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The morphology and differentiation of stromal cells in the cortex of follicles in the bursa of Fabricius of the chicken

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Abstract

Mesenchymal reticular cells (MRCs) form a supporting system in the cortex of the bursal follicle. The stellate-shaped MRCs exhibit a low electron density, which is helpful for their identification. A remarkable feature of MRC is the formation of multiple blebs in the nuclear envelope. The large, irregularly shaped blebs—which are perinuclear spaces—may be detached from the nuclear membrane, creating a sac-like granular endoplasmic reticulum (GER). Inside the bleb, membrane-bound bodies originate from cytoplasmic impressions. The cytoplasm contains a few round mitochondria, in which the internal membranes form either ovoid vesicles or the entire internal structure is indistinct. These mitochondria may be associated with the blebs. The classical Golgi complex with cis and trans faces cannot be recognized, but the accumulation of very small vesicles occurs around two or three stacked flat cisterns. The MRC forms a continuous layer along the corticomedullary basal lamina (CMBL), and during cell migration between the cortex and medulla, it may contribute to the temporary closure of the gap in the CMBL. At the outer surface of the cortex, transitory cells between the MRC and fibrocytes of the interfollicular connective tissue are present, and both cells can produce GER by blebbing. This finding suggests that MRCs and fibrocytes may have a common origin. The other stromal cell is the macrophage (Ma), which may fuse together to form multinucleated giant cells. The definition of histological classification of the third type of stromal cell is questionable, but certain morphological features may be referred to as progenitors of MRCs.

KEYWORDS

blebbing of nuclear membrane, bursa of Fabricius, formation of granular endoplasmic reticulum, inner structure of mitochondrion, mesenchymal reticular cell

1 | INTRODUCTION

The nucleus is essential for living and proliferating cells because it contains genetic material. During the interphase, the genetic material is present in both active and inactive forms, which histologically appear as eu- and heterochromatin, respectively. Generally, the pattern of eu- and heterochromatin is a characteristic feature of a cell, which is helpful for its identification in tissues. A double-layered nuclear membrane or envelope separates the nuclear material from the cytoplasm (Anderson & Beams, 1956). However, a number of pores in the nuclear membrane facilitate communication between the nucleus and cytoplasm (Maul, 1977). The space between the outer and inner nuclear membranes is termed the perinuclear cistern, which is often continuous with the rough endoplasmic reticulum. Generally, rough endoplasmic reticulum is organized in stacks of flat cavities or cisterns. Ribosomes appear studded on the cytoplasmic surface of the cisterns; therefore, it is also called the granular endoplasmic reticulum (GER). Numerous studies have reported alterations in the nuclear envelope during the golden age of transmission electron microscopy. In young, differentiating, and growing cells (Gulyas, 1971a; Szöllösi, 1965), changes in the nuclear membrane appear as nuclear blebbing and annulated lamellae (Gulyas, 1971b). Nuclear membrane blebs have been described in different mammalian zygotes, including cattle (Crozet, 1984), sheep (Crozet, 1988), chimpanzees (Maul, 1977), humans (Sathananthan & Trounson, 1985), rat pronucleate eggs (Szöllösi & Szöllösi, 1988), fetal and neonatal human oocytes (Baker & Franchi, 1969; Hertig & Adams, 1967; Zamboni et al., 1966), as well as rabbit blastocysts (Hadek & Swift, 1962). Blebbing has previously been induced by cell hybridization of oocytes and thymocytes (Szöllösi & Szöllösi, 1988). Moreover, Scalzi (1967) observed bleb formation in degenerating cells in the taste buds of the rabbit foliate papillae. Bleb formation has also been reported in rat pancreatic acinar cells (Clark Jr., 1960); however, both nuclear membranes participate in these blebs. Several years ago, we described bleb formation in guinea pig thymocytes, but this kind of "bleb formation" included some nuclear material. It is believed that this "bleb formation" might be related to nuclear membrane reconstitution in mitotic telophase (Törö & Oláh, 1966). Different variations of nuclear membrane has been called "nuclear blebbing," which seems to be related either to undifferentiated or degenerated cells. In the present study, the nuclear membrane bleb is used for the local dilation of the perinuclear space, which is formed by the outpocketing of the outer leaflet of the nuclear membrane into the cytoplasm.

