Dermatology Practical & Conceptual

Tape Stripping — Searching for Minimally Invasive Biomarkers in Atopic Dermatitis

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ABSTRACT Atopic dermatitis (AD) is nowadays entering a new era of more targeted treatments. However, to make personalized medicine, which we are currently striving for, a reality, a reliable set of validated biomarkers is needed. The most practical seem to be biomarkers that can be obtained easily and minimally invasively. Tape stripping (TS) is a method that provides such an opportunity. This review summarizes the potential biomarkers of AD identified by the minimally invasive TS method. Thymic stromal lymphopoietin (TSLP), interleukin (IL)-13, CC chemokine ligand 17 (CCL17)/thymus and activation-regulated chemokine (TARC) and stratum corneum (SC) lipids can be used as predictive biomarkers for AD occurrence. CCL17/TARC also holds great promise for being reliable biomarkers for AD severity as well as treatment response. Nitric oxide synthase 2 (NOS2)/inducible nitric oxide synthase (iNOS) which high expression is specific for psoriasis may be a good biomarker for differential diagnosis between psoriasis and AD in challenging clinical situations. AD children with food allergy (FA) have a unique endotype characterized by selectively altered expression of various molecules in the skin that can indicate FA coexistence. Unfortunately, although numerous potential biomarkers have been found, none of these candidates have been validated and implemented into routine clinical practice, which still separates us from the possibility of a precise approach to AD patients.

Introduction

Atopic dermatitis (AD) is a chronic and highly heterogeneous inflammatory skin disorder with severe itching affecting approximately 20% of children and up to 10% of adult patients worldwide [1]. The disease is characterized by different endotypes that drive specific phenotypes [2]. Multiple factors such as disease chronicity, age of onset, ethnicity,

immunoglobulin E (IgE) levels, filaggrin mutation status, and underlying molecular mechanisms orchestrate the phenotype of AD [2]. Immune polarization in AD is primarily towards Th2/Th22, with variable Th1 and Th17 components [2]. In the phase of acute lesions, which are erythematous, wet, and highly inflammatory, accumulation of cytokines from the Th2 and Th22 axes and, to a lesser extent, Th17 is observed [2]. With disease chronicity, lesions turn lichenified, dry, thick, and hyperpigmented, which is accompanied by the intensification of Th2 and Th22 responses with significant increases in Th1 cytokines but no further increases in Th17 cytokines [2]. Apart from the typical Th2/Th22-dependent immune response, adult AD patients exhibit greater expression of Th1 cytokines than pediatric AD patients, whereas pediatric AD patients have higher involvement of Th17 cytokines than adults [2,3]. Additionally, the morphology and distribution of AD lesions change as patients age [2,3]. Asian AD patients have higher Th17 and lower Th1 axis activations than European American AD patients, who are characterized by immune polarization mainly towards Th2, Th22, and Th1. African American AD patients exhibit primarily Th2/Th22 axis activation with parallel attenuation of Th1/Th17 [2,4]. According to the IgE levels, AD can be categorized into the IgE-high, extrinsic subtype presented in 80% of patients, and the IgE-normal, intrinsic subtype in the remaining 20% [2,3]. Moreover, extrinsic AD is associated with traditional immune polarization towards Th2, eosinophilia, personal and family atopic background, and a higher percentage of filaggrin (FLG) mutation, whereas greater Th1 and Th17/Th22 immune responses, delayed disease onset, preserved barrier function, and increased metal contact hypersensitivity characterize patients with intrinsic AD [2,3].

With the development of novel targeted, highly specific therapies for AD over the past few years, we are seeing a revolution in the field of treatment for this disease. However, due to the high heterogeneity of AD, we will not be able to fully benefit from these therapies, which are regrettably also very expensive, without a precise medical approach [2] Therefore, it is essential to search for reliable biomarkers, based on which it will be possible to accurately stratify patients and then apply appropriate preventive strategies or therapy precisely tailored to the patient's needs, resulting in a medical care system with higher efficacy, less risk to the individual, and lower overall costs [5]. In other words, a validated set of biomarkers is an essential instrument in the toolbox of precision medicine in AD. A recently published review article on behalf of the International Eczema Council highlights the great unmet need for minimally invasive biomarkers, which would enable the implementation of precision medicine in AD [6].

