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The Role of the Thymus Gland in Atopic Dermatitis

Glen Alvin[1*] and Mike Chan[1,2,3]

[1]European Wellness Academy GmbH, Germany/Malaysia

[2]European Wellness Centers, Switzerland, Germany

[3]FCTI Research & Development GmbH, Germany

ABSTRACT

The thymus gland is a vital organ for maintaining a vigilant immune system. It develops at the perinatal stage, maturing during childhood and involutes during adolescence. The thymus secretes numerous cells, chemokines and lymphokines to sustain its function. The Thymus and activation-regulated chemokine (TARC/CCL17) is a member of the T-helper 2 chemokine that aids in immunosurveillance in allergic disease. The TARC is a robust objective biomarker involved in the pathogenesis of Atopic Dermatitis, enabling the monitoring of many aspects of the disease. Arguably, it is currently the most sensitive clinical biomarker of Atopic Dermatitis. TARC has enabled atopic dermatologic management to be precise and personal. The regeneration of the thymus gland will be favourable to conserving many of its essential tasks in the body.

***Corresponding author**

Glen Alvin, European Wellness Academy GmbH, Germany/Malaysia. Tel: +60168106434.

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Introduction

The word '*thymus*' is derived from the ancient Greek language, meaning "*soul*". The thymus gland (TG) starts growing from birth to 2–3 years old, reaching its maximum weight of 30–40 g. This gland thrives throughout childhood until it begins to shrink during adolescence. An admirable quality of thymic development is its rapid growth with solid proliferation and differentiation of epithelial and lymphoid cells to ensure a sound immune system during childhood. The thymus gland (TG) is the key to a healthy immune system. It supports the body's defence mechanism by providing surveillance and protection against diverse pathogens, tumours, antigens, and mediators of tissue damage. Infants born with thymic dysfunction suffer from T-cell mediated cellular immunity defects predisposing to infections and autoimmune diseases [1-5].

The Thymus Gland and The Skin

The thymus is a soft gland behind the mediastinum, between the sternum and pericardium. This gland is a symmetrically sized bi-lobed organ connected at the midline. Each thymic lobe consists of multiple lobules, enclosed by an external capsule housing an outer cortex and an inner medulla. Highly active substances called thymic factors or thymic peptides, involved in T-cell maturation and immune functions such as antibody production and phagocytosis, are synthesised by the TG. The human TG produces thymic proteins, such as thymopoietin, thymosin-α, thymulin, thymic humoral factor, hormonal thymic factor, and serum thymic factor. TG hormones unleash key immune signals, called "lymphokines", like interleukin 2(IL2), interferons, and colony-stimulating factors for a well-functioning immune system. An impressive paradoxical feature of the TG is that it is affected by immunosenescence, an age-related involution resulting in diminishing thymic mass, loss of thymic structure, and the disorganisation of its architecture [2,3,5,6].

Microscopically, the TG is a highly complex structure comprised of the thymic stroma and developing thymocytes. Its stroma contains dendritic cells, macrophages, epithelial, mesenchymal, and vascular elements. The thymic stroma accommodates significant non-hematopoietic cell populations, including thymic epithelial progenitor cells/thymic epithelial stem cells (TEPC/TESC), lymphoid progenitor cells (LPC), mesenchymal stem cells (MSC) and Foxn1-dependent thymic epithelial cells (TEC). It is the TEPC/TESC that synthesises γδ and αβ T cells in the thymus. Central to the thymic microenvironment are the TECs, divided into cortical (c)TEC or medullary (m)TEC. Both cell populations are morphologically and functionally distinct, mediating disparate aspects of T cell development. TECs serve as the scaffold for T cell development by furnishing growth factors for T cell proliferation and ligands for T cell antigen receptors (TCRs) selection. The localisation and interaction of thymocytes with the TEC subsets is crucial for proper T cell export. The cTEC are responsible for securing thymocyte precursors' commitment to the T cell lineage with the aid of Notch ligand Dll4 and for steering thymocyte expansion via the delivery of growth factors and cytokines. The mTEC regulates the migration of selected thymocytes from the cortex into the medulla; this process is expedited by the chemokines CCL19 and CCL21. They also oversee the accumulation and positioning of dendritic cells in the medulla via secretion of the

chemokine XCL1 and regulate the functional commitment of γδ T cells within the thymus. Interestingly, the subsets of mTEC with their expression profile have identified tuft cells and keratinocytes (KC) with. One of the primary subsets of T cells in the epidermis is the γδ T cells, also known as dendritic epidermal T cells (DETC) due to their dendritic morphology. [2,4,7-9]