In birds, one of the primary lymphoid organs is the bursa of Fabricius (BF), which comprises 12–15 folds filled with follicles. The follicles consist of medullary and cortical regions (Figure 1). The follicular medulla develops between 11 and 13 embryonic days, while the development of the follicular cortex begins around the time of hatching and is completed by the end of the second week of life. It is believed that the follicular medulla of the BF is responsible for B-cell differentiation and maturation, whereas the cortex is a transit zone for B-cell migration. Dendritic cells, which are located in the follicular medulla, are the key cells involved in innate and adaptive immune responses. The early development of the medulla and the location of dendritic cells have drawn the attention of the scientific community toward the structure and function of the medulla, presuming that the medullary area of the bursal follicle is the primary lymphoid organ. For these reasons, the follicular cortex has not received satisfactory attention to date. The aim of this morphological study was to provide a detailed description of cortical stromal cells: mesenchymal

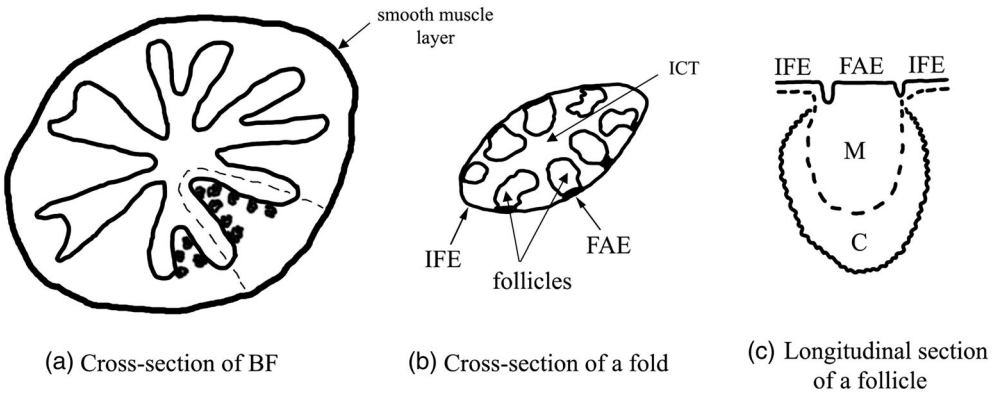

FIGURE 1 Schematic diagram of the bursa of Fabricius, bursal fold, and follicle. (a) The dashed line indicates a bursal fold, which is filled with vesicles (black dots). (b) The follicles (irregularly shaped vesicles) attach to the surface epithelium of the fold at a point known as the follicle-associated epithelium (FAE). Within the FAE, about 90% of surface epithelium is the interfollicular epithelium (IFE). The interfollicular connective tissue (ICT) separates the follicles and receives the blood and lymphatic vessels. (c) The corticomedullary basal lamina (dashed line) separates the cortex (C) and medulla (M)

