Serum levels of A PRoliferation-Inducing Ligand (APRIL/TNFSF١٣) in children with atopic dermatitis

Thesis

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Hebat-Alla Saad Awad Atteia

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LIST OF ABBREVIATIONS

AD:	**Atopic dermatitis**
AEC:	**Absolute eosinophil counts**
APCs:	**Antigen-presenting cells**
APRIL:	**A PRoliferation-Inducing Ligand**
APTs:	**Atopy patch tests**
BAFF:	**B-cell activating factor of the TNF family**
BCMA:	**B-cell maturation antigen**
BLyS:	**B-lymphocyte stimulator**
CLA:	**Cutaneous lymphocyte-associated antigen**
DC:	**Dendritic cell**
EDTA:	**Ethylene diamine tetra-acetate**
EH:	**Eczema herpeticum**

ELISA:	**Enzyme linked immunosorbent assay**
EM:	**Eczema molluscatum**
ERC:	**Extracellular signal-regulated kinase**
GM-CSF:	**Granulocyte-Macrophages-colony stimulating factor**
IAP:	**Inhibitor of apoptosis**
IFN-γ:	**Interferon-γ**
IgE:	**Immunoglobulin E**
IL:	**Interleukin**
JNK:	**c-Jun $NH_{۲}$-terminal kinase**
LDH:	**Lactate dehydrogenase**
LFA-۳:	**Lymphocyte function antigen**
LSS:	**Leicester Sign Score**
MAPK:	**Mitogen-activated protein kinases**
MCP:	**Monocyte chemoattractant protein**
MnSOD:	**Manganese superoxide dismutase**
MoDC:	**Monocyte-derived DC**

PBL:	**Peripheral blood leucocytes**
PKR:	**Protein kinase receptor**
SCORAD:	**SCORing Atopic Dermatitis**
SE:	**Seborrheic eczema**
SEB:	**Staphylococcus enterotoxin B**
SPT:	**Skin prick tests**
SSS:	**Simple scoring system of Costa**
TACI:	**Transmembrane activator and calcium modulator cyclophilin ligand interactor**
TARC:	**Thymus and activation-regulated chemokine**
Tg:	**Transgenic**
Th٢:	**Type ٢ helper T cells**
TI:	**T-cell-independent / Thymus-independent**
TNF:	**Tumor necrosis factor**
TRAF:	**TNF receptor-associated factors**
TSLP:	**Thymic stromal lymphopoietin**
TWEAK:	**TNF-like weak inducer of apoptosis**

XIAP: **X-linked inhibitor of apoptosis**

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SCORAD index of atopic dermatitis disease severity

INTRODUCTION

Atopic eczema or dermatitis (AD) is a chronic inflammatory skin disorder and known to be caused by a combination of multiple factors, including genetic predisposition, skin barrier dysfunction, immunological deviation and environmental allergens. Most AD patients have elevated concentration of total and allergen-specific serum IgE. Some patients also have IgE against self-antigens, such as manganese superoxide dismutase (MnSOD) ***(Bieber, .).*** The lipophilic yeast *Malassezia* belongs to the commensal skin microflora, however, it can induce specific IgE and T-cell reactivity in AD patients ***(Scheynius et al.,).*** Seborrheic eczema (SE) is another chronic inflammatory skin disorder associated with *Malassezia* reactivity but without IgE production ***(Naldi and Rebora,).***

Although the exact role of B-cells in AD is not fully understood, the contribution of B-cells to AD etiopathogenesis has become evident by studies showing that B-cell-depleting treatment with anti-CD٢٠ antibodies improved AD skin lesions with reduced mRNA expression of IL-٥ and IL-١٣ and decreased infiltration of T and B-cells in skin, whereas total and allergen-specific IgE levels were not reduced, suggesting other functions than antibodies production of B-cells in the disease mechanisms ***(Simon et al., .).*** It has become appreciated that aberrant regulation and activation of B-cells

result in chronic inflammatory and autoimmune-mediated disorders. They contribute to the disease pathogenesis not only by being the antibodies producers, but also as APCs (antigen-presenting cells) and cytokine/chemokine producers. Accordingly, B-cell directed therapy, including antibodies against B-cell specific markers and inhibitors of survival and signalling factors for B-cells, is currently introduced for the treatment of chronic inflammatory diseases ***(Nagel et al., ٢٠٠٨d).***

The tumour necrosis factor (TNF) family is intimately connected to the regulation of cellular pathways. The TNF ligand members BAFF (B-cell activating factor of the TNF family) and APRIL (a proliferation-inducing ligand) are two crucial survival factors for peripheral B-cells. APRI, a new member of the TNF ligand superfamily (TNFSF١٣), is a type II transmembrane protein. It is named for its capacity to stimulate the proliferation of tumour cells in vitro. Subsequent publications also called this ligand TRDL-١ or TALL-٢, respectively. APRIL and BAFF also termed (B-lymphocyte stimulator [BLyS], TALL-١, THANK, zTNF٤) form a new subfamily of TNF-like ligands that are expressed in haematopoietic cells. Both ligands can bind the two members of the TNF receptor family, namely the transmembrane activator and calcium modulator cyclophilin ligand interactor (TACI), as well as B-cell maturation antigen (BCMA). In addition, BAFF binds to BAFFR and APRIL interacts with heparan sulphate proteoglycans. They can promote Ab class switching independently of the CD٤٠/CD٤٠L pathway ***(Matsushita et al., ٢٠٠٨).***

BAFF and APRIL are expressed mainly by innate immune cells, to a less extent by T-cells and activated B-cells, as well as non-haematopoietic tissue resident cells. APRIL expression is low in normal tissues, but is elevated in several types of tumors and transformed cell lines. APRIL stimulates proliferation of tumor cell lines and increases tumorigenicity in nude mice ***(Medema et al.,*** ***).*** BAFF is expressed as both surface-bound and soluble factors, whereas APRIL is processed inside the cell and released as a soluble protein. However, APRIL can be attached to the cell surface by being a natural fusion protein with TWEAK (TNF-like weak inducer of apoptosis), called TWE-PRIL, sharing receptors with APRIL. Thus, these factors form a network of mediators interacting with an overlapping set of receptors ***(Mackay and Schneider,*** ***).***

The role of B-cells in the pathology of allergy is undisputable, and their contribution beyond IgE production has to be appreciated ***(Nagel et al.,*** ***).*** However, the factors influencing B-cell activation and homeostasis in allergic diseases, in both systemic and target tissue environments, need to be characterized. APRIL is essential molecule for B cell development, survival, and proliferation.

Although the functions of APRIL have not been fully evaluated, studies reported increased levels of APRIL in serum or target tissues in various autoimmune diseases, and often correlated to disease progression namely; systemic lupus erythematosus ***(Becker-Merok et al., ٢٠٠٦; Lee et al., ٢٠٠٧; and Hopia et al.,*** ***)***, rheumatoid arthritis ***(Becker-Merok et al.,*** ***٠٦; Bombardieri et al.,*** ***; and Gheita et al.,*** ***),*** systemic sclerosis ***(Matsushita et al., ٢٠٠٧ and***

Bassyouni et al., ***),*** inflammatory myopathies ***(Szodorayet al.,*** ***),*** primary biliary cirrhosis ***(Migita et al.,*** ***),***

AIM OF THE WORK

This study aimed is to explore the expression of APRIL in children with atopic dermatitis in relation to disease activity and disease severity.