

LOCALIZATION OF CYTOPLASMIC ANTIGENS OF CELLS OF DIFFERENTIATED LAYERS OF THE EPIDERMIS IN EPITHELIUM OF THE HUMAN THYMUS

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The discovery of antigens common with antigens of muscle tissues in the cytoplasm of the myoid cells of the thymus [15] provided the basis for the search for other heterologous organ antigens in the epithelial tissue of the thymus and, in particular, antigens common with epithelia of epidermal type. It was shown that an antigen common with the cytoplasm of cells of the basal layer of the epidermis and other covering epithelia of epidermal type is present in the cytoplasm of cells of the epithelial reticulum of the human and animal thymus [10]. An antigen common with the intercellular adhesive substance of covering epithelia is present in the intercellular spaces of Hassall's corpuscles [10]. Our previous investigations showed that the blood of patients with myasthenia gravis contains antibodies against antigens of cells of the epithelial reticulum and of Hassall's corpuscles of the human thymus, common with the cytoplasm of cells of differentiated layers of the epidermis. Two reacting zones have been observed in the cytoplasm of the epithelial cells of the skin: a perinuclear zone and the cytoplasm proper [2]. Antibodies to epidermal antigens also have been found in healthy human serum [4].

The aim of this investigation was to determine the localization of antigens in the epithelium of the thymus common with antigens of cells of differentiated layers of the epidermis, antibodies to which are found in the blood of patients with myasthenia gravis, rheumatic fever, and erysipelas and also of healthy blood donors.

EXPERIMENTAL METHOD

Frozen sections through the thymus and skin were treated with serum (dilution 1:8-1:20) for 18 h at 4°C. After washing with phosphate buffer (pH 7.2-7.4) for 20 min the sections were incubated for 45 min in FITC-labeled globulin fraction against human IgG (from the N. F. Gamaleya Research Institute of Epidemiology and Microbiology, Moscow). The reaction of sera from patients with myasthenia gravis (157 cases), rheumatic fever (60 cases), and erysipelas (110 cases) and of clinically healthy individuals (70 cases) with epithelium of the human thymus and skin was studied.

To determine the organ and tissue specificity of the reaction with antigens of epithelium of the thymus and skin the sera were adsorbed with a suspension of cells from scrapings of epidermis, a suspension of blood group AB erythrocytes, and a homogenate of tissues of the human thymus, liver, kidney, heart, and brain. The serum was mixed in a dilution of 1:8 with the cell suspension or tissue homogenate in the ratio of 1:2 and incubated for 1 h at 37°C and 18 h at 4°C.

EXPERIMENTAL RESULTS

Depending on the characteristics of the reaction with epithelium of the thymus and skin, the test sera were divided into three groups. Sera of the first group (blood donors, patients with myasthenia gravis) reacted only with antigen of the cytoplasm proper of cells of differentiated layers of the epidermis and contained no antibodies to the perinuclear zone (Fig. 1a). The second group comprised sera (blood donors, patients with myasthenia, rheumatic fever, and erysipelas) which contained antibod

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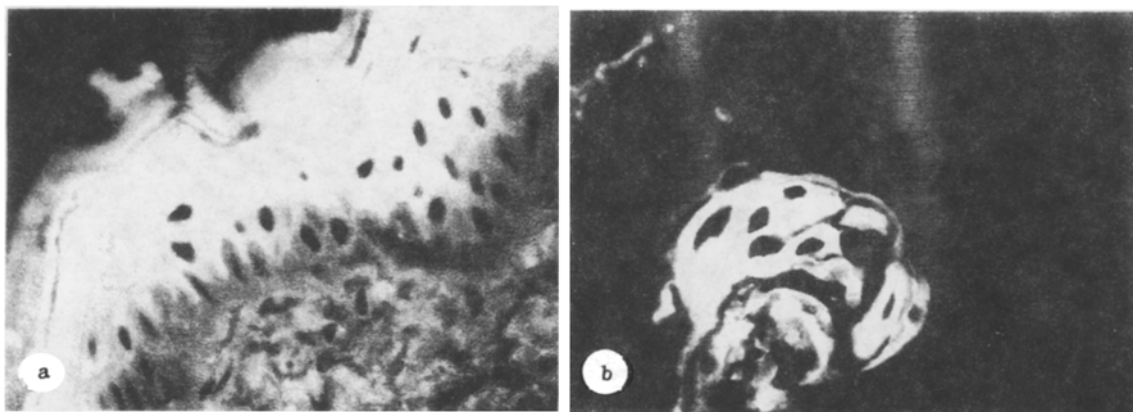


Fig. 1. Sections treated with serum of a healthy blood donor. a) Section through human skin treated with donor's serum. Reaction with antigen of cytoplasm proper of differentiated epidermal cells; b) section through human thymus treated with the same serum. Reaction in cytoplasm of cells of Hassall's corpuscles.