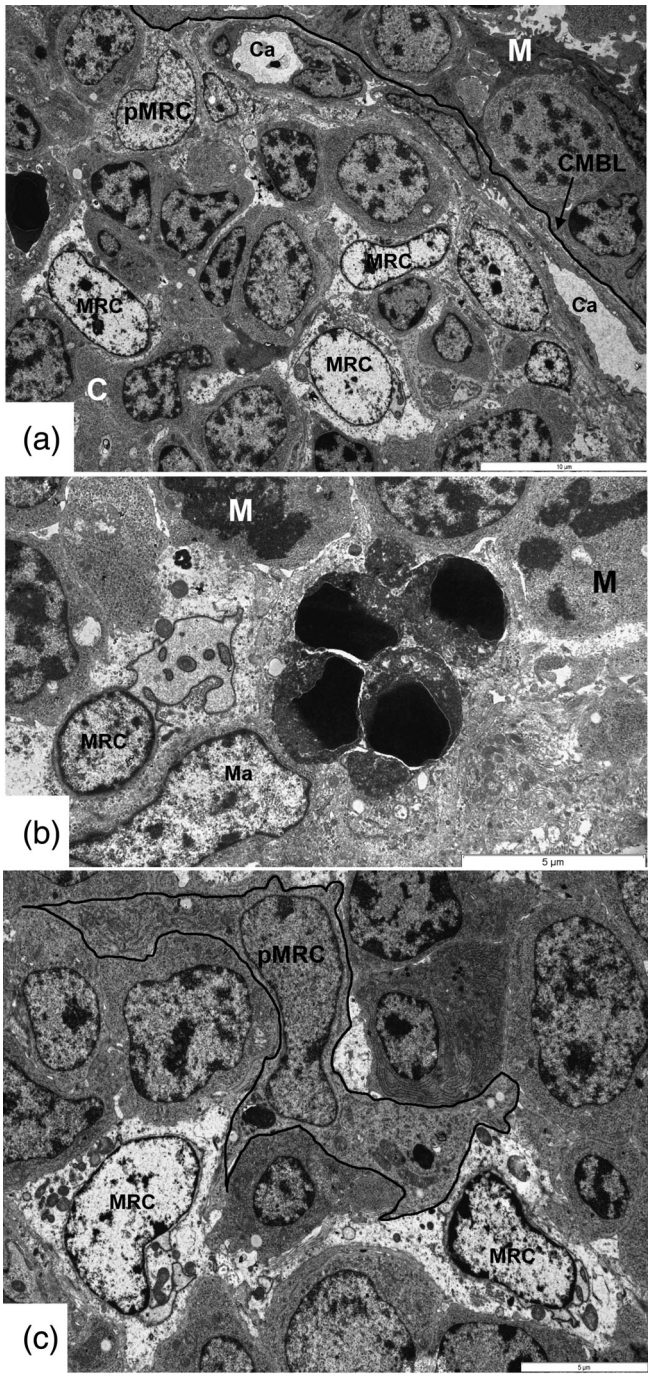

FIGURE 2 Survey of the follicular cortex (a) The corticomedullary basal lamina (CMBL, outlined) separates the cortex (C) and medulla (M). Beneath the CMBL, a capillary (Ca) network supplies both the cortex and medulla. The 3D, low electron dense mesenchymal reticular cells (MRCs) support the cortex. Progenitor of MRC (pMRC) Mag. 4×. (b) Adjacent to the blebbing MRC, a cortical macrophage (Ma) shows four apoptotic cells. Besides the stromal cells two mitotic cells (M) occur. Mag. 10×. (c) A third type of stromal cells (outlined). The elongated cytoplasm resembles that of MRCs. Mag. 6×

reticular cells (MRCs), macrophages (Mas), and a third type of stromal cells. Stromal cells are partially responsible for the cortical microenvironment (ME). Recent electron microscopic studies have revealed some unique cytological features of MRCs and suggest that in MRCs, the formation of GER takes place by nuclear membrane blebbing, which has not yet been described in avian species.

2 | MATERIALS AND METHODS

2.1 | Animals

In this study, 10-, 12-, and 14-day-old embryos as well as 2-, 7-, 15-, 19-, 27-, and 42-day-old White Leghorn layer types (Charles River) were used. Histological observations were made from two birds per age group. The chickens were reared under standard conditions, according to the general requirements of chickens: 26°C ambient temperature, feed (sterilized broiler grower mix), water (tap water) ad libitum, and light cycle of 12 hr.

Bursal development has three distinct periods: (a) formation of epithelial anlage of the BF between 4, 5, and 9 days of incubation; (b) formation of follicular medulla and colonization of hematopoietic stem cells. This stage requires intense cell migration between 10 and 14 days of incubation; and (c) formation of cortex between embryonic day 20 and post-hatching day 18. The BF exists in a steady-state condition between 3 and 12 weeks of age. When bleb formation was noticed in young 8- to 15-day-old chickens in coronavirus-infected and control birds, we planned to determine whether bleb formation is a unique feature of the MRCs at this stage or whether it is a general phenomenon in the cortical MRCs. Consequently, three stages of bursal development were selected for studying the bleb formation and mitochondrial alterations in MRCs: (a) epithelial bud formation from the surface epithelium (establishing medulla, embryonic days 10–14); (b) cortex formation (embryonic day 20 to 18 days post-hatching; and (c) steady-state condition (3–12 weeks of age). Transmission electron microscopy did not reveal any differences in bleb formation between the three groups. The chickens were euthanized via cervical dislocation. All methods used in these animal studies were approved by the Ethical and Animal Welfare Committee of Ceva Phylaxia Co.

2.2 | Transmission electron microscopy

The tissue samples were fixed in 4% glutaraldehyde overnight and after washing in Millonig phosphate buffer, they were postfixed in 1% osmium tetroxide for 2 hr. Subsequently, the tissue samples were dehydrated in graded ethanol and propylene oxide embedded in a Polybed/Araldite 6005 mixture (Polyscience Inc. Warrington, PA). The ultrathin sections were contrasted with uranyl acetate as well as lead citrate, and examined with a JEOL JEM-1200EX (JEOL USA, Inc.) electron microscope at 80 kV.

