REVIEW

MYOID CELL OF THE HUMAN THYMUS: A STRANGER IN THE NIGHT OF MYASTHENIA GRAVIS

Andrei Dragoș Cumpănaș[1], Raluca Ștefana Ioana Moș[1], Marius Raica[1]

[1]Victor Babes University of Medicine and Pharmacy, Department of Microscopic Morphology/Histology, Angiogenesis Research Center Timisoara, Romania

ABSTRACT

Myoid cells are of common occurrence in the medulla of the thymus of different species, usually identified by electronmicroscopy and/or immunohistochemistry. Although known from many decades, the role of myoid cells in normal conditions is virtually unknown. Many investigators suggested that myoid cell is a crucial player in myasthenia gravis. Myasthenia gravis is an autoimmune disease, characterized by the production of auto-antibodies that act on the neuromuscular junction further interfering with the transmission of the depolarization wave. Although the exact pathogenesis mechanism of myasthenia gravis is still unknown, myoid cells in the thymus might play an important role in the initiation of this condition. The present article will review the role of myoid cells of the thymus while trying to establish their possible implications in myasthenia gravis.

Key words. myoid cells, myasthenia gravis, desmin, immunohistochemistry, acetylcholine receptor, muscle creatine kinase, Myf5, myogenin.

THYMUS MICROENVIRONMENT

The thymus, being a primary lymphoid organ, provides an extraordinary environment for the maturation of T cells. Differentiation of T cells occurs as they pass from the outer compartment (the cortex, consisting mostly of immature T cells) to the inner compartment (the medulla, consisting of mature T cells). Actually, the first step in maturation is the acquisition of a T cell receptor (TCR) as well as the coexpression of CD4 and CD8 (double positive T cell-DP). However, once the DP T cell stage has been reached, only a few T cells will leave the thymus and enter the circulation. The selection of the T cell is done mainly by the interaction between TCR and self-peptide major histocompatibility complex (MHC) ligands. If the immature DP T cells bind loosely with the MHC ligand this leads to death by neglect. However, if the immature DP T cells binds too tightly to the MHC ligand, these T cells would be able to produce apoptosis of self-cells resulting in autoimmune disease. They are, however, prevented from entering the circulation by a process known as negative selection. If the DP immature T cells bind to the MHC ligand and have an intensity of the response between that of neglect selection and negative selection, then these T cells will go further on to lineage differentiation. In the end, the mature T cell will either express CD4 or CD8 [1].

The T cell diferentiation occurs by interaction between the TCR and the MHC ligand on the thymus epithelial cells (TEC) [2]. Also, as shown by Suniara et al. fibroblasts have been proven to play an important role in early T cell development. In the absence of mesenchymal cells and the formation of the network of fibroblasts inside the thymus, poor lymphoid development has been proven [3].

In the medulla and cortico-medullary area there are found not only T cells, but also a large variety of cells that contribute to the general architecture of the organ and play diffferent roles in the initiation, development and maintaining of the immune system. Invastigations of the thymus medulla based on conventional morphology and molecular methods have shown the constant presence of B lymphocytes, antigen presenting cells, mast cells, and three types of stromal epithelial cells. A very unusual cell with this location is a spindle-shaped cell with distinct striations, very similar to a skelatal muscle fiber in terms of contractile filaments found in the cytoplasm. This type of cell is called thymic myoid cell and it has been first reported by Mayer in 1888 in the thymus of the frog. It was Mayer that named them „myoidzellen", based on the strong acidophilia of the cytoplasm and elongated shape [4].

ORIGIN AND DEVELOPMENT OF MYOID CELLS

This class of cell, although its function still unknown, proves to be a constant feature in the thymus of different species of vertebrates,ranging from lungfish Neoceratodus forsteri [5] to amphibians[4], reptiles, birds and mammals [6,7,8]. Its origin is also disputed among scientists and a final decision has not yet been reached.

Myoid cells are said to resemble epithelial cells in their early stages of development [6]. Moreover, these cells are connected by desmosomes. Also, in 1982, Cooper and Tochinai cultured the thymus of a sub-Saharian frog, Xenopus. They noted that, if in early-stage-thymus, only epithelial cells could be seen, in later-

stage-thymus, both epithelial, lymphoid and myoid cells could be observed. These finding made some argue that thymic myoid cells originate by transdifferentiation of endodermal epithelial cells [8].

