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TOLL-LIKE RECEPTOR and AUTOIMMUNITY (Graves's disease): Literature Review

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Abstract

Graves's disease is an autoimmune condition that affects thyroid. The primary mechanism of Graves' disease is the results of adipokines, specifically leptin, IL-6, TNF, PAPMs molecular patterns, damage to DAMPs, and TLR molecules. In APC, homologous proteins known as Toll-like Receptors (TLR) serve as receptors or antigens. There are various types of TLRs depending on the type of antigen. There are currently 10 human TLRs named TLRs 1-10, TLR-2 and TLR-4 are equally significant in the emergence of autoimmune disorders. According to scholars based on latest research TLR-2, TLR-3, and TLR-9 are increased in Grave diseases. The purpose of this study is to identify the mechanism of TLR which is involved in the immune response in Graves' disease. The search for relevant scientific data was carried out by entering search queries based on keywords: TLR, autoimmunity, Graves's disease. The search was conducted through PubMed, Elsevier journals, and ScienceDirect as well as other highly cited publications.

***Keywords**: TLR, grave's disease, autoimmune*

1. Introduction

Graves's disease is an autoimmune disease caused by excessive thyroid hormone production. Iodine is also known as a micronutrient for the formation of thyroid hormone [1]. Thyroid hormone functions to regulate all the work of the human body, plays a role in cell maturation, brain development and plays a role in the secretion of other hormones. Manifestations of Graves' disease are tremors, tachycardia (increased heart rate), increased appetite but drastic weight loss, and enlarged thyroid glands. Graves disease is stimulated by thyroid stimulating hormone (TSI) otherwise known as thyroid stimulating antibody (TSAb). The site of thyroid synthesis is in the

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thyroid cells, lymph nodes and even the bone marrow. The immune system that plays a role is B cells which play a role in the formation of immunoglobulins to stimulate thyroid formation [2].

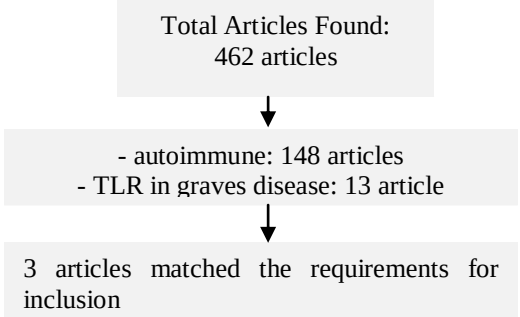
TLRs are proteins expressed by monocytes, dendritic cells and macrophages to recognize certain antigens. The *toll-like receptor* (TLR) is just one of several different classes of *Pattern Recognition Receptors (*PRRs) including *Nod-like receptors* (NLR*), C-type lectin receptors* (CLR), *AIM2-like receptors* (ALR), *RIG-I-like receptors* (RLR) and DNA sensors. intracellular including cyclic GMP-AMP synthase (cGAS) [3][4][5]. TLRs consist of a single membrane transmembrane helix that functions to connect extracellular ligand-binding domains to intracellular signaling domains [6]. TLRs contain leucine flanked by cysteine characteristically in their extracellular regions involved in ligand binding. Currently there are 10 types of functional TLRs in humans, namely TLR 1 to TLR 10 [7]. TLRs can recognize *pathogen-associated molecular patterns* (PAMPs) consisting of structures as diverse as flagellin, nucleic acids, saccharides (mainly mannose and lipopolysaccharide), peptidoglycans (such as lipoteichoic peptidoglycan), and lipoproteins. The adaptive immune response is triggered by recognition of these antigens, mediated by the production of proinflammatory cytokines together with stimulation of *antigen-presenting cells* (APCs).

2. Method

This research design is an identification of research journals within a period of 5 years, namely from 2018-2022. The research journals reviewed are those contain cytokines that play a role in Graves's Disease.

Article Selection Method

Several inclusion criteria in this study were a) articles reviewed in this study related TLR that play a role in autoimmune; b) Using TLR mechanism that plays a role in Autoimmune disease. The Exclusion criteria in this study were cytokines that play role in other than in TLR mechanism in autoimmune and journals published before 2018.



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Article Search Method

How to find articles in this study is examined methodically, starting with selecting research topics and generating English keywords for journal searches. The database used is PUBMED, SCIENCEDIRECT to search for articles throughout the year, from January 2021 to December 2022. The keywords are in English used are "Autoimunne", "TLR", and "TLR Mechanism". The next step is to identify the title of the article that best fits the research we want. Then, abstract identification and overall content analysis were completed to provide study findings that match the researcher's objectives.

Search results in Figure 1. Then the researchers filtered the relevant article titles and inclusion criteria, in order to obtain 3 appropriate article.

Analysis studies

According to the researcher's objectivities. Pertinent literature and data gathered utilizing the method of random controlled trial (RCT).