Tape stripping (TS) is a minimally invasive way of obtaining stratum corneum (SC) and some of the stratum granulosum (SG) samples using adhesive tapes. The technique is simple, painless, and causes neither bleeding nor scarring. It is only associated with mild discomfort and a temporary red mark on the skin [7]. SC samples collected by TS are suitable for detecting several biological entities such as proteins, proteases, lipids, and RNA, providing a wide range of immune and epidermal barrier biomarkers for both lesional and nonlesional skin [8]. Until recently, the only method to obtain biomarkers from the skin was through a painful and scarring skin biopsy, which may also be complicated by infections and poor healing [6]. TS technique appears to be a promising and reliable alternative to skin biopsies in evaluating skin biomarkers in AD patients, especially infants, in whom conventional, painful skin biopsy may be difficult to perform and practically contraindicated [9]. In addition, due to the non-invasive nature of TS, this technique allows repeated skin samples to be taken from the same patient in a short time for various purposes, such as therapy monitoring or clinical trials, and longitudinal studies [9]. Skin biopsies in these cases would be challenging. The main limitation of TS seems to be that only biomarkers present in or diffuse into the superficial layers of the epidermis can be captured [9]. Moreover, previous tape strip reports in AD described limited sample detection rates [6], but recently global transcriptomic studies in young children and adults with AD have shown improved rates of detection, which were almost 100% per sample and marker [10,11].

Objectives

In this review, we provide a summary of potential AD biomarkers identified by the minimally invasive TS method (Table 1).

Methods

A comprehensive search of the literature using the PubMed electronic database with the search queries,,atopic dermatitis AND tape strips", atopic dermatitis AND tape stripping", „atopic dermatitis AND potential biomarkers", „atopic dermatitis AND biomarkers", „atopic dermatitis AND skin biomarkers", „atopic dermatitis and epidermal biomarkers", and „atopic dermatitis AND minimally invasive biomarkers" was performed. The search period was from the inception of the database to 8 May 2023. Based on the title and abstract analysis, we included articles concerning the potential biomarkers in atopic dermatitis identified by the tape-stripping method. At this step, we excluded records not related to the topic, non-English manuscripts, personal opinions, and duplicates or related to skin biopsy instead of tape strips. After reading the full manuscripts, some were excluded (not relevant or providing information concerning only skin

Table 1. The table shows the molecules that were tested by the tape stripping (TS) method as potential biomarkers. So far, none of them has been validated and implemented in routine clinical practice.

The potential biomarkers of atopic dermatitis (AD) identified by the TS method	
Biomarkers for AD occurrence	TSLP, a panel of biomarkers: positive family history of atopic diseases, IL-13, 26:1-SM, and O30:0(C22S)-CER; phytosphingosine, CCL17/TARC
Diagnostic biomarkers	IL-34, FLG, FLG2, LOR, FA2H, NOS2/iNOS[a]
Biomarkers for AD severity	IL-18, CXCL8, VEGF-A, Flt-1, IL-33, IL-23p19, IL-19, S100As, PI3, IL-36G, DEFB4B, STAT3, LL-37, IL-17C, K16, IL-4R, CD11b, CD11c, CCL17/TARC, CTACK, IL-8, TSLP, CCL2, Hbd-2, VEGF, MIF, MMP12, ICOS, IL-13, CCL26, IL-22, IL-17F, IL-26, CAMP/LL-37, FOXP3
Biomarkers of barrier function	TSLP, Gal-7, SERPINB3, TARC/CCL17, CCL22, IL-22, IL-17A, trihydroxy-linoleic acid
Biomarkers for monitoring treatment response	TARC/CCL17, IL-8, CSF1, CCL13, CCL23, KYNU, IL-6R, CCL20, IL-34, FABP7, NGF, IL-37
Biomarkers for comorbidities (Food allergy)	FLG, KRT5, KRT14, KRT16