The immune system is a complex network of cellular and molecular components subdivided into the thymus-dependent (adaptive) and thymus-independent (innate) arms, which function synergistically in immune responses. The thymus is the site of T lymphocyte (T cell) development and plays an essential role in adaptive immunity. Immature T cells, called thymocytes, undergo 2 selection steps in maturing. A negative selection stage purges the repertoire of T cells expressing auto-reactive TCRs. The T cells are then screened based on their response to peptides presented by the body's own major histocompatibility complex (MHC), leading to MHC-restricted T cell recognition. Hence, the thymus unleashes self-tolerant T cells, which recognise foreign peptides, notably pathogens [4,8].

The TG is the birthplace of T cells. Bone marrow derived CD34+ stem cells migrate to the TG, where they mature to acquire the expression of the TCR. Each T cell evinces its exclusive receptor, composed of a heterodimer of 2 chains (TCRα and TCRβ). This diverse TCR repertoire is the key to the T-cell's ability to recognise the vast array of potential targets. However, this repertoire is restricted in every individual, as each T cell's capability to bind with a self-peptide is limited by the major histocompatibility complex (MHC). This ensures that the T cell recognises a foreign peptide antigen bound to proteins encoded by specific MHC alleles, most commonly MHC class I and II molecules for CD8+ and CD4+ T cells, respectively. *Sgnotto* et al. reported that IgG modulates αβT cell cytokine synthesis in the human thymus. The IgG of AD individuals induced intracellular production of IL-17 and IL-10 by intrathymic T CD4 and T CD8 cells. TGF-β was also detected at a higher frequency in response to AD IgG in TCD8 cells [10,11].

T cells orchestrate immune responses by indirectly showering membrane-associated signals that promote the expansion and differentiation of B cells (humoral immunity), which produce antibodies that destroy foreign and infected tissues. T cells detect foreign antigens through diverse TCRs designed to mediate immunity without collateral damage to native tissues. In a parallel system, regulatory CD4(+) T helper cells, called T-regulatory lymphocytes (Tregs), perceive self-peptides and control self-reactive pathogenic T cells. Tregs allow the tolerance to food and saprophytic bacteria of the gastrointestinal tract, skin, and mucosa and even intolerance to antigens of the fetus during pregnancy. There are 2 types of Tregs: natural cells (tTreg), which arise in the thymus, and induced cells (iTreg), produced in peripheral tissues during an immune response. The supervisory function of Tregs is compromised in the pathogenesis of autoimmune and neoplastic diseases of the skin. This is mainly due to the domination of other immune cells in the skin, such as Th2 in atopic dermatitis. This dynamic self–nonself-discrimination process is the basis of immune tolerance [10,12].

It is the aptitude of T-cells to identify foreign antigens that enables them to maintain homeostasis. When a positive T-cell response to self-antigens erupts, clonal selection activates specific T cells that can recognise the antigen. A flood of antibodies is secreted, and T-cell mitosis surges, resulting in an escalated quantity of specific T-cells. This is the immediate response to the presence of a pathogen. Upon eradicating the pathogen, the remaining activated T cells undergo apoptosis, leaving a few to survive as memory immune cells. Thus, the subsequent response to the same pathogen will be even faster and more effective [1].

The TG is also a vital organ of the endocrine system. The hormones secreted by the TG include *thymulin*, *thymosin*, *thymopoietin* (*thymin*), and *thymic humoral factor*. These hormones are fashioned by the TECs, which synthesise cytokines (IL-1, IL-), granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor, which succour thymocyte differentiation [2].

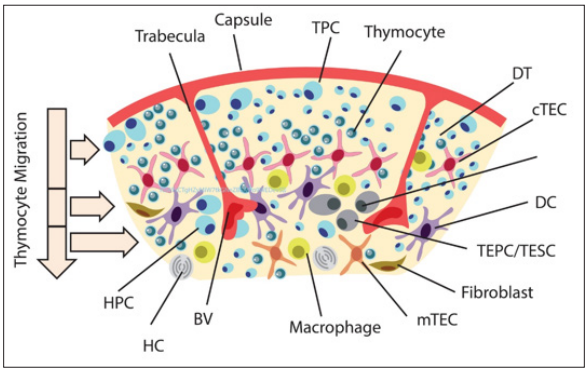

Figure 1: Hematopoietic precursor cells (HPC) enter the thymus via venules (BV) arising from the corticomedullary junction (CMJ) and migrate progressively towards the capsule. Numerous committed CD4-CD8- T precursor cells (TPC) are located at the subcapsular region, while immature CD4+CD8+ cortical thymocytes migrate through the cortex and CMJ to the medullar zone. The medulla contains CD4+ and CD8+ naïve thymocytes that will eventually move to the periphery. The cortex and the medulla are also abundant in macrophages, fibroblasts and dendritic cells (DC) [7].

