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Progress in Histochemistry and Cytochemistry 48 (2013) 1–46

PROGRESS IN HISTOCHEMISTRY AND CYTOCHEMISTRY

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Metallophilic macrophages of the rodent thymus

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Accepted 3 December 2012

Abstract

For a very long time, we studied the metallophilic macrophages of the rodent thymus and in this review our results on morphological, histochemical, enzymehistochemical, immunohistochemical, ultrastructural and functional features of these cells, as well as the molecular regulation of their development, will be presented. Furthermore, the differences between species will also be discussed and the comparisons with similar/related cell types (metallophilic macrophages in the marginal sinus of the spleen, subcapsular sinus of the lymph nodes and germinal centers of secondary lymphoid follicles) will be made. Metallophilic macrophages are strategically positioned in the thymic cortico-medullary zone and are very likely to be involved in: (i) the metabolism, synthesis and production of bioactive lipids, most likely arachidonic acid metabolites, based on their histochemical and enzymehistochemical features, and (ii) the process of negative selection that occurs in the thymus,

Abbreviations: AcP, acid phosphatase; Aire, autoimmune regulator; AF, aldehyde fuchsin; ANP, atrial natriuretic peptide; cDCs, conventional dendritic cells; CMZ, cortico-medullary zone; DCs, dendritic cells; IDCs, interdigitating cells; IGF-I, insulin-like growth factor I; LAMP-1, lysosome-associated membrane protein 1; LTβ, lymphotoxin β; LTβR, lymphotoxin β receptor; MHC, major histocompatibility complex; NASDCE, naphthol AS-D chloroacetate esterase; NSE, nonspecific esterase; PAS, Periodic Acid-Schiff; PTAs, peripheral tissue antigens; S1P, sphingosine-1-phosphate; Sirpα, signal regulatory protein ά; SD, succinic dehydrogenase; TCR, T-cell receptor; VCAM-1, vascular cell adhesion molecule-1.

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0079-6336/$ – see front matter
http://dx.doi.org/10.1016/j.proghi.2012.12.001

based on their ultrastructural features and their reactivity after the application of toxic or immunosuppressive/immunomodulatory agents. Taken together, their phenotypic and functional features strongly suggest that metallophilic macrophages play a significant role in the thymic physiology.

1. Introduction

Among lymphoid organs, the thymus holds a unique position not only due to its indispensible function as a predominant site of T-lymphocyte production and its exquisite structure, but also due to the fact that practically until recent days its physiological significance remained undefined.

The presence of the thymus gland within the body has been recognized a very long time ago (for review, see Rezzani et al., 2008). Still, the true function of this organ remained mysterious for millennia. Hence, different imaginative (relation to lymph flow or respiration), sometimes even amusing roles (no function at all), have been claimed for the thymus. However, an endocrine function has been most often ascribed to the thymus gland, probably due to the fact that with puberty it enters a phase of remarkable involution (for review, see Rezzani et al., 2008). Only in recent times did the actual role of this organ become apparent and now we are celebrating the golden anniversary since the immunological function of the thymus was first documented 50 years ago (Miller, 2011). Now, we know that the thymus is a primary/central lymphoid organ where self-restricted, but simultaneously self-tolerant, T-lymphocytes showing a vast T-cell receptor (TCR) repertoire are produced in a specific tissue microenvironment capable to provide suitable conditions for complex cellular interactions required for T-lymphocyte production to occur.

Here, it is necessary to express a thorough feeling that seminal discovery of the true function of the thymus provided an immense impetus to immunological investigations in general and in this manner fostered the flourishing development of immunology.

The key events in understanding the function of the thymus and major breakthroughs, in short, are presented as follows. First, using the neonatally thymectomized mice, it has been shown that the thymus is necessary for the production of lymphocytes and development of cellular immunity (Miller, 1961; Arnason et al., 1962; Martinez et al., 1962). If the thymus is lacking from the body, the immune system shows the profound structural and functional alterations (Janković et al., 1962; Waksman et al., 1962). Second, during their sojourn in the thymus, the maturing T-lymphocytes (called thymocytes during that period) are subjected to a meticulous process of "positive selection", which renders them capable of recognizing the foreign molecules only when presented within the context of self-major histocompatibility complex (MHC) molecules (Bevan, 1977; Zinkernagel et al., 1979). Presentation of self-molecules, produced by β5t-containing thymoproteasome (a recently identified proteasome component that is specifically expressed in thymic cortical epithelial cells) within the context of MHC molecules is believed to represent the basic mechanism underlying the process of thymic positive selection (Takahama et al., 2010). Only those