MORPHOLOGY AND PATHOMORPHOLOGY

Thymalin in Developing Respiratory Organs of Human Fetus

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We studied the appearance of immunomodulator thymalin in human respiratory organs during early embryogenesis. Thymalin accumulated in young cells of airway epithelium. In the alveolar part thymalin-positive cells were diffusely spread. Mature T cells ($CD3^+$) and the main regulatory elements ($CD4^+$ and $CD8^+$) were detected during the same period in the lungs in the absence of thymic microenvironment. The function of immune elements forming in fetal lungs is local protection of the fetus from potentially aggressive maternal cells and infectious agents entering the body through the trachea and fetal blood vessels.

Key Words: *human fetus; thymalin; respiratory organs*

Some authors suggest that the lungs can be considered as the peripheral part of the immune system [7] possessing endocrine function [1]. These hypotheses are confirmed by the data on the presence of cells with T lymphocyte markers in human fetal lungs starting from weeks 8-15 of gestation: mature lymphocytes ($CD3^+$), cells with receptors to sheep erythrocytes ($CD2^+$), T helper/inductors ($CD4^+$), suppressor/cytotoxic ($CD8^+$) cell *etc.* By week 20 of gestation the number of $CD4^+$ and $CD8^+$ cells increases to 26.3 and 32.1%, respectively, and than remained at this level [2]. Differentiation of T cells requires the presence of a thymic immunomodulator. However, the location of this immunomodulator in the fetus remains unclear. We previously showed the release of thymalin by developing thymic epithelium on gestation weeks 5-6, *i.e.* before the appearance of lymphocytes in the thymus [9]. It can be hypothesized that thymalin distantly affects fetal lung tissues and stimulates proliferation and differentiation of T cells. On the other hand, thymalin can be produced by some unknown cells in the lungs. S. A. Blinova [1] described the morphophysiology of endocrine cells belonging to the APUD system of human fetal lungs and showed that they were heterogeneous and released biogenic amines and polypeptides. According to published data, these cells originate either from the nerve crest or develop from the tissue in which they are situated. These endocrine cells are always present in the airways [1] and developing respiratory compartments of the lungs and interact with monoclonal antibodies to various peptides. They appear during the early periods of histogenesis, their weight increased by birth and then returned to the previous level.

We elucidated whether developing human fetal lungs contain cells producing thymalin, a stimulator of T cell proliferation and differentiation. Thymalin is a complex polypeptide weighing 1000-6000 Da [5,6]. We previously showed that thymalin is involved in the differentiation of T cells and activates expression of specific receptors on their surface. Thymalin is used in clinical practice for correction of immunodeficiency [8].

MATERIALS AND METHODS

Developing thymus and lungs of human fetuses were studied on weeks 8-23 of gestation. The fetuses were

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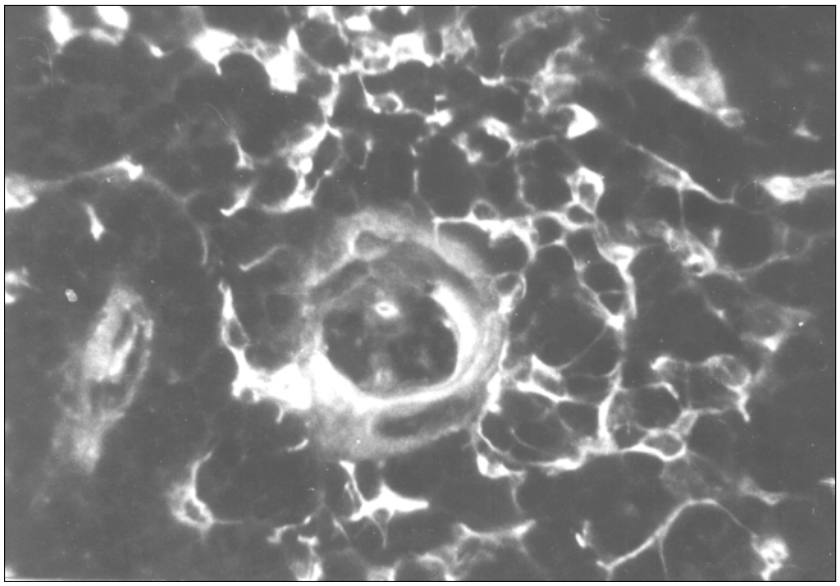

Fig. 1. Thymalin in reticuloepithelial cells of thymic medulla of 20-week fetus. Indirect Coons' method, ×800.

obtained from healthy women with preterm delivery. Fragments of organs were frozen in liquid nitrogen. Cryostat sections were fixed in cold acetone, washed in cold buffered isotonic NaCl for 15 min, incubated first with rabbit antithymalin antiserum [4] and then with FITC-labeled asinine serum to rabbit globulin. The sections were incubated in a humid chamber and examined under a LUMAM-P3 fluorescent microscope. Standard controls were used: with intact serum and buffered isotonic NaCl solution.

