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Introductory Chapter: The Multispectrum Faces of Atopic Dermatitis

Celso Pereira

1. Introduction

Atopic dermatitis is a chronic or recurrent inflammatory skin disease usually related to the atopic march and atopic morbidity. Although the onset of symptoms occurs predominantly at pediatric ages, the disease can start at any age and even the elderly.

A constellation of conditioning factors has been identified, most of them sustained by genetic and epigenetic aspects favoring a Th2 cell profile, intrinsically associated with many other factors of the skin itself, namely the localized immunoinflammatory responses, the skin barrier dysfunction, dysbiosis, neuroimmune dysregulation and obviously environmental determinants and many others conditions [1]. As a consequence, different phenotypes and endotypes result from multiple heterogeneous and complex pathogenic mechanisms that are clinically expressed with different levels of severity and in the specific location of the lesions [2].

At pediatric ages, the thickness of the skin is markedly reduced compared to adults, as well as the population and diversity of resident cells [3]. In case of skin inflammatory disease the homeostatic disruption on cells as well on the matrix structures determines intrinsic changes in the skin's adaptive immunity facilitating an inducible skin-associated lymphoid tissue (iSALT) with critical consequences [4].

The microbiome has a particular interest in all medical areas and aim of profuse scientific interest in the last decade. However, it was the results of the Sanford study that surprisingly came to prove the magnitude and diversity of cell-free DNA in our body [5]. In fact, the placental microbiome is decisive in the fetal period. So, gut and skin newborn microbial flora is markedly dependent on the maternal clinical condition and the type of delivery, eutocic or instrumented [6, 7]. However, the postnatal period, depending on intrinsic and exogenous factors, will allow the acquisition of new microorganisms. It therefore occurs a process of specialization in niches, and the subsequently interaction with the host comes to allow functional differentiations in this own flora having obvious consequences on mucosal structures [7].

The skin microbiota in the healthy individuals is highly variable between designated areas of moist, such as the surfaces of the antecubital and popliteal fossae, and areas of naturally drier skin or sebaceous skin areas, particularly regarding the proportions of the *Phyla Actinobacteria*, *Firmicutes*, *Proteobacteria* e *Bacteroidetes* [8].

Dysbiosis in atopic dermatitis resulting from increased expression of *Staphylococcus* genera, particularly *S aureus* species, has been consensual for a

long time and the acute outbreaks had been frequently described corroborate this increase with a parallel decreases in *Streptococcus* or *Propionibacterium* species [9]. The overexposure in the skin of *S aureus* and, less frequently to *Malassezia furfur*, results on environment specific conditions that favor a local immunoinflammatory hyperactivation in opposition to the protective effect of *Acinetobacter* species [10].

Atopic dermatitis also has an apparent correlation between the intestinal axis and the cutaneous mucosa, with over-expression of *Clostridium difficile* and *Faecalibacterium prausnitzii* species, reduction of short-chain fatty acids metabolites, which may enable future and potential extra-cutaneous therapeutic implications [2, 9, 11, 12].

This recent data amplify the complexity of the pathophysiology and immunological mechanisms in atopic dermatitis already accepted, namely: the skin barrier dysfunction, the type 2 inflammatory immune response and other important cell axes such as the dependents of cell ways Th22, Th1, Th17 or *JAK-STAT* signaling pathway [13].

The enormous complexity of pathways and mechanisms involved in atopic dermatitis is based on a huge heterogeneity of polygenic determinisms, so the genome-wide association studies (GWAS) only allow confirming the heritability identification in a very limited number of patients. The best documented gene mutation is related to filaggrin, but is only present in around 30% of the European population [14]. Concerning skin barrier dysfunction other genes has been also described (loricrin, keratin-16 periplakin e *SPINK5/LEKTI*), but it requires more research to assess the magnitude and prevalence in a large patients samples studies [2]. Likewise for a typical type T2 inflammation the dysfunctions of IL-4 and IL-13 loci are also far from being present in all patients [2].

Pruritus is one of the hallmarks of atopic dermatitis and can have a dramatic and severe impact on the quality of life of patients at all ages. From a clinical and pathophysiological point of view, the pruritus induced by histaminergic pathway is not a standard feature in opposition to other atopic diseases. In addition to the classic inflammatory type T2 cytokines (IL-4 and IL-13), the IL31 and, to a lesser extent, TSLP, are strictly related to pruritus signaling, particularly in severe forms. Despite the presence of IL-4R α in afferent neural fibers, these neural structures also have IL-31R α receptors, activated by the release of this cytokine by T2 cells, but also by mast cells, dendritic cells and activated keratinocytes [15].

Thus, pruritus is, rather than a clinical sign dependent on the inflammatory process, but itself an active intervening part on the pathogenic mechanism, allowing increased keratinocyte IL-31 release by damage and scratching, and also an increased activation of dermal dendritic cells via TSLP. Symptomatic control is, therefore, decisive, in terms of the immense discomfort experienced by the patient and also because allow a negative feedback to the underlying skin inflammation [13].

In the light of the above, inhibition of IL-4R α receptors by dupilumab allows for a significant control of pruritus thresholds in a very expressive number of patients. However, in others, this control is not achieved. Trials with nemolizumab, an anti-IL-31R α monoclonal, look like it is highly effective in controlling itching, but with significant clinically adverse effects [15].

In an interesting experimental model with human mast cell lines, an alcoholic extract of *Commiphora myrrha* reduced not only the release of histamine, but also the production and release of IL-31 by kinase suppressor regulated by an extracellular signal and activation of *NF κ B* [16]. If these results are confirmed *in vivo*, this essential oil could have an enormous impact in the routine clinic associated with a reduced burden economic impact.