Thymic stromal lymphopoietin (TSLP) is a four-helix bundle epithelial cell-derived cytokine found in the skin (keratinocytes), gut, lungs and thymus that signals via TSLPR, a heterodimer of the IL-7 receptor alpha chain (IL-7Rα), which is closely related to the typical receptor-γ chain (γc). TSLPR has a low affinity for TSLP, but when combined with IL-7Rα, it generates a high-affinity binding site for TSLP and triggers signaling. TSLP catalyses the polarization of dendritic cells (DCs), mast cells, basophils, eosinophils, neutrophils, and NKT cells to steer and amplify T helper (Th) 2 cytokine synthesis. TSLP stimulates mast cell mediator release and activates immature myeloid dendritic cells, which subsequently primes CD4+T cells to forge allergy-promoting cytokines (IL-4, IL-5, IL-13, and TNF-α) and induce the production of TH2-attracting chemokines (CCL22 and CCL17). It also promotes T cell proliferation in response to T cell receptor (TCR) activation and Th2 cytokine production. TSLP is released into the systemic circulation when the epidermal barrier becomes defective. TSLP's role in driving Th2-mediated inflammation is seen by its upregulation in the keratinocytes of atopic dermatitis (AD) skin lesions, and serum TSLP levels are elevated in subjects with AD. The human TSLP gene is located on chromosome 5q22.1 next to the atopic cytokine cluster on 5q31. The TSLP protein is highly expressed in epidermal keratinocytes of the suprabasal layer of lesioned human AD skin and is absent from non-lesional skin [3,13,14].

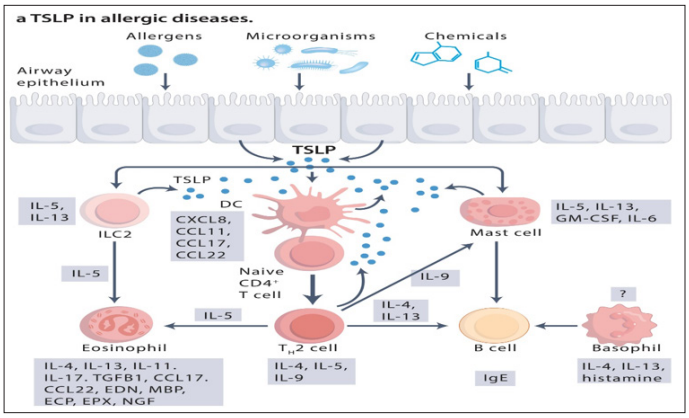

Figure 2: The systemic release of TSLP triggered by epithelial cell exposure to allergens, microorganisms and chemicals. TSLP promotes and amplifies T helper 2 (TH2)-type immunity, which enhances the immune response to antigens or allergens, leading to the development and progression of an allergic disease [3].

