MORPHOLOGY AND PATHOMORPHOLOGY

Morphological Characteristics of Histions of Developing and Atresic Human Ovarian Follicles

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The morphology of tissue elements of human ovarian follicles was studied in the course of normal folliculogenesis and in some forms of its disorders. Signs of abnormal development of follicles were detected that are typical of different stages of their development under the conditions studied.

Key Words: *ovary; follicle; atresia*

Ovarian follicles at successive stages of development may be regarded as self-refining morphological systems consisting of generative elements and somatic tissues. Although the development of these systems (histions) is governed by adenohypophyseal mechanisms, an important role in their regulation is played by the system of interactions between their tissue and cellular components. Understanding the morphological basis of these interactions is important with regard to follicular selection. Some features of the intercellular and interstitial relationships in histions may play a crucial role in selection, all other conditions being equal for all developing follicles. Solving this problem is desirable from a practical viewpoint as well, for failure of the dominant follicles to form can be a cause of sterility.

In this study we followed the time course of the histological and submicroscopic organization of follicular histions in human ovaries.

MATERIALS AND METHODS

The objects of our examination were fragments of ovaries from healthy women of reproductive age who had died in car accidents, from women with a biphasic menstrual cycle suffering from chronic adnexitis and tubal sterility, and from women with anovulation "of ovarian genesis" without adrenal or hypothalamo-pituitary diseases. The status of follicular histions was assessed by general histological, electron microscopic, and histochemical methods.

RESULTS

The term "healthy follicle" is commonly used to denote ovarian follicles without signs of atresia; we will use it, too.

Microscopic and submicroscopic analysis of the primordial follicles showed that the bulk of them were at various stages of degeneration in the gonads of all the groups examined. In some follicles the sex cells looked intact at the light-optic level, but electron-microscopic analysis revealed destructive changes in the system of their organelles. Individual folliculocytes of such follicles were completely electron-transparent with manifest signs of destruction. Microcysts were forming at the site of numerous primordial follicles. The structure of oocytes and follicular cells of healthy primordial follicles was different: granulosa cells looking moderately electron-dense formed solid contacts and contained mature organelles, evidently getting ready

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Fig. 1. Fragment of basal part of granulosa membrane of a minor antral follicle (human ovary, anovulation). Collagen masses lie adjacent to the thickened basal membrane of the follicle. ×10,000.

for reproduction and the formation of a multilayer membrane. The structure of the oocytes of these follicles was intact.

It is possible that the structural status of follicular cells plays a certain role in the elimination of primordial follicles during normal folliculogenesis and its changes. Although degeneration of oocytes in primordial follicles is considered to be primary [1], the opposite situation is possible, with the initial changes developing in the follicular epithelium.

The formation of a transparent coat, which becomes an integral part of the histion, is one of the signs of progressive development of a follicle. A study of ovarian fragments from each of the tested groups showed no signs of formation of a transparent coat in individually growing follicles with a 2-3-layer granulosa. In such cases, moderate signs of destruction presenting as a thickening of the nucleolemma and disorganization of the lamellar complex, granular cytoplasmic reticulum, and mitochondria are seen in the nuclei and membrane organoids of folliculocytes. In oocytes the initial signs of destruction present as cytosol clarification and discomplexation of the organelles. Since the granulosa cells contribute to the formation of the oocyte transparent membrane, it may be assumed that disorders in the formation of this membrane can to a certain extent be due to destructive processes in folliculocytes.

The development of a thecal follicular membrane is an important event in folliculogenesis. Starting from this moment, the follicle comes in contact with blood and is first exposed to its hormonal environment. The follicle initiates a series of structural and biochemical changes, becoming antral. Signs of parafollicular orientation of connective tissue cells, that is, signs of the formation of a connective-tissue membrane, were absent in some follicles with a multilayer granulosa (late preantral follicles) in the ovaries of the groups examined. The granulosa of these follicles was disorganized and the basal membrane hyalinized. At a submicroscopic level, the granulosa cells were characterized by different degrees of destruction, although the oocyte ultrastructure was better preserved. This might be because the follicular epithelial cells produce a thecal organizer promoting the formation of the theca.

After the transition of growing follicles into late preantral ones, the internal thecal membrane assumes an important role. Signs of differentiation of the internal thecal membrane were absent in individual pre- and minor antral follicles in the sterile group. Collagen masses and fibroblasts were adjacent to the thickened basal membrane of such follicles (Fig. 1). The cytoplasm of follicular cells was electron-clear and contained organelles changed to such an extent that they were unrecognizable, and the

