mgr Dominika Łacheta

Immunologiczne aspekty orbitopatii Graves'a

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

Promotor: dr hab. n. med. Mirosław Szczepański

Katedra i Zakład Biochemii
Wydział Lekarski
Warszawski Uniwersytet Medyczny

Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych

Warszawskiego Uniwersytetu Medycznego

Warszawa 2021 r.

Title of dissertation: Immunological Aspects of Graves' Orbitopathy

Abstract

Graves' orbitopathy (GO) is one of the extrathyroidal symptoms of Graves' disease (GD) that is characterized by hyperthyroidism, induced by circulating autoantibodies directed against the thyrotropin receptor (TSHR). GO is manifested by proptosis, double vision, impaired colour vision and deterioration of visual acuity. Literature data indicate that chronic inflammation of the orbital soft tissues underlies GO; and infiltration of immune cells, production of glycosaminoglycans and differentiation of orbital fibroblasts into adipocytes and myofibroblasts result in extraocular muscle edema, adipose tissue expansion and orbital tissues fibrosis. The remodeling of tissues leads to increased intraocular pressure and extraocular muscles compression on the optic nerve.

A review of the literature on the immunological mechanisms involved in the pathogenesis of GO was used to prepare the review article "Immunological Aspects of Graves' Ophthalmopathy". The paper focuses on orbital fibroblasts and immune mechanisms that play a key role in the development of inflammation, expansion, remodeling and fibrosis of the orbital tissues. The article also discusses the role of autoantigens in the pathogenesis of GO, taking into account potential therapeutic targets in the treatment of the disease.

The continuation of the research in the field of immunological mechanisms, involved in the pathogenesis of GO, concerned the analysis of the expression of selected innate immunity proteins in the microenvironment of the orbital adipose tissue. The research involved the multi-ligand receptor for advanced glycation end products (RAGE) and its ligand – HMGB1 protein (high mobility group box 1). RAGE which belongs with other receptors to the family of pattern recognition receptors (PRRs) plays a key role in the activation of innate immunity. The major ligand for RAGE is the endogenous HMGB1 protein, released during cellular stress, tissue damage or necrosis. The HMGB1 protein, with other endogenous particles, belongs to the group of the damage associated molecular patterns (DAMPs). Stimulation of PRRs by DAMPs results in the activation of inflammation as well as the activation of tissue repair mechanisms.

The conducted studies were used to prepare the original research article „RAGE and HMGB1 Expression in Orbital Tissue Microenvironment in Graves' Ophthalmopathy". The studies hypothesized that the RAGE/HMGB1 axis participates in the pathogenesis of GO, and the intensity of these proteins expression correlates with the clinical condition of GO patients. Elevated expression levels of these proteins were shown in the orbital adipose tissue of GO patients compared to the normal control. Moreover, a statistically significant correlation between RAGE expression and the occurrence of dysthyroid optic neuropathy (DON) and elevated TRAb levels (anti-TSHR antibodies) were demonstrated. Furthermore, in the research paper the presence of RAGE- and HMGB1- positive inflammatory cells closely located to the vessels was shown, indicating their potential participation in driving the inflammatory process. This is the first published paper showing RAGE and HMGB1 expression in the orbital adipose tissue using immunohistochemistry.

RAGE and HMGB1 may participate in the development of inflammation in the orbital tissues, playing a crucial role in the pathogenesis of GO. A thorough understanding of the participation of immune processes in GO pathomechanism is a way to create new, effective and safe methods of treatment as well as to improve monitoring of the disease activity.