AD = atopic dermatitis; IL = interleukin; CCL = CC chemokine ligand; CXCL = C-X-C motif chemokine ligand; CSF1 = colony-stimulating factor 1; CTACK = cutaneous T cell-attracting chemokine; DEFB4B = β-defensin 4B; FABP7 = fatty acid binding protein 7; FA2H = fatty acid 2-hydroxylase; FLG = filaggrin; Flt-1 = vascular endothelial growth factor receptor 1; FOXP3 = forkhead box P3; Gal-7 = galectin-7; ICOS = Inducible T-cell COStimulator; hBD-2 = human b-defensin-2; KRT = keratin; PI3 = phosphoinositide 3-kinase; K16 = keratin 16; KYNU = Kynureninase; iNOS = inducible nitric oxide synthase; S100As = S100 calcium-binding protein A; LL-37 = cathelicidin; LOR = loricrin; MIF = macrophage migration inhibitory factor; MMP12 = matrix metallopeptidase 12; NGF = nerve growth factor; NOS2 = nitric oxide synthase 2; STAT3 = signal transducer and activator of transcription 3; TARC = thymus and activation-regulated chemokine; TSLP =thymic stromal lymphopoietin; VEGF = vascular endothelial growth factor.

[a]potential biomarker for differential diagnosis between psoriasis and AD

biomarkers identified by skin biopsy instead of tape stripping). Finally, we also included other suitable records that we found by searching references through other articles we found. Potential minimally invasive skin biomarkers identified by tape stripping were analyzed and summarized.

Results

Potential Biomarkers for AD Occurrence

The identification of biomarkers that can select infants at risk of developing AD would allow the implementation of target preemptive interventions. Currently, the best-known risk factor for AD is FLG mutations, carried by approximately 10% to 40% of these patients [12]. A positive family history of AD is another well-established risk factor [4]. Since, for instance, the application of emollients from birth has been proposed as a preventive measure in high-risk infants [13]. However, two recently published trials did not confirm that daily use of emollients during the first year of life prevents AD in high-risk children [14,15]. Perhaps we may also need additional preventive strategies for AD. However, to establish a primary prevention strategy, it is essential to find biomarkers that can predict the development of AD. The effective prevention of AD would undoubtedly represent an important public health breakthrough.

In the prospective birth cohort study, the expression of epidermal thymic stromal lymphopoietin (TSLP) was proposed as a potential early biomarker for predicting AD development in infants. Children with high TSLP expression at 2 months were 5.3 times more likely to develop AD by age 24 months (95% CI, 1.3-21.4) [16]. Berdyshev et al [17] indicated a panel of biomarkers that predicted the onset of AD by the age of 24 months with an OR of 54.0 (95% CI, 9.2-317.5). It was the combination of a positive family history of atopic diseases, high IL-13, high 26:1-SM, and low O30:0(C22S)-CER levels in skin tape strips [17]. Rinnov et al [18] found that children who developed AD in the first 12 months of life had an altered SC lipid composition. Among the examined lipid markers, reduced phytosphingosine level may serve as a single predictor of the occurrence of AD with a prediction accuracy of 75.6% [18]. Another study has shown that elevated CCL17/TARC levels in SC at 2 months of age increased the risk of AD development within the first 2 years of life (aHR: 1.85; 95% CI: 1.18-2.89; P = 0.007) [19].

Noteworthy, all of these studies focus on biomarkers that predict the development of AD in infants. Since we have learned that AD represents a disease that can occur at any age [20,21], the availability of biomarkers predicting adult-onset AD or AD in the elderly would be very useful.

Moreover, childhood AD can have periods of long remission and then recur in later stages of life [20,21]. Such prognostic biomarkers would be also very helpful in terms of the prevention of AD.