However, experiments involving chimera of chick and quail have contradicted the epithelial transdifferentiation hypothesis, stating that in fact these cells have a neuroectodermal origin. It was observed that when placing a quail neural tube on a chick embryo, quail myoid cells would develop in the chimeric thymus [7].

Other opinions argue for the origin of myoid cells in the muscle precusor cells of the covering mesodermum [9]. This view could be sustained by the fact that myoid cells of the thymus as well as muscle cells coexpress some proteins, such as acetylcholine receptor, troponin T and desmin. Moreover, it was observed through real-time PCR that compared with thymic epithelial cells (TEC), thymic myoid cells have an overexpression of muscle-specific genes such as the 5 subunits of the acetylcoline receptor, MCK (muscle creatine kinase), muscle associated receptor tyrosin kinase (Musk), rapsyn, utrophin, ErbB2, ErbB3 and troponin T [10].

MYOID CELLS STRUCTURE

Myoid cells have common features with skeletal muscle fibers. These cells have also been described in other regions of the body, ranging from the testes (where they are involved in the contraction of semineferous tubes) [11] to the bone marrow [12]. In electron microscopy, myoid cells posses an irregular nucleus, with fine chromatin granules and a distinct nucleolus. Myofibrils are arranged around this central nucleus, giving this cell a characteristical banding. The cytoplasm of the myoid cells, with large amounts of myofibrils, has different patterns of organisation of myofibrils, ranging from concentric perinuclear arrangement to parallel-to-cell-surface arrangement. These feature could motivate the role of myoid cells (TMCs) in contraction or in the cell trafficking of the thymus [13].

Between these myofibrils, other cellular organelles are present: ribosomes, mitochondria, sarcoplasmic reticulum [6].

Immunohistochemically, TMCs express acetylcholine receptor (AChR), MCK (muscle creatine kinase), muscle associated tyrosin kinase receptor (Musk), rapsyn, utrophin, ErbB2, ErbB3 and troponin T [10].

To the moment, the physiological role of thymic myoid cells is unknown. However, multiple studies have shown different functions of the thymic myoid cells. They have been described to have a role in myogenesis during postnatal skeletal muscle regeneration. Not being involved in muscle repair and grown, thymic myoid cells prove to be a useful source for myoblast transfer [14]. Also, these cells are said to protect thymic epithelial cells (TECs) from apoptosis. In order to investigate the effect of myoid cells on TECs, TECs were both cultured alone and cocultured with myoid cells. It was observed that the TECs cocultured with myoid cells proved a strong decrease of annexin-V-FITC positive thymocytes [2].

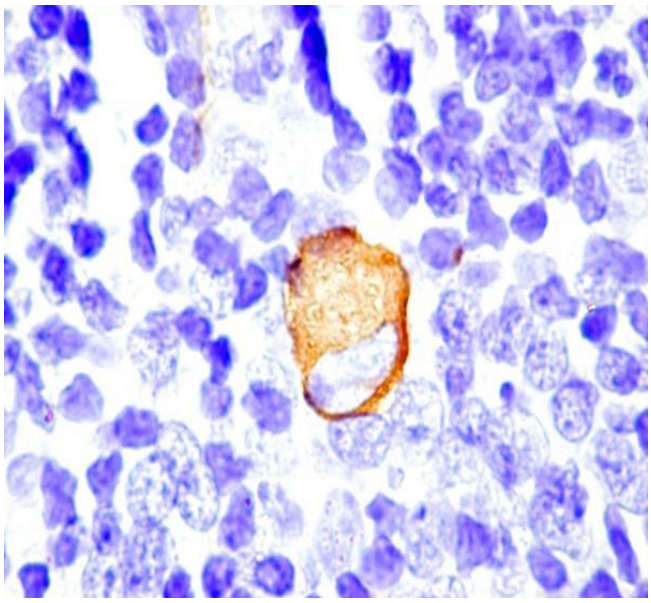

Figure 1.
Myoid cell demonstrated with anti-desmin immunoreaction. Magnification x900

MYOID CELLS AND MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune disease. The type of immunoglobulin commonly implicated in myasthenia gravis is either IgG1 or IgG3. The autoimmune nature of this disease has been proven by administration of IgG from patients with MG to healthy animals. In these animals, the characteristic of MG were by these means reproduced [15].