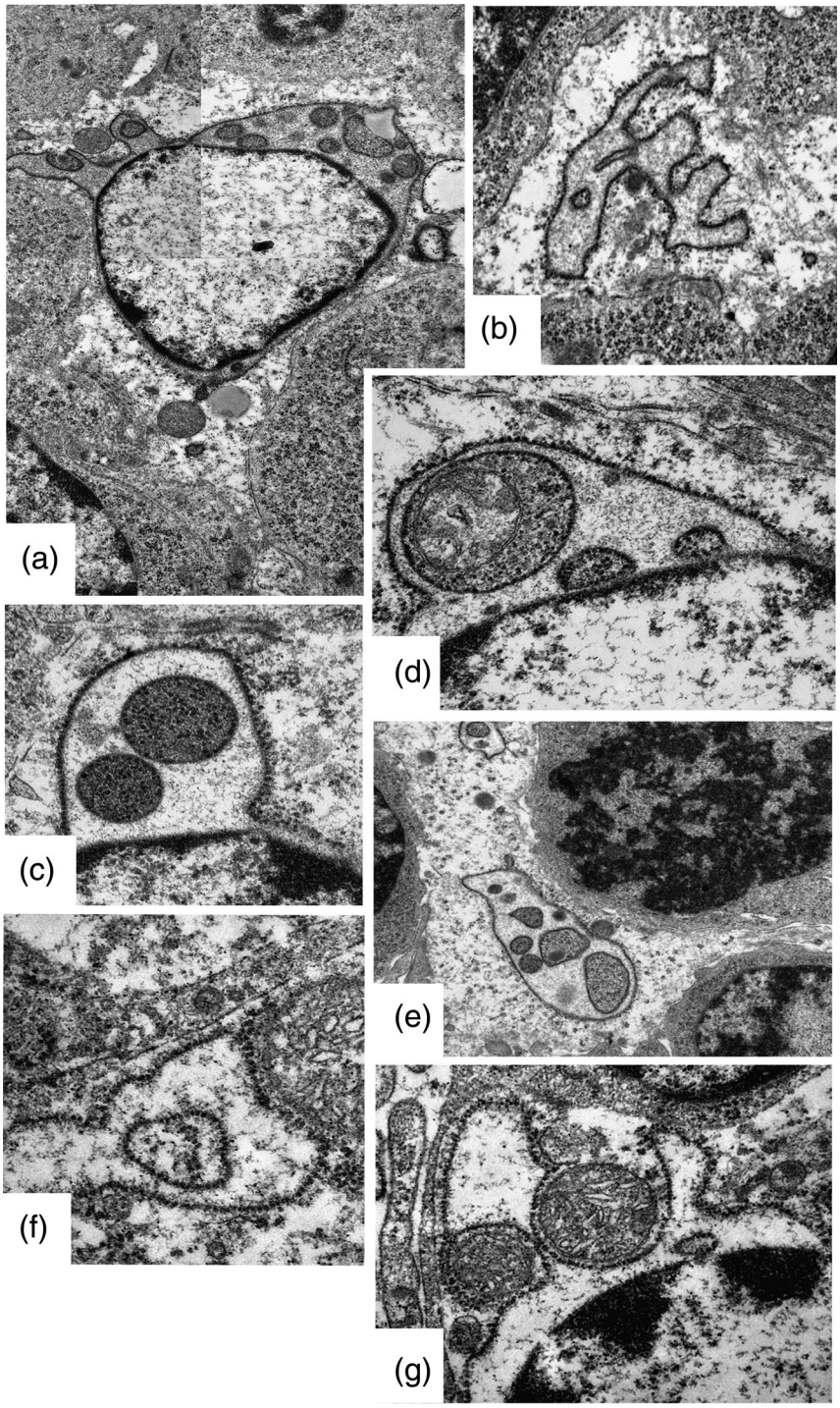

FIGURE 3 Bleb formation in mesenchymal reticular cell (MRC). (a) MRC with multiple blebbing. Mag. 30×. (b) Highly irregular bag-like granular endoplasmic reticulum (GER) in a process of MRC. Mag. 25×. (c) Ribosomes studding the left side of cytoplasmic surface of bleb. The invaginations of cytoplasm; intrableb bodies have granulated substance of higher electron density than the cytoplasm. Mag. 50×. (d) In the bleb, a mitochondrion with indistinct inner structure can be observed. Mag. 50×. (e) the detached bleb from the nuclear envelope may have different size and shape, as well as electron dense cytoplasmic invaginations or bodies. A mitotic cell adjacent to the MRC (M). Mag. 15×. (f) A mitochondrion associated with bleb shows irregularly arranged ovoid vesicles. Mag. 50×. (g) The two mitochondria are present in the invagination of the bleb. Mag. 30×