Potential Diagnostic Biomarkers of AD

To date, the diagnosis of AD is most commonly based on Hanifin and Rajka criteria, which were primarily developed based on the pediatric population. The clinical picture of AD in adult patients is characterized by marked heterogeneity. Reliable biomarkers for the diagnosis are lacking, and a diagnosis of AD, especially adult-onset AD, can be challenging [20]. Furthermore, there is a range of diseases that can mimic AD in both children and adults [22]. For this reason, there are unmet needs for biomarkers to confirm the diagnosis or distinguish AD from other diseases with similar manifestations, which would be incredibly useful in challenging cases.

Guttman-Yassky et al [11] has described IL-34 as a perfect single-gene classifier to discriminate early-onset AD skin from normal skin with almost 100% accuracy. Moreover, they found that epidermal barrier markers, such as FLG, FLG2, loricrin (LOR), and fatty acid 2-hydroxylase (FA2H), were also effective discriminators. A comprehensive transcriptome analysis in patients with AD and psoriasis identified nitric oxide synthase 2 (NOS2)/inducible nitric oxide synthase (iNOS) expression as a single gene biomarker that can differentiate these two conditions with 100% accuracy (AUC = 1.0) by quantitative PCR and almost perfectly

(AUC = 0.97) using the RNA-seq data [10]. Psoriasis skin exhibited significantly elevated levels of NOS2/iNOS expression, whereas AD skin exhibited no discernible increase in expression [10]. Thus, the differential expression of NOS2/iNOS between psoriasis and AD skin suggests its potential utility as a valuable biomarker for distinguishing between these two dermatological conditions, particularly in challenging clinical situations.

The usefulness of TS for differential diagnosis in patients with overlapping features of AD and psoriasis also finds reflection in real-life clinical practice. In patient presenting with concurrent psoriasis and AD, the analysis of tape strips revealed pronounced expression of Th17-related products, along with NOS2/iNOS, which is specific for psoriasis, as well as Th2-related products characteristic of AD confirming the overlap of the two diseases. The coexistence of these two conditions was also previously confirmed by a skin biopsy [23]. This suggests that TP can serve as a diagnostic tool in challenging clinical situations, replacing the need for invasive skin biopsies to distinguish between AD and psoriasis. However, there are still numerous biomarkers differentiating AD from many other diseases that need to be discovered.

Potential Biomarkers for AD Severity

In the era of more targeted therapies for AD, knowing the exact severity of the disease seems crucial for planning the appropriate timing, and intensity of treatment.

In the study by McAleer et al [24], among the examined SC markers, the levels of IL-18, CXCL8, VEGF-A, and Flt-1 in non-lesional skin showed the highest correlation with AD severity and barrier function among AD infants [24]. The investigation by Guttman-Yassky et al [11] among children with early-onset AD showed the greatest number of significant correlations between disease severity and lesional biomarkers, including the expression of Th2 (IL-33, IL-4R) and Th17 (IL-23p19) cytokines, Th17/Th22 (IL-19, S100As, PI3, IL-36G, β-defensin 4B (DEFB4B), STAT 3, and cathelicidin LL-37), innate (IL-17C), hyperplasia (epidermal proliferation marker K16), Th2 (IL-4R), and cellular (CD11b and CD11c) biomarkers. In another assessment of biomarkers, the levels of CCL17/TARC, CTACK, IL-8, and IL-18 in both lesional and non-lesional tape-stripped skin were indicated as crucial biomarkers of AD severity in children [25]. Cytokines such as IL-8, IL-18, and TSLP have demonstrated a positive correlation with SCORAD in lesional AD skin in the study conducted by Lyubchenko et al [26]. Furthermore, IL-8 appears to be a useful biomarker of local severity in both acute and chronic AD lesions [27]. Hulshof et al [28] has pointed out CCL17/TARC, CXCL8, and CCL2 as the most promising biomarkers to assess the severity of AD in children. In non-lesional AD skin, all 3 biomarkers significantly correlated with objective SCORing AD (oSCORAD), whereas in lesional AD skin, only CXCL8 significantly correlated with oSCORAD. Clausen et al [29] found a significant positive correlation between hBD-2 in lesional skin and both disease severity (SCORAD) and skin barrier function (TEWL) [29]. VEGF has been proposed as an indicator of the acute inflammatory condition of skin lesions in patients with AD [30]. Macrophage migration inhibitory factor (MIF) was suggested to be a marker of the local severity of AD, as its level in SC significantly correlated with the severity of the local skin lesion [31]. Other suggested biomarkers by He et al in lesional skin that may reflect the clinical severity of AD (according to TSS and IGA score) included markers of general inflammation (matrix metallopeptidase 12 (MMP12)), T-cell activation (inducible T-cell COStimulator (ICOS)), Th2 (IL-13, CCL17/TARC, and CCL26/eotaxin-3), Th22 (IL-22), Th17 (IL-17F, IL-26, and cathelicidin antimicrobial peptide (CAMP)/LL37), and T-regs (FOXP3). [10] CCL17/TARC may be useful in the evaluation severity of lesions of AD, especially in acute ones as its level in SC was strongly correlated with acute phase parameters of lesions such as erythema, edema/papule, and oozing/crusts but not with itching and excoriation or chronic parameters such as lichenification and xerosis [32]. Additionally, CCL17/