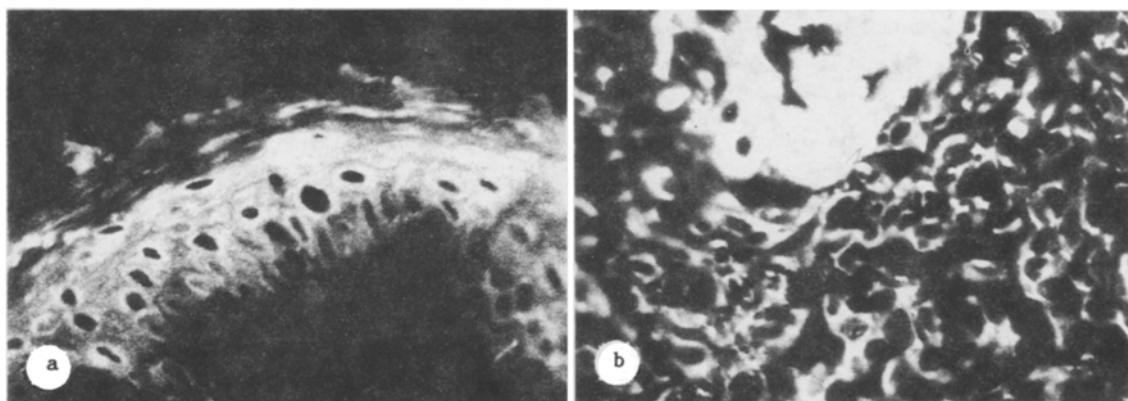


Fig. 2. Sections treated with serum from patient with myasthenia gravis. a) Section through human skin treated with serum from patient with myasthenia gravis. Reaction with antigens of cytoplasm proper and of perinuclear zone of cells of differentiated layers of epidermis; b) section through human thymus treated with the same serum. Reaction with antigens of cytoplasm of cells of epithelial reticulum and Hassall's corpuscles.

ies to antigen of the perinuclear zone and of the cytoplasm proper of cells of differentiated layers of the epidermis simultaneously (Fig. 2a). The third group comprised sera (patients with rheumatic fever and erysipelas) in which the level of antibodies to antigens of the perinuclear zone was higher than the titer of antibodies to antigens of the cytoplasm proper of differentiated epidermal cells. As a result, with certain definite dilutions of the sera of this group a reaction could be observed only with antigens of the perinuclear zone of differentiated cells of the epidermis (Fig. 3a).

In a parallel study of the reaction of the first group of sera with tissue slices of the thymus and skin they were found to react only with cytoplasmic antigens of cells of Hassall's corpuscles and not with the cell cytoplasm of the epithelial reticulum of the thymus (Fig. 1b). The titer of antibodies to cytoplasmic antigens of Hassall's corpuscles and of cells of the differentiated layers of the epidermis was identical and varied in different individuals from 1:40 to 1:200 depending on the nature of the disease.

When sera of the second group were applied to sections of the thymus a reaction was observed in the cell cytoplasm not only of Hassall's corpuscles, but also of the epithelial reticulum of the cortex and medulla of the thymus (Fig. 2b). The level of antibodies to antigens of the cytoplasm proper of cells of the epidermis and Hassall's corpuscles was identical, and varied in different individuals from 1:40 (erysipelas) to 1:200 (healthy blood donors, patients with rheumatic fever and myasthenia gravis). The titer of antibodies to antigen of the perinuclear zone of differentiated epidermal cells and cells of the epithelial reticulum of the thymus also was identical. Normally it did not exceed 1:20, but varied in patients with these diseases from 1:20 to 1:128. Sera