In about 85% of patients, the antibodies are targeted against acetylcholine receptors (AChR).[16] By blocking the AChR, these antibodies block the neuromuscular junction, resulting in further neuromuscular transmission. Shortly, fatigue and muscle weakness install (especially the function of eye muscles is altered) [17].

However, cases of myasthenia gravis patients without any anti-AChR antibodies have been reported. These type of MG is reffered to as Anti-AChR negative myasthenia gravis. In these patients, antibodies bind to muscle specific kinase (MuSK). MuSK is a type of tyrosine kinase receptor. The result of the binding between the antibody and the MuSK receptor is the dispersion of AChR clusters. Thus, it can be infered that MuSK receptor has a significant role in mantaining AChR clusters. Usually, MuSK positive patients have more severe forms of diseases than AChR positive MG patients [18].

The thymus has been proven to be the main site where the pathogenesis of myasthenia gravis starts. In patients with MG, thymectomy does not only alleviate

symptoms but also decreases the dose of required immunotherapy [19]. In a very recent clinical trial, 126 patients with AChR positive MG were placed in two groups randomly. The first group, would undergo a transsternal thymectomy and receive prednisone treatment. The second group, on the other hand, would undergo medical managment and receive prednisone treatment. After 3 years, the quantitative myasthenia gravis score (QMT score) was better for the first group than the second one [20].

Although myoid cells' biological role is still unknown, they have proved to be very interesting to scientists as they might be implicated in the pathogenesis of myasthenia gravis.

FURTHER DIRECTIONS AND PERSPECTIVES

Going back to what we previously described in the thymus microenvironment section: when double positive DP T cells bind too tightly to the MHC ligand, they are prevented from entering circulation by negative selection. In myasthenia gravis, however, there is destruction of some self-structures, such as the AChRs. This means that somewhere along the negative selection process something goes wrong. However, the myoid cells in the thymus, as well as the thymic epithelial cells, both possess AChRs on their surfaces.

So, in the medulla of the thymus there is a cell (the myoid cell) with a structure so closely related to that of the muscle. T cells could bind too avidly to the AChR of the myoid cells, leading to further activation of B cells and production of IgGs that would not be able to perceive the difference between AChRs of the myoid and muscle cells (in fact, there is no difference between them).

In 1996, Wakkach et al, showed that while thymic epithelial cells (TEC) expressed AChRs similar to that of the muscular tissue, the levels of AChRs were insufficient for explaining the onset of MG [21] However, it might be the myoid cells who are implicated in the onset of MG. But, myoid cells, as proven, protect the thymic epithelial cells from apoptosis. Even if the AChR of the myoid cells might be implicated in MG's onset, the fact that these cells further reduce the apoptosis of TECs (which also express AChRs) might contribute to the production of more IgG against similiar-to-muscle cells, resulting in the initiation of the disease or the worsening of the state of the patient.

On the other hand, another direction might be based on what Bo Hu et al found. Their team implemented Myf5-deficient mice and myogenin-deficient mice. Myf5, or myogenic factor 5, is a protein with a major role in regulating myogenesis. Myogenin also plays a key role in the development of striated skeletal muscle fibers. Myf5-deficient mice showed a partial deficiency of TMCs while myogenin-deficient mice showed a complete loss of TMCs. In this study, no TMC reappearance was seen, implying that TMCs cannot regenerate, in the absence of myogenin. This information suggest that the development of the TMC is controlled by myogenin. Thus, Myf5 and myogenin deficiency mice could be used in order to establish the implications of myoid cells in myasthenia gravis [22].

Based on what we know nowadays about the myoid cells, it seems clear that we need more data, more experimental models, and new approaches of their role(s) in normal and pathological conditions. It is important to remember that myoid cells are usually not reported on conventional biopsies of the thymus, as they are acidophilic elements hidden in the medulla. Even the `normal` number of myoid cells in normal condition and myasthenia gravis is not very clear and requires detailed morphological studies. It is believed that understanding the molecular biology of myoid cells we will have a more precise landscape not only of myasthenia gravis, but maybe also of other autoimmune diseases.

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