3 | RESULTS

3.1 | Histological analysis of the follicular cortex

The bursal follicle consists of the cortex and medulla, which are of mesodermal and ectodermal origin (Nagy & Oláh, 2010), respectively. At the corticomedullary (CM) border, the basal lamina (BL) separated the cortex and medulla. In the cortex, translucent MRCs constructed a 3D supporting system (Figure 2a). Inside the cortex, immediately below the BL, there was a dense capillary network that supplied both compartments (Figure 2a). The inner border line of the cortex was corticomedullary basal lamina (CMBL). Parallel to the CMBL, the MRCs formed a layer, which was discontinuous between the CMBL and capillaries. The outer surface of the cortex was distinct, but not a complete, histologically identifiable structure. In a lymphoid organ, besides the vascular bed, stromal cells provide a ME. In the bursal cortex, the MRCs (Figure 2a), Mas (Figure 2b), and a

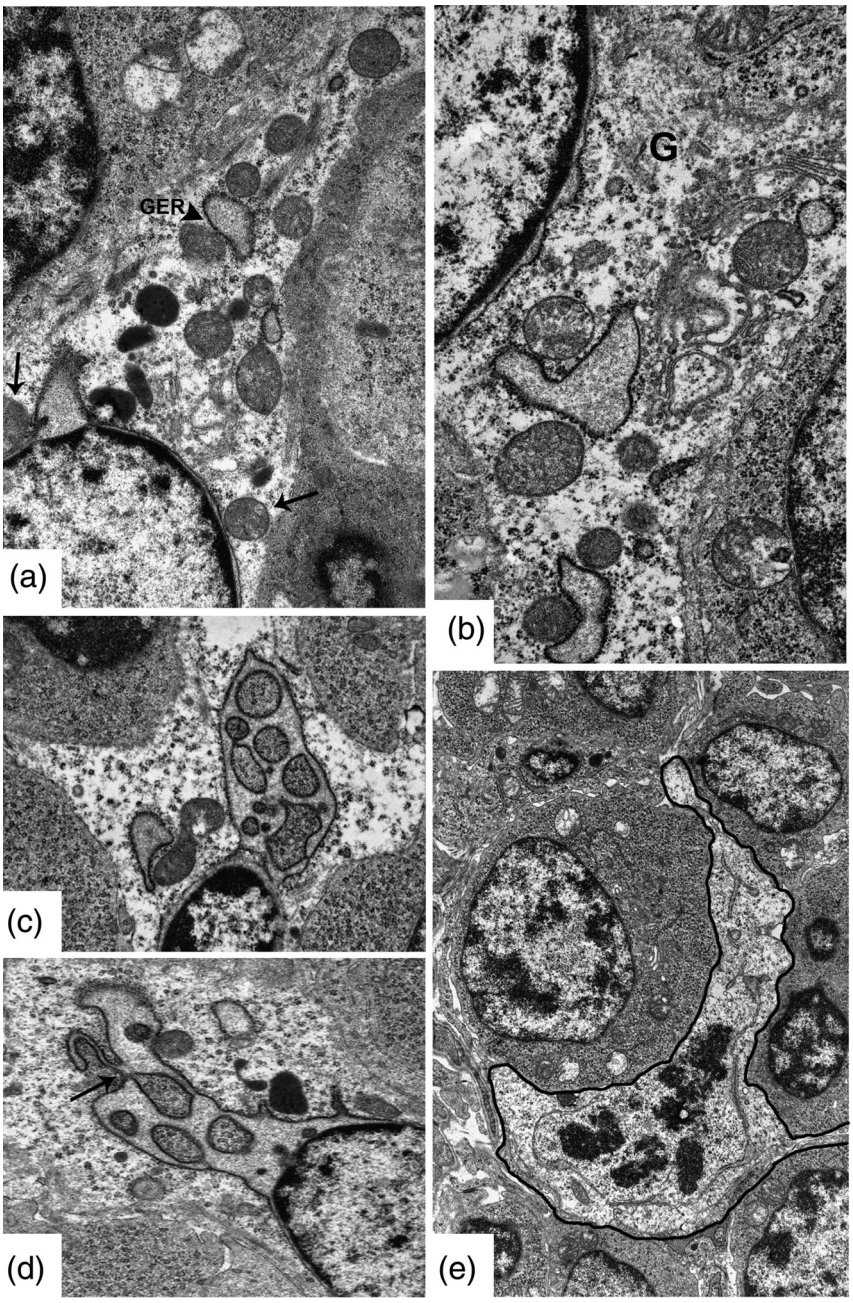

FIGURE 4 Cytological structure of mesenchymal reticular cell (MRC). (a) Two mitochondria associate with the outer leaflet of nuclear envelope (arrow), and others are in close proximity of "bag"-like granular endoplasmic reticulum (GER, arrowhead). Occasionally, high electron dense bodies may be found in the cytoplasm. The inner structure of mitochondria is indistinct. Mag. 25×. (b) Mitochondria associated with "bag"-like GER. Small vesicles appear scattered around Golgi-like cisternae (G). Mag. 30×. (c) Several intrablebbing inclusions clearly exhibit higher electron density than the cytoplasm. A "bag-like" GER associates