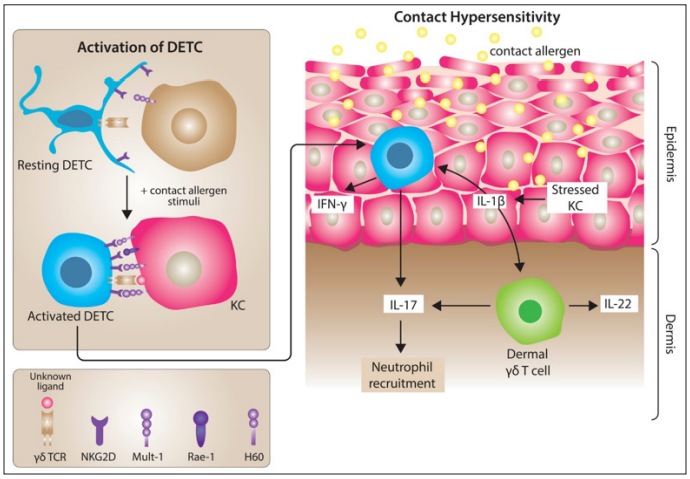

Figure 3: The inflammatory response triggered by an allergen on the skin surface

The skin, the external body surface, is frequently attacked by environmental pathogens. The skin is aided by immune cells that act as sentinels, and effector cells reside among the keratinocytes, fibroblasts, and endothelial cells for skin immunity. Bitter taste receptors (T2Rs) are G protein-coupled receptors (GPCRs) involved in bitter taste perception on the tongue. There are 25 expressed T2Rs in humans, including T2R38, expressed in epithelial cells of the respiratory tract, colon, placenta, and skin, and T2R14 is functionally expressed in epidermal keratinocytes. The C–C chemokine receptor type4 (CCR4) and type10 (CCR10) are important GPCRs that regulate the homing of lymphocytes (mainly T cells) to the skin. Chemokine receptors, particularly the Thymus and activation-regulated chemokine (TARC/CCL17), a ligand for CCR4, modulate the trafficking of distinct leukocyte subsets into peripheral tissues. Thymus and activation-regulated chemokine (TARC/CCL17) is a member of the T-helper 2 chemokine family. The TG expresses it, and it attracts CCR4 cells. CCL17/TARC is expressed on keratinocytes in the epidermis, vascular endothelial cells, T cells, and dendritic cells of lesional skin in AD. CCR4 participates in lymphocyte-endothelial interactions during lymphocyte recruitment to cutaneous sites. T2R38 is functionally expressed on skin-infiltrating lymphocytes as CD4+ and CD8+ T cells from lesional AD skin. The T2R38 expression levels in the skin correlate with serum TARC and IgE levels in AD patients [15-18].

Abnormally high serum TARC levels signal cutaneous inflammation's accelerated pathogenesis with a positive feedback-based mechanism. The epidermal keratinocytes (KC)23 and epidermal dendritic cells (DC)24 are considered the primary source of TARC in AD. Once the epidermis is under attack by some aggravating factor, the KCs and DCs, which TSLP activates, arouse TARC. The TARC, in turn, attracts Th2 cells, thus inducing the initial phase of tissue inflammation. The Th2-mediated cytokines, interleukin (IL)-4, IL-5, and IL-13, accelerate IgE production or eosinophil activation, amplifying allergic inflammation. The disease management strategy for controlling inflammation must address this cascade of reaction [16].

Once an allergen is detected on the skin, the allergen-stressed KC produces copious amounts of IL-1β and upregulates γδ TCR and NKG2D ligands such as Mult-1, Rae-1, and H60. These ligands bind to NKG2D receptors expressed on resting DETC to activate them. The activated DETCs change their morphology from highly dendritic to round and produce IFN-γ, IL-13 and IL-17. In the dermis, dermal γδ T cells produce IL-22 and IL-17, triggered in response to the contact allergen, which is central for neutrophil infiltration into the skin. γδ T cells are essential in regulating IgE sensitisation and mediate the human atopic state. γδT cells are a minority subset of T cells that express T-cell receptors composed of γ and δ chains (γδTCRs). Their functional plasticity enables them to be secreted by either IL-17 or IFN-γ. They induce CD40L expression on their surface, and CD40L is known to be imperative for isotype switching in B cells, and its expression on γδ T cells contributes to the production of IgE. Local stress and γδ T cells in the skin are essential in generating systemic atopic responses [9,19].

The Thymus Glands Affect Atopic Dermatitis

Atopic dermatitis (AD) is a chronic recurrent skin disease characterised by the hyperresponsiveness of the skin to an allergen and severe itching that exhibits pathological conditions such as dry skin, hyperkeratosis, erythema, oedema, pruritus, and scab. AD is accompanied by psychological changes, such as sleep disruption and social maladjustment due to severe itching. The pathogenesis of AD is complex, with various factors, such as abnormal skin barrier and genetic, environmental, psychological, and immunological factors. Skin damage from scratching is an immunopathological aspect of AD. Immune cells infiltrate damaged skin and secrete inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and IL-6. The activation of T helper 2 (Th2) cells increases the serum immunoglobulin E (IgE) concentration and activates mast cells and basophils, thus worsening the inflammatory response on atopic skin. Circulating AD-related biomarkers are consistently displayed in moderate to severe patients. Some of the Th2 chemokines with increased expression during an exacerbation of AD include thymus and activation-regulated chemokine (TARC/CCL17), CCL26/ eosinophil attracting chemokine (eotaxin-3), CCL27/ CTACK, CCL18/pulmonary and activation-regulated chemokine, and macrophage-derived chemokine (MDC/CCL22). The primary sources of TARC/ CCL17 in AD skin include keratinocytes, vascular endothelial cells, T cells, and dendritic cells21. TARC and MDC bind to their CC chemokine receptor (CCR4) receptor,