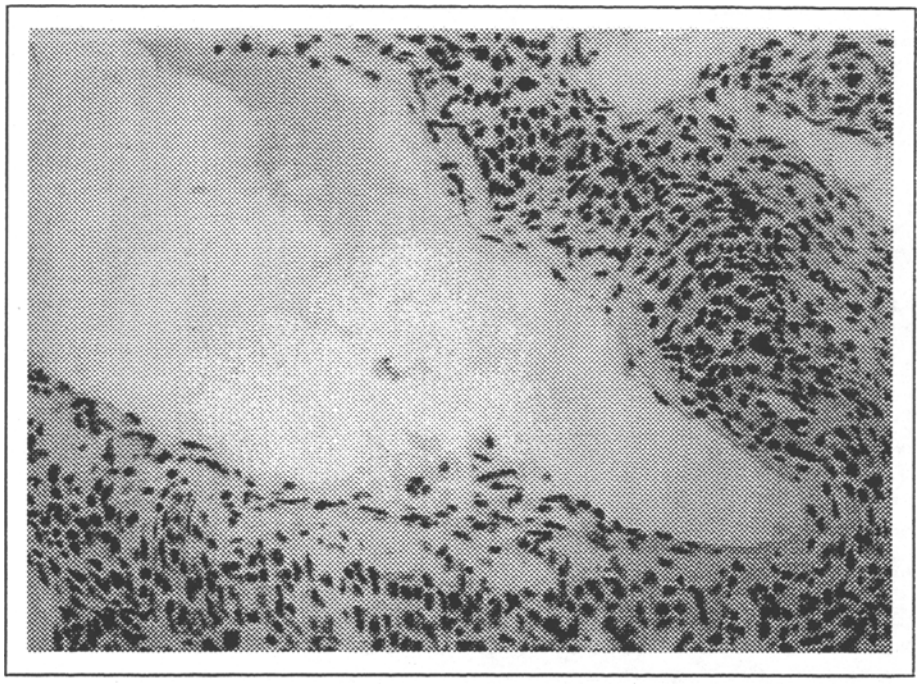

Fig. 2. Fragment of atresic antral follicle (normal human ovary). Complete disappearance of granulosa membrane, basal membrane hyalinized, moderate hypertrophy of the theca. Here and in Fig. 3: hematoxylin–eosin staining. ×473.

cells themselves did not form the compact contacts and gap junctions typical of them and were disorganized. The disorders in the process of formation of the theca interna found in patients with anovulatory states and ovarian sterility may be one of the components in the pathogenesis of these diseases.

Atresia of the antral follicles during all the states examined may present as one of two forms with a specific type of transformation of follicular histions. One variant is as follows: both membranes are preserved in the follicles for some time, but later the granulosa degenerates and no longer exists as an element of the histion; the theca in such cases is virtually intact, and the basal membrane coming in contact with the follicular fluid is hyalinized (Fig. 2). Changes in the granulosa and basal membrane lead to a breakdown of the two-cell mechanism of estrogen synthesis, and this mechanism is confined to the intact theca, which fact is proved by the positive reaction to 3β-ol-steroid dehydrogenase (3β-ol-SDH) which we recorded. In the other form of atresia both follicu-

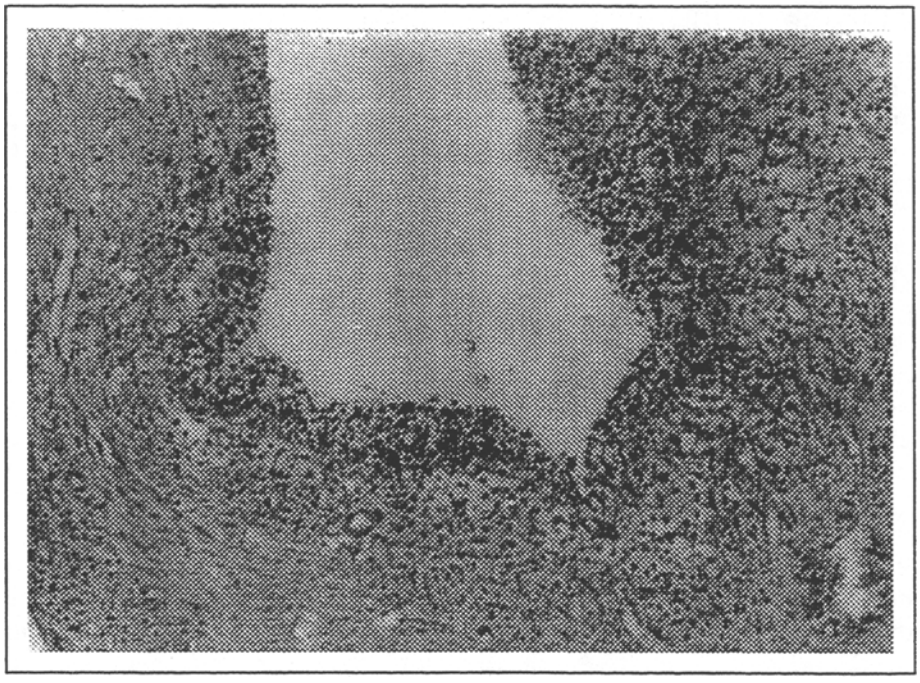

Fig. 3. Fragment of atresic antral follicle (normal human ovary). Both follicular membranes are intact and hypertrophic.

lar membranes are preserved, and the basal membrane is intact (Fig. 3). The cells of the theca interna, characterized by very active hypertrophic growth, are rich in 3β-ol-SDH; certain amounts of this enzyme are present in the granulosa of these follicles, thus proving its independent role in steroid production.

Our studies showed that a "natural selection" of follicles takes place in the majority of developing follicles because of imperfect morphology of granulosa cells; this selection consists in a rearrangement of the sequence of formation of structural constituents of histions - the transparent membrane, theca, and theca interna - and in the existence of two forms of atresia of the antral follicles.

An important role in follicle selection is known to be played by the system of neurovascular supply to the gonad and follicular histions. Our data indicate that ovarian forms of female sterility and inflammatory diseases of the gonads are attended by hyalinosis of arteries in the stroma and parafollicular regions. This is associated with an appreciable reduction in the activity of the transmitter background of interstitial and parafollicular adrenergic perivascular nerves. Interestingly enough, a similar complex of changes has been described for menopausal ovaries [1,2], when anovulation becomes a natural state.

Hence, our findings indicate that the status of tissue components of ovarian follicles and their relationships may play an important role in the process of the positive development of follicles.

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