TARC has been considered an indicator of AD's systemic disease severity, as it correlated with laboratory parameters reflecting the systemic severity of the disease, such as the serum IgE level and the blood eosinophil count [32]. It should be mentioned that serum CCL17/TARC levels according to many studies, appear to be the most reliable biomarker for AD severity in both adult and pediatric patients currently available [6].

Biomarkers of Barrier Function in AD

Sano et al [33] found that the TSLP expression level was correlated significantly with SCORAD and epidermal barrier functions, such as TEWL. Importantly, among items within SCORAD, a significant correlation was shown only with the itching score and xerosis score, which is regarded as a reflection of epidermal barrier dysfunction in AD [33]. According to these results, the hypothesis was put forward that the expression level of TSLP in SC might be a useful biomarker of AD severity, especially epidermal barrier status. In addition, it seems to be applicable for estimating the effects of the use of moisturizing products on skin dryness because, after treatment with moisturizer, the level of TSLP was reduced [33]. Using an in vivo model of skin barrier disruption, it has been shown that the level of galectin-7 (Gal-7), which plays a role in maintaining epidermal homeostasis, was significantly correlated with TEWL [34]. Skin tape strip proteomic analysis has shown that among 45 identified proteins in non-lesional AD skin, SERPINB3 expression had the highest positive correlation with TEWL, while KRT10 expression had the highest negative correlation with TEWL [35]. Lyubchenko et al [26] has found that the levels of CCL17, CCL22, TSLP, IL-22, and IL-17A in lesional AD skin positively correlated with skin TEWL measurements in the pediatric cohort. According to results obtained by Chiba et al.[36], the trihydroxy-linoleic acid levels in the SC significantly correlated with TEWL, which makes it another possible biomarker of barrier function in AD easily measured by TS.

Potential Biomarkers for Monitoring Treatment Response of AD

The effective treatment of AD is a highly desirable goal. According to the data, up to over 55% of adult patients with moderate to severe AD complain of inadequate disease control [37]. Considering the high heterogeneity of AD, the "one-size-fits-all" approach may not be successful in these patients because treatment response may differ depending on immune differences in particular AD endotypes/ phenotypes [3]. Biomarkers for monitoring treatment response may provide objective information on how effective a particular drug is in each patient. This would have significance in terms of selecting appropriate therapies for patients and consequently ensuring successful treatment outcomes. We greatly need biomarkers predicting treatment response to a particular drug, which is essential in the current era of new targeted therapies in AD. Based on these biomarkers we would be able to identify patients who will likely benefit most from particular drugs and stratify them before treatment initiation.

