loss of SCFA, which can be used to prevent inflammation through TREGs [65].

3.2. Findings within the Blood

The difference in the metabolomic ecosystem between AE-afflicted and healthy individuals seen within the skin was also found to be true for the circulatory system [66][67][68]. The correlation between the skin and blood matrix is corroborated by Agrawal et al. [69], where sweat metabolites and serum have been found to overlap in lipid profiles. However, this is not universal for all metabolites. A study by Töröcsik et al. [70] found that lipid arachidonic acid was significantly changed in skin biopsies but not in serum, and further non-targeted research should be performed to determine the overall metabolic overlap between these two matrices [46].

According to unsupervised statistics, the untargeted AE and HE metabolome was not separated within the blood [67], but instead differences appeared to be more on the singular molecule-to-molecule basis. It is also possible that global differences were better parsed out after stratifying for the individual endotypes within AE. Deficiency in cytoskeletal protein DOCK8 can result in AE, but the metabolic profiles are distinct between DOCK8-deficient and AE WT individuals [68]. This implies the potential for metabolomics to differentiate between genetic subgroups of AE, such as with the FLG endotype. The filaggrin mutation has been shown to display a unique plasma metabolome and filaggrin-associated metabolites correlate with high IgE levels [66]. This suggests a filaggrin-IgE relationship, which was also seen in the case of

omalizumab treatment, and although it is a known drug for urticaria, omalizumab is currently under consideration for treatment in AE.

3.3. Infantile AE Findings as a Precursor for the AE Metabolome

Affected infants have a unique immunological profile compared to adults with AE [31] and this may also be the case for the infantile metabolome. In the case of lipids, SCFA appear to be a conserved metabolite group seen in both infants and adults. For infants, SCFA, butyrate and valerate are present in persistent AE and HE cases, but their levels are lower in individuals with transient AE who later recovered [71]. SCFAs are suggested to protect AE through Tregs or the modulation of *S. aureus* growth. These results suggest a protective effect of these SCFA in short-term AE cases but a dysregulation or inability to compensate and protect the skin from inflammation in chronic AE. Lower levels of SCFA butyrate and propionate in early life (~6 mo. after birth) are associated with AE development within 2 years of age [72], further supporting the protective effect of SCFA against the development of AE. This association with SCFA is possibly a result of early weaning where SCFA-producing bacteria from breast milk have not yet been fully established within the gut [72]. Another possible cause of early-stage AE is high amounts of long-chain saturated fatty acids within the breast milk of mothers with AE children [73]. Exposure to long-chain saturated fatty acids in milk can result in an accumulation of type 3 innate lymphoid cells (ILC3) within the gut [73]. These lymphoid cells can then migrate to the skin, thereby triggering the first inflammation of the AE cycle [73]. SCFAs are not the only conserved metabolite type seen in AE individuals across the ages. Hexoses, including glucose, are present in high amounts in both newborns and infants [74]. Glucose drives inflammatory expression in early-stage AE [74] and is associated with the expression of bacterial virulence factors within the gut of infants with AE [72]. Amino acid expression is also suggested to have a protective effect against infantile AE with an inverse correlation with inflammasome expression [74]. Overall, this highlights several conserved mechanisms that occur across both early-stage and advanced stage AE.

Besides conserved mechanisms, studying AE at the infantile level allows for a unique opportunity to observe the abiotic environmental impacts on AE development. Pollution, such as parabens, has been suggested to be a major factor in the development of AE.

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