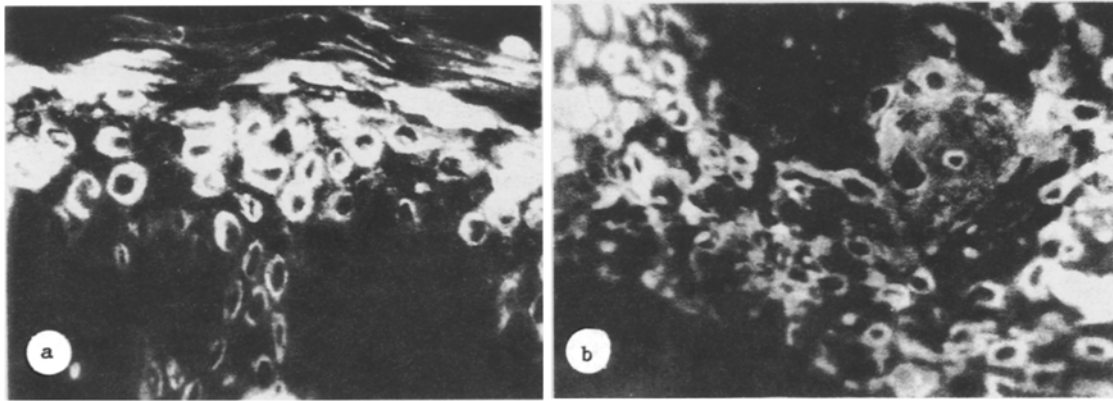


Fig. 3. Sections treated with serum of patient with rheumatic fever. a) Section through human skin treated with serum from patient with rheumatic fever. Reaction with antigen of perinuclear zone of cytoplasm of cells of differentiated layers of epidermis; b) section through human thymus, treated with the same serum. Reaction with cytoplasmic antigen of cells of epithelial reticulum and perinuclear zone of cells of Hassall's corpuscles.

of the third group, used in a dilution at which a reaction was preserved only with the perinuclear zone of differentiated epidermal cells, reacted with the cytoplasm of cells of the epithelial reticulum of the cortex and medulla of the thymus and of the perinuclear zone of the cells of Hassall's corpuscles (Fig. 3b). The titer of antibodies to antigen of the perinuclear zone of the epidermal cells and of the cytoplasm of the epithelial cells of the thymus was identical and varied in different individuals from 1:32 to 1:128. Adsorption by a suspension of epidermal cells or tissue homogenate of the human thymus completely abolished the reaction of the sera with epithelial cells of these organs. Adsorption with tissue homogenate of other organs or with a suspension of blood group AB erythrocytes did not affect the intensity of the reaction of the sera with epithelium of the thymus and skin.

These results confirm previous data on the presence of antigens common with the epidermis in cells of the epithelial reticulum and Hassall's corpuscles of the human thymus [2, 10]. They are also evidence that antibodies to epidermal antigens are also present normally in such different pathological processes as erysipelas, rheumatic fever, and myasthenia. The difference in the character of changes in the thymus in rheumatic fever and myasthenia [3, 5-7], and also in the skin of patients with erysipelas and rheumatic fever suggests that autoantibodies present under normal conditions and in diseases have a different physiological effect on cells of the thymus and skin, and may perhaps be directed against different antigens, which have a similar localization in the epithelium of these organs.

Differences in the reaction of the sera with epidermal antigens of the thymus depending on the character of the pathological process will be the subject of a special communication.

The use of sera from healthy blood donors and patients with various diseases, with different levels of autoantibodies to epidermal antigens enabled their location in the epithelium of the thymus to be determined. It was found that the antigen (antigens) of the perinuclear zone of differentiated epidermal cells are located in the cytoplasm of cells of the epithelial reticulum of the cortex and medulla, and in the perinuclear zone of cells of Hassall's corpuscles. Thus two epidermal antigens — antigen of the cambial elements and antigen of the perinuclear zone of differentiated epidermal cells, are present in cells of the epidermal reticulum of the thymus. The latter also is present in very small amounts in the cells of Hassall's corpuscles. By contrast, antigens of the cytoplasm proper of differentiated epidermal cells are not found in cells of the epithelial reticulum, and are present only in the cytoplasm of cells of Hassall's corpuscles.

The ability of keratinocytes to produce lymphokines and thymic hormones (thymopoietin and TMF) led to the hypothesis that the skin is an organ of immunity [14]. We also know that factors present in the thymus and characteristic of secretory epithelium, namely lactoferrin and secretory component [8, 10], have an immunomodulating effect on lymphocytes not only of the thymus [9], but also of peripheral lymphoid organs [11, 12]. It has been shown in relation to myoid cells of the thymus that they secrete myoid antigens into the internal medium of the thymus [1, 5, 6] and produce thymocyte mitogenic factor (TMF) in vitro [13]. Furthermore, the nosologically specific character of the change in the myoid cells in pathological processes affecting the skeletal muscle and myocardium has been noted [1, 5, 6].

These facts suggest that the antigenic similarity of the thymic epithelium and tissues of other organs reflects the unity of their functions and is associated with the fact that ability to produce factors influencing differentiation and functional activity of elements of the immune system is not the exclusive prerogative of the thymic epithelium but is characteristic of the tissues of other (perhaps of all) organs. On the basis of the foregoing arguments, the heterologous organ antigens present in the thymus must evidently be regarded as a set of immunomodulating factors characteristic of other tissues, and concerned in the formation of tolerance to responsible for the committedness of certain subpopulations of T lymphocytes in relation to the tissues of different organs. The acquisition of these vector properties enables the above-mentioned cells to migrate into the corresponding organs and to perform the function of immunologic surveillance under normal and pathological conditions. The existence of a duplicate system of immunomodulating factors of nonlymphoid genesis may be the factor responsible for completing the process of differentiation of T cells, which begins in the thymus, and it may also perform certain functions of the thymus when the latter is damaged or has undergone age involution.

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