The treatments currently recommended by different guidelines and consensus from different international scientific societies are strictly guiding in pharmacological and non-pharmacological care plans, namely: general measures, hydration to minimize barrier defects, topical treatments, systemic anti-inflammatory drugs for specific conditions and biological treatment for severe forms. Naturally, many of the new therapies are very expensive, which limits their access to many patients around the world [2, 13, 17].

However, several articles have pointed out other strategies that appear to be promising and highly elective in atopic dermatitis.

Emollients are essential to care, and it has been suggested an additional inclusion of ceramides or plant extracts with anti-inflammatory activity, despite the need for robust evidence [18–20].

Regarding anti-inflammatory therapy, the different classes of corticosteroids, calcineurin inhibitors and an inhibitor of the intracellular enzyme phosphodiesterase 4 represent the drugs currently available for topical treatment. Inhibitors of the JAK–STAT and tyrosine kinase pathways are currently in clinical trials. Delgocitinib (a pan-JAK inhibitor) has recently been approved in Japan for the treatment of adults with atopic dermatitis [2, 21].

Regarding systemic therapy it is recommended to severe presentations of atopic dermatitis, and in recent years it has been seen a profusion of new approaches with new biological drugs, some of them already available and many others in clinical trials [22, 23]. This topic is developed in a specific chapter in this book.

The spectrum of action of these new drugs, targeting glycoproteins (IgE), cytokines, chemokines (or their receptors), cell signaling pathways and cell surface receptors, should be submitted to a extensive drug-safety monitoring and rigorous pharmacovigilance programs, because most of them are generally ubiquitous in multiple cells, tissues and organs and could have potential uncontrolled consequences, even in short-term treatments. In addition, this profusion of new drugs is not accompanied by biomarkers that allow a specific selection for different phenotypes and endotypes, in a pathology as heterogeneous as atopic dermatitis.

The new data that comes from the knowledge of dysbiosis in atopic dermatitis must be consistent with new research lines. These findings will allow new therapeutic approaches in earlier stages and more primary pathophysiological conditions that support the immune-inflammatory process and support the chronicity and clinical severity.

The presence of cutaneous biofilms in severe clinical forms and with skin recurrent infections and impetiginization has extremely relevance on the clinical point of view [24]. Current treatment strategies do not establish nor allow the elimination of these structures on the skin surface. However, a growing number of *in vivo* and *in vitro* investigations have demonstrated that topical extracts of some medicinal plants had the ability of biofilms dysruption from bacteria (*Staphylococcus spp* e *Streptococcus spp*) or fungi (*Malassezia furfur* and *Candida spp*) [24, 25].

Like many other chronic conditions in which dysbiosis is subject to extensive research, also in allergic diseases and atopic dermatitis in particular, several studies sustain that in the treatment plan new approaches will be necessary, some of which with very promising *in vitro* and *in vivo* results [26]. There are countless potential manipulation and modulation possibilities of dysbiosis, but additional studies are still necessary to prove the efficiency and safety criteria [27].

Topical application of bacterial lysates or bacteriophage-derived enzymes seems to be one of the most feasible strategies. This strategy tends to, selective, replace strains considered commensal identified on the skin of healthy individuals or others comproved strains with competing effect for *S aureus* [27]. Another researches

address the topical application of non-replicating probiotics that may allow a negative modulation in the viability of dysbiotic bacterial flora [28].

Bacterial lysates administered sublingually have been in clinical use since the 1970s, for the prevention of infectious risk in respiratory pathology. Resulting from lysis of heat-inactivated bacterial strains, the composition can be selected and adjusted to a very diverse number of strains [29]. Without an obvious reason, its use in the clinic was markedly decreased in the late 1990s, but it has recently been a subject of interest and rediscovery given the potential of the mechanisms of action. In this context, the designation of “trained immunity-based vaccines” has been proposed since these vaccines allow effects on both innate and adaptive immunity [30, 31]. Among the most relevant mechanisms are the antimicrobial cytokine response, overexpression of TLRs; production of specific IgG and induction of regulatory T responses and regulation of dendritic cells [31]. In patients with strongly impetiginized forms, there is the possibility of personalized prescription with one extract containing strains adjusted to dysbiosis. This formulation administered at sublingual region, adjacent to the MALT structure, is highly promising from an immune point of view, compared to the oral formulas, which is usually restricted to formulations and fixed compositions of lysates [32].

Other potential treatment strategies involve the autologous bacterial transplant, allogeneic bacterial transplant or even fecal microbial transplantation. On these grounds, further and robust research is necessary [33–35].

Likewise, well-designed studies are needed to define the position and the role of probiotics, prebiotics or symbiotics in atopic dermatitis. This subject is developed in a chapter of this book, as well the specific criteria for phototherapy in select patients.

In view of the enormous clinical heterogeneity, of the physiopathological mechanisms, the treatment of atopic dermatitis is a real concern over the opportunities and therapeutic options already available and all other strategies under development and trials [2, 16–23, 36, 37].

So, nowadays the atopic dermatitis treatment is a real challenge in view of the enormous clinical heterogeneity, the physiopathological mechanisms, the immunogenic aspects and the tremendous variability regarding age, race and ethnicity [37].

In this context, the opportunities with the available therapeutics and all the other strategies under development will certainly allow us to increasingly personalize the management plan and in a future that is believed to be close the identification of robust biomarkers for phenotypes and endotypes, as also on monitoring approach.

The scientific review of some of these aspects in the chapters of this book will certainly be tools of great interest and importance in the knowledge of a pathology with colossal prevalence and a tremendous impact on the quality of life of these patients and their families.

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