**REFERENCES**


**PHARMACOLOGICAL SOLUTIONS FOR ATOPIC DERMATITIS**

Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin disease that is pruritic and recurrent. Since the 2000s, the discovery of a preventive treatment for this severe dermatosis has been a special line of research in the dermatology industry. In this context, BIOalternatives proposes a range of in vitro tests to select and characterize compounds for the treatment of this pathology.

**EPIDEMIOLOGY**

Ad is the most common dermatosis affecting children: 65% of the patients are less than a year old and 85% are below 5 years. The prevalence of this pathology is constantly on the rise and currently affects 10 to 25% of the population. This increase is related to the lifestyle in industrialized countries, where 20% of the children suffer from this dermatosis.

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BIOalternatives offers a wide range of in vitro tests to help you select and characterize compounds and to study their effects at various major stages of the physiopathology of atopic dermatitis. Here are a few examples:

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**PHYSIOPATHOLOGY**

The cause of AD is often linked to an epidermal barrier dysfunction, generally due to a mutation in the filaggrin gene. This structural anomaly facilitates skin lesions and leads to increased skin permeability, promoting the entry of antigens. Barrier dysfunction and antigen entry are at the root of the sensitization stage of AD. It is in a second stage, called the effector stage, that the appearance of pathological symptoms is noticed. This stage may be divided into several steps: initiation, activation of dendritic cells, polarization of Th2/Th22 lymphocytes as well as activation of other agents of AD (mast cells, etc.) and finally, an inflammatory loop between the keratinocyte and the infiltrating cells, leading to pathological skin.

**THE MOST FREQUENT DERMATOSIS IN CHILDREN**

Pruritus resulting from xerosis and histamine release, is the main symptom of Atopic Dermatitis.

**CLINICAL SIGNS**

The symptoms of AD mainly appear on the skin. Pruritus, an intense itching resulting from xerosis (skin dryness) and histamine release, is the main symptom of this pathology [Ref: MAST-0001 ; BLOO-0008]. Following this itching, excoriations appear on the skin and form lichenification patches (skin thickening). These skin lesions are accompanied by the formation of oozing scabs as well as erythema and papules. Moreover, in contrast with psoriasis, cutaneous keratinocytes in AD patients express few antimicrobial defense molecules (β-defensin) [Ref: NHEK-0035 ; NHEK-0037]. This explains why this dermatosis often occurs with complications, among which the most common are bacterial or viral superinfections. For example, Staphylococcus aureus, which is often found in skin superinfections, exacerbates skin inflammation by secreting toxins and may cause impetigo.
The skin lesions facilitate the passage of an antigen that the subject has previously been sensitized to. This antigen may be mimicked by a microbial pattern or a double stranded viral RNA, particularly poly(I:C) which can be recognized by receptors such as the Toll-Like Receptor 3 (TLR3). Moreover, the same lesions cause the membrane of certain keratinocytes to rupture, leading to a release of cytoplasmic IL-1α that may bond with the IL-1R receptors located on the neighboring keratinocytes. This double stimulation by an antigen (poly(I:C)) and cytokines (IL-1α) causes specific keratinocyte signaling pathways (NFκB, MAP kinases, etc.) to become activated, leading to early cytokines (IL-1α) causing specific keratinocyte signaling pathways involved in AD [Ref: NHEK-0090; EPID-0069]. TSLP subsequently activates various cell populations (mast cells, plasma cells, basophil cells and macrophage cells) and predominantly, dendritic cells (DC) via the TSLP-R/IL-7Rα heterodimeric receptor.

TSLP is the key cytokine of the initiation step of Atopic Dermatitis.

### ATOPIC DERMATITIS MODEL

**Step 1:** Initiation: keratinocyte activation, TSLP and chemokine release

**Step 2:** Dendritic cells activation and T lymphocyte polarization

**Step 3:** Th2/Th22 immune response and other agents of atopic dermatitis (mast cells, T lymphocytes, plasma cells and eosinophil cells)

**Step 4:** Inflammatory loop, chronicity and skin lesions

The Th2 and Th22 TL migrate to the lesion area, where they release type Th2 (IL-4, IL-5, IL-13, IL-31, TNF-α) and Th22 (IL-22) cytokines respectively [Ref: PBMC-0009]. These Th2/Th22 cytokines have different functions in the immune response:

- IL-4 maintains the CD4+ TL differentiation in TL of type Th2/Th22 as well as the massive secretion of IgE by plasma cells. These secreted IgE bind to the FcεRI receptors located on the mast cells, basophil cells and macrophage cells, thus sensitizing them to the allergen.
- IL-31 contributes to the release of histamine by mast cells (major cause of itching) [Ref: MAST-0001; BL 00-0008]. The IL-31 is considered to be "the itching cytokine" but its mechanism of action is still unknown.
- IL-22 activates various types of infiltrating cells, such as monocytes and macrophage cells. Moreover, it stimulates the secretion of various chemokines and innate immunity molecules by the keratinocyte.
- IL-22 significantly modulates the keratinocyte metabolism, which results in abnormal epidermal differentiation.
- In conjunction with these inflammatory cytokines, the sensory neurons secrete neuropeptides (CGRP and substance P) [Ref: NS-0004; NSNB-0001] that stimulate various cell populations (mast cells, T lymphocytes, plasma cells and eosinophil cells) and contribute to vasodilation and itching.

### DENDRITIC CELL ACTIVATION & T LYMPHOCYTE POLARIZATION

After activation by TSLP, DC proliferate and differentiate into mature DC capable of producing numerous chemokines and innate immunity molecules. These mature cells express type II major histocompatibility complex (MHC II) and OX40L ligand on their surfaces. DC then migrate to the lymph nodes where the antigen is presented to the immature T lymphocytes (CD4+ TL). This stage is carried out by an interaction between MHC II and the T Cell Receptor (TCR) of the TL, and by the binding of OX40L with its receptor located on the surface of the TL. The presentation of the antigen facilitates the polarization of CD4+ TL into TL of type Th2 and Th22, which are essential to the immune response of AD [Ref: CD4TL-0005]. This Th2/Th22 dominant immune response is characteristic of atopic dermatitis.

### INFLAMMATORY LOOP INVOLVED IN ATOPIC DERMATITIS

Atopic dermatitis is a common skin disease that depends on the interaction between genetic and environmental factors. This dermatitis leads to the establishment of an inflammatory loop composed of several steps:

1. **Initiation:** keratinocyte activation, TSLP and chemokine release
2. **Dendritic cells activation and T lymphocyte polarization**
3. **Th2/Th22 immune response and other agents of atopic dermatitis**
4. **Inflammatory loop, chronicity and skin lesions**

The activation of different signaling pathways (STAT6, STAT3, NFκB, MAPK) stimulates the production of chemokines leading to the inflammatory loop.
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