with mitochondrion in the translucent cytoplasm. Mag. 25×. (d) Large blebbing with several cytoplasmic invaginations. One of the invaginations seems to be detaching from the surface of the bleb (arrow), demonstrating the mechanism of formation of intrableb bodies. Mag. 20×. (e) Mitosis in a mature MRC (outlined). Mag. 12×

third type of stromal cells (Figure 2c) may have contributed to ME. The number of the third type of stromal cells is low, about 1% of cortical cells. The cells had a bulky organelle-rich cytoplasm (Figure 2c). However, there were no histologically appreciable differences in the cytology of MRCs based on the age of the chicken.

3.2 | Mesenchymal reticular cell

The MRC is stellate-shaped, with translucent nucleus and cytoplasm, which helps in the identification of cell and cell processes (Figure 2a,c). The shape of the nucleus varies, and the heterochromatin attaches to the nuclear envelope (Figure 2a–c). The most remarkable feature of the MRC was bleb formation by the nuclear envelope (Figure 3a). The MRC is unique when taking into consideration the characteristics of its GER, mitochondria, and Golgi complex. Generally, the GER appears as flat cisternae or cavities that are frequently stacked, and the cytoplasmic surface is studded with ribosomes. However, in the MRC, the GER looks like a sectioned, irregular "bag" with several impressions (Figure 3b).

Within the blebs, variable sizes and numbers of membrane-bound bodies with increased electron density were observed (Figure 3c), along with the occasional mitochondrion (Figure 3d). The observation of mitochondria