The TS technique was applied to assess the effect of topical therapy in a few studies. The results put CCL17/ TARC and IL-8 in the light of promising biomarkers for monitoring topical therapy effect. After 6 weeks of using emollient, CCL17/TARC, and IL-8 expression decreased in moderate AD patients, which was correlated with reduced disease severity [38]. Additionally, it has been demonstrated that the expression of IL-8 in SC was significantly reduced after topical corticosteroid treatment and correlated with visual improvements in symptoms of AD [39]. Moreover, TS may be useful for assessing treatment response to systemic targeted drugs such as dupilumab. He et al [40] found that many key immune proteins were significantly decreased in lesional skin after dupilumab treatment, further correlating with the improvement of clinical symptoms of AD, as measured by EASI. These included markers of immune cell infiltration such as macrophages (CSF1), immune markers related to Th2 (CCL13, CCL23), Th17 (KYNU), and innate immunity (IL-6R) [40]. CCL20, IL-34, and FABP7 were also observed to be useful in monitoring therapeutic response to dupilumab treatment [41]. Quantitative analysis of nerve growth factor (NGF) in AD stratum corneum has found that the level of NGF reflects the severity of the disease and may also help assess the therapeutic effects of AD [42]. The expression of NGF has been significantly downregulated after antihistamine and/or topical steroid treatment and correlated with the decrease in the severity of AD lesions and laboratory severity parameters of the disease, such as eosinophil count, and LDH level [42]. IL-37, an anti-inflammatory cytokine, is also believed to be a reliable biomarker to monitor cutaneous therapeutic response. An association between SCORAD score improvement and up-regulation of IL-37 following treatment of mometasone has been observed [43].

TS method can be a useful tool for treatment response. Traditional monitoring methods for treatment response often rely on subjective assessments or clinical observations. TS method provides objective evidence of changes occurring in the skin, allowing for a more accurate assessment of the efficacy of a treatment and tracking changes over time. Furthermore, the procedure can be easily repeated at different time points to monitor the progression of treatment response over time. The data obtained from TS can help us make informed decisions about treatment regimens and determine whether to escalate or reduce the intensity of the treatment or change medications resulting in ultimately improved patient outcomes.

Potential Biomarkers for Comorbidities of AD

Patients with AD often have not only allergic comorbidities but also others such as neuropsychiatric, autoimmune, metabolic diseases, or cardiovascular diseases [44]. There is a great need to seek biomarkers associated with comorbidities in AD. Evaluation of candidate biomarkers for comorbidities in AD by TS is limited; there are a few reports regarding food allergy (FA) in AD patients.

Skin tape strip proteomic analysis has shown that AD children with FA have a unique endotype characterized by selectively altered expression of keratins, proteases, inflammatory mediators, alarmins, glycolytic enzymes, and antioxidant defense proteins in non-lesional skin in comparison to children without FA as well as nonatopic children [35]. FLG breakdown products FA together with keratin 5 (KRT5), KRT14, and KRT16 have been proposed as prognostic biomarkers for coexisting food allergy in children with AD [45].

Studies that identify candidates for biomarkers predicting the development of diseases such as neuropsychiatric, autoimmune, gastrointestinal, malignant, and cardiovascular in AD patients are generally underdeveloped [46]. Identifying who is at risk of comorbidity may ensure a more holistic approach to these patients and targeted preventative strategies development. Unfortunately, this ability remains a key unmet need in patients with AD.

Conclusions

Numerous potential biomarkers have been proposed as a result of extensive work. But so far, none of these candidates have been validated and implemented into routine clinical practice. Reliability, clinical validity, a high positive predictive value, prediction of the therapeutic response, and disease progression are the seven most essential features that future validated biomarkers should fulfill, according to members of the BIOMAP project [47]. Currently, CCL17/TARC holds great promise for being reliable biomarkers for AD severity as well as treatment response in children and adults. In Japan, CCL17/TARC serves as a useful clinical biomarker for monitoring treatment efficacy, and since 2008 its serum levels have been commercially measured under health insurance support [6]. The TS technique allows us to obtain this biomarker in a minimally invasive way, both in children and adults. Considering the complex and heterogeneous nature of AD, it appears that in clinical practice, we need multiple sets of biomarkers rather than a single biomarker. The concept of personalized medicine in AD seems to be within reach. However, reliable biomarkers are essential to moving a step forward, without which we won't fully benefit even from the most expensive therapy.

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