3. Result and Discussion

The involvement of TLRs in the early inflammatory immune response is responsible for their ability to develop autoreactive B and T cells. Such autoimmune responses are thought to result from molecular mimicry of pathogen-derived antigens to self-antigens or a form of nonspecific activation of the innate immune system that results in the production of T-cells and antibodies specific for self-antigens, thereby implicating TLRs in various autoimmune diseases. Graves disease increases the secretion of cytokines such as IL-1, IL-2, IL-6, IL-4, IL-10, IL-8, IL-13, IL-12, IL-14, TNF-α and IFN-γ (Polak et al, 2019; Grim et al, 2019). Thyrocytes in It has been found that thyrocytes in Graves's Disease patients do not undergo apoptosis, and around them there is an infiltrate consisting mostly of Th2 cells, which secrete small amounts of IL-2, TNF-α and IFN-γ. However, they are capable of producing large amounts of IL-4, IL-5 dan IL-10.

TLR and Graves's Disease

TLR signal transduction occurs through the involvement of MyD88 (myeloid differentiation factor 88), TAK1 kinase (TGF-beta-activated kinase), TAK1-binding protein kinase (TAK1-binding protein), IRAK kinase ((IL-1)-1R1 associated protein kinase) and tumor necrosis factor receptor-associated factor—TRAF6 (TNF receptor-associated factor 6) [9]. TLR ligation can cause abnormal activation and inflammatory reactions in autoimmune diseases. Most research has concerned with

intra-cellular TLRs, such as TLR-3, TLR-7 and TLR-9, but recent studies have also shown that cell surface TLRs, especially TLR-2 and TLR-4, play an equally important role in disease development. autoimmune [10].

The basic mechanism in Graves' disease is the result of adipokines in the form of leptin, IL-6, TNF-α, PAPMs, DAMPs and TLR. Adipokines in adipose tissue exhibit autocrine, endocrine and paracrine properties in tissues and organs. Peng et al's study (2016) reported TLR 1-10 expression in peripheral blood assessed by the RT-PCR method, an increase in TLR-2 was found in Graves's patients [11]. This is in accordance with the study of Polak et al (2019), in patients with Graves's disease, the percentage of CD4+, CD8+ and CD19+ cells on TLR-2 showed a significant increase and the percentage of CD4+, CD8+ and CD19+ B cells in TLR-4 also increased. Significant correlation in TLR-expressing lymphocytes as a clinical parameter and cytokine concentration in peripheral blood [8]. In Graves' patients, there is a relationship between TLR-2 antigen expression on CD4+ T lymphocytes and TLR-4 antigen expression on CD4+ T lymphocytes, a relationship between TLR-2 antigen expression on CD4+ T lymphocytes and FT3 concentration. Pre-treated patients also had a correlation between TLR-2 antigen expression on CD8+ T cells and TLR-4 antigen expression on CD8+ T cells and between TLR-2 antigen expression on CD19+ lymphocytes and TLR-4 antigen expression on CD19+ lymphocytes. Whereas after treatment, there was a significant correlation between TLR-2 antigen expression on CD19+ B lymphocytes and TLR-4 antigen expression on CD4+ T cells as well as TLR-2 antigen expression on CD19+ B lymphocytes and TLR-4 antigen expression on CD19+ B lymphocytes.

The expression of TLR-2, TLR-3, and TLR-9 on monocytes is increased in Graves' patients. In addition, after specific agonist stimulation, the percentage of CD14+ cells expressing TLR2 increased in Graves' Disease *peripheral blood mononuclear cells* (PBMC). Similarly, increased expression of TLR-3 and TLR-9 in Graves' patients was also found under TLR-3 and TLR-9 stimulation. Expression of *high mobility group box 1* (HMGB1) and RAGE was found to be upregulated in PBMCs from AITD patients at rest and under TLR9 stimulation. The HMGB1, a protein released from damaged or necrotic cells, is involved in many chronic inflammatory diseases. The HMGB1-DNA complex binds to RAGE and then activates a TLR-9-mediated inflammatory response, and previous studies have shown that extracellular HMGB1 can bind to CpG ODNs and stimulate their transfer to TLR-9 in inflammatory diseases. The findings of Peng et

al (2016) demonstrated that HMGB1 and RAGE play an important role in the development of chronic inflammation in autoimmune thyroid disease through activation of the TLR9 pathwa [11].

Receptor activation has been shown to have the ability to regulate the production of pro-inflammatory cytokines. Increased IL-6 and decreased IL-10 production in PBMCs from Graves's patients in response to specific ligands for TLR-2, TLR-3, or TLR-9 and increased TNF-α expression in response to TLR-3 and TLR-9 ligands. In contrast, TNF-α secretion after TLR-2 agonist stimulation in PBMCs from Graves' Disease patients and controls, suggests that TNF-α production is not associated with TLR-2 activation in PBMCs. PBMCs from patients with AITD are more sensitive to responses induced by TLR agonists, resulting in the secretion of pro-inflammatory cytokines [11][12].

4. Conclusion

TLR that play role in Graves's disease are TLR-2, TLR-3, TLR-4, TLR-9. Other component like SOCS and TRAF proteins are considered to be major regulators of the TLR pathway. Studies remain limited to relatively small articles. Deeper knowledge of TLR families could help the development of more targeted therapies for Graves's diseases.

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