RESULTS

In fetuses aged 5-6 weeks thymalin-positive cells were diffusely scattered over epithelial thymus primordium before the appearance of lymphocytes. We previously showed that thymalin produces a distant effect on the liver containing few T cells under extrathymic conditions of their differentiation [9]. By weeks 11-12, when the cortical matter and medulla are clearly seen in the thymic lobules and it contains up to 85% T cells, thymalin-positive cells are concentrated mainly in the medulla (Fig. 1).

During weeks 8-15 of gestation thymalin-positive cells were clearly seen in the airways (trachea and large bronchi). They were present in the surface epithelium and belonged to younger elements (Fig. 2). In the stratified epithelium they were located in the basal and intermediary layers; differentiated ciliary cells contained no thymalin. Thymalin-positive cells occupied the same place in the excretory ducts of the developing tracheal glands. Thymalin-positive cells in the respiratory part are large irregularly shaped cells diffusely spread in the organ (Fig. 3). These cells were not found in the bronchiolar epithelium.

Hence, our findings indicate that cells containing thymic factor appear in the developing human lungs at the early stage of fetogenesis. The fetus develops under sterile, but not antigen-free conditions, which determines early development of a philogenetically based defense system including immunological and endocrinological components. Our results are in line with the findings of other authors [1], who detected cells producing not only biogenic amines, but also polypeptides, e.g. thymalin, in fetal lungs [1]. The presence of thymalin confirms early appearance of mature T cells ($CD3^+$), cells with receptors to sheep erythrocytes ($CD2^+$), and the main regulatory cells ($CD4^+$ and $CD8^+$) in developing lungs. These cells form in the fetus without the direct effect of thymic microenvironment. Presumably, the presence of thymalin-producing cells is the leading factor in this process. The main function of the local immune system in fetal lungs is protection from potentially aggressive maternal cells and from infectious agents. Early and more complete maturation of T cells promotes elimination of maternal immunocompetent cells or micro-

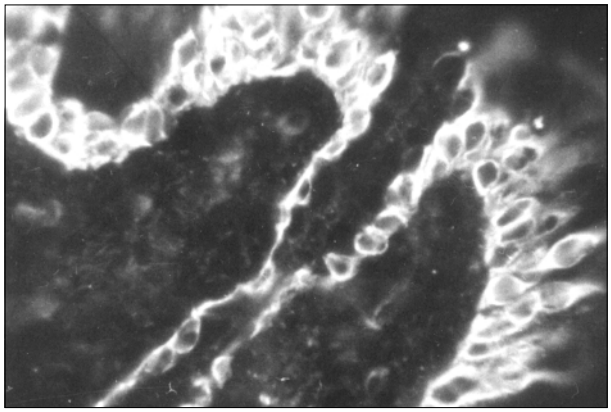

Fig. 2. Thymalin-positive cells in tracheal epithelium. Indirect Coons' method of a 20-week fetus, ×800.

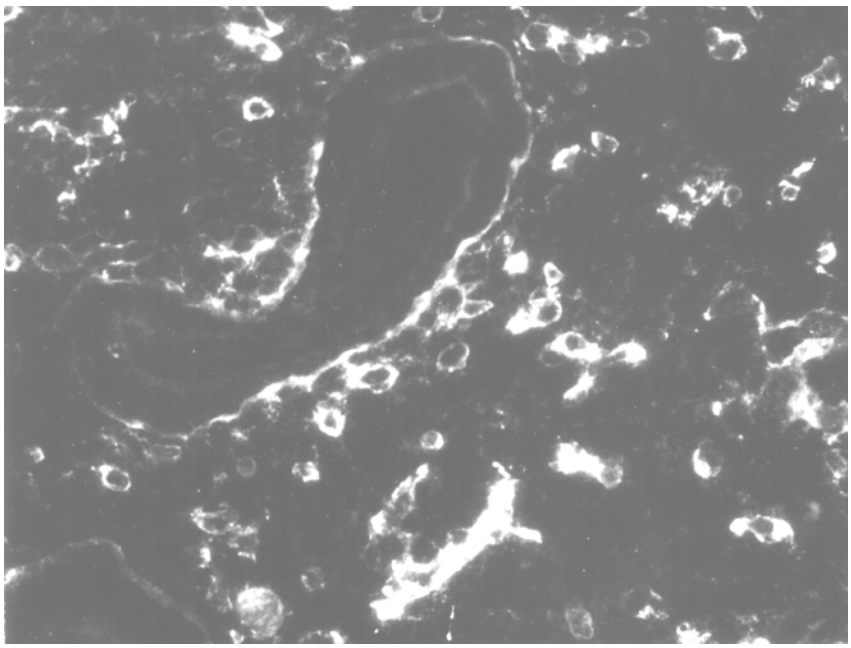

Fig. 3. Thymalin-positive cell diffusely scattered in developing lungs of 8-10-week fetus. Indirect Coons' method, ×400.

organisms entering the body through the trachea or blood vessels [3]. Thymalin accumulates only in young cells in the tracheal, bronchial, and ductal epithelium. In the developing alveolar part of the lung parenchyma thymalin-positive cells are diffusely scattered.

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