provoking Th2 cells to the inflammatory site where they infiltrate the skin. TARC and MDC levels are significantly elevated in AD patients, and these levels are proportional to the clinical severity of the disease. This enables clinicians and patients to objectively monitor disease activity in the body, as CCL17/TARC is reliable for assessing nonvisible/subclinical active AD-related inflammation5. The normal serum CCL17/TARC level in healthy adults is less than 450 pg/mL; its level in healthy children differs depending on age. The TARC serum level of 700 pg/mL is the threshold for mild AD in children. Saito et al. confirmed that TARC levels falling to 837 pg/mL or less within 3 months in recovering AD patients results in long-term remission. When the pattern of waning and waxing of AD and the fluctuations in serum TARC levels were compared, it was clear that AD did not follow a natural course but followed non-regulated inflammatory floating, influenced by topical treatment application. Thus, the expression of CCR4 is considered a significant indicator of inflammatory skin diseases, such as AD and TARC, and MDC are essential biomarkers of Th2-dominant inflammatory skin diseases. CCL17/TARC has become a useful clinical biomarker for monitoring treatment efficacy and ensuring successful treatment outcomes in experimental and clinical scenarios. substantiated that the reduction of specific lipids and an elevation in TARC/CCL17 levels at 2 months of age was associated with AD during the first year of life [14-23].

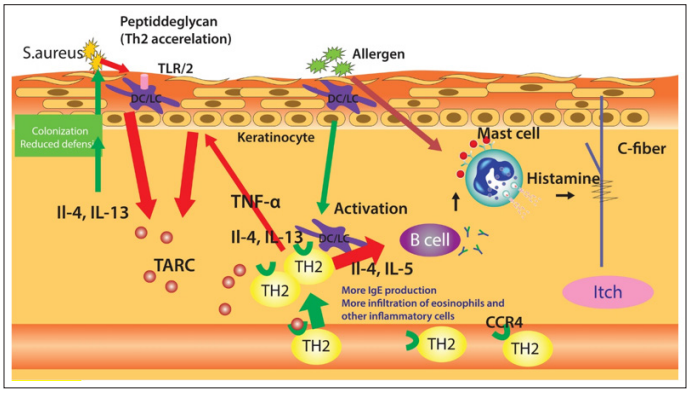

Figure 4: The stimulation of TARC and the inflammatory cascade it triggers in AD [20]

The thymus is an essential organ in the cellular immune response of early life. Olesen et al. confirmed that the thymus index was 32% higher in children with active AD. The larger size of the thymus is compatible with increased thymic activity and emission of T lymphocytes, and thymectomy has been proven to reduce the risk of AD. It eventually declined with age in all children, including those with AD. However, thymic shrinking was only proportional in healthy subjects. Some of the tissue biomarkers predicting AD onset in newborns are TARC and IgE in the umbilical cords of newborns and natural moisturising factor levels in neonates' skin, which is known to correlate with trans epidermal water loss strongly. Moisturisers are the main ally for preventing AD in high-risk infants as they alter skin microbiome and reduce skin pH in this population. [17,24].

The development of targeted therapies for allergic diseases has elucidated the need for cytokines to function in a new role as biomarkers supporting disease diagnosis and management. Their biological characteristics make them reliable biomarkers that point to the correct diagnosis, objectively monitor disease activity, indicate treatment response, and predict disease progression. A biomarker is a biologically defined characteristic that can be measured as an indicator for normal biological processes, pathogenic processes, and responses to an alien exposure or intervention. A direct correlation has been discovered between TARC levels and the clinical severity of AD; this enables TARC levels to serve as a diagnostic tool to assess disease severity in patients with AD. Many successful AD patient managements have been done by observing serum TARC levels to monitor disease activity and therapy [16,25].

demonstrated that serum TARC was the most reliable objective biomarker for AD disease severity. At the same time, Himadri et al. reported that TARC is a reliable, objective biomarker of the severity of atopic dermatitis (AD), with high sensitivity and specificity. Their study verified that TARC levels were significantly correlated with the Scoring Atopic Dermatitis (SCORAD) index, peripheral eosinophils count, and LDH in AD children older than 2 years. Reliable biomarkers in AD quickly establish a diagnosis, assess disease severity, predict the course of the prognosis, determine the risk of developing comorbidities, and evaluate the therapeutic response, resulting in effective personalised AD treatment [23,26,27].

Conclusion

The sustenance of a productive thymus gland beyond adolescence is an excellent method of prolonging its clinical benefits to the body.

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