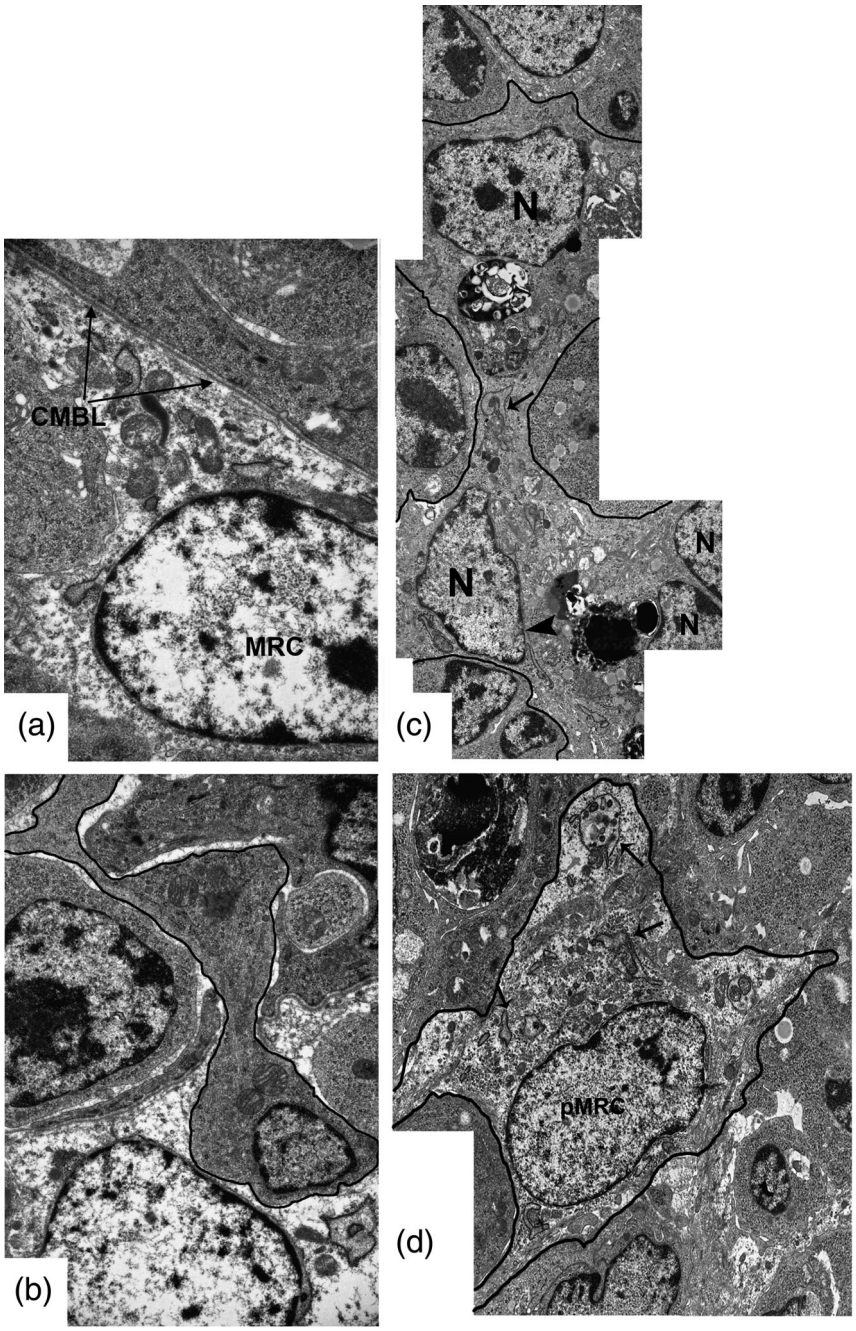

FIGURE 5 Functional morphology of mesenchymal reticular cell (MRC) and macrophage (Ma). (a) MRC leans against the corticomedullary basal lamina (CMBL). Mag. 20×. (b) A probable lymphocyte (outlines) in migration through the hole of CMBL. Beneath the CMBL, an MRC surrounds the migrating cell. Mag. 20×. (c) Cortical Ma (outlined) shows apoptotic cells and "bag"-like granular endoplasmic reticulum (GER, arrow). Arrowhead indicates the formation of GER from nuclear envelope. Among the three nuclei (N), there is no cell membrane (the montage consists of five shots). Mag. 25×. (d) Progenitor cell of MRC (pMRC). The cell nucleus and cytoplasm exhibit moderate electron density. The cytoplasm is rich in organelles, small vesicles, and scattered "bag"-like GER elements (arrow). Cell membrane (outlined). Mag. 12×

within a bleb is unusual and may be the result of cytoplasmic invagination within the bleb. These intrableb membrane-bound bodies are numerous—especially in large, detached blebs—and may contain ribosomes contributing to the higher electron density (Figure 3e). In MRCs, the number of mitochondria is low, and they may be spherical or malformed. The inner membrane of the mitochondrion does possess any septae or tubules. It either forms oval-shaped vesicles (Figure 3f,g) or the entire inner structure is indistinct (Figure 4a,b). Furthermore, there is a conspicuous tight topographical connection between the nuclear as well as GER membranes and the mitochondria (Figure 4a,b). In Figure 3g, the larger mitochondrion is present in the invagination of the bleb, while the smaller one seems to be partially involved in the bleb. A smooth endoplasmic reticulum is seemingly absent in these cells, but the cytoplasm may contain several irregularly shaped, dense bodies (Figure 4a). A typical Golgi complex with cis- and trans faces cannot be seen, but two or three stacked flat cisternae with small vesicles resemble the Golgi complex (Figure 4b). Generally, in MRCs, more than one bleb is formed, and after elongation and enlargement, the bleb can detach from the nuclear envelope and appear in the cytoplasm as a GER (Figure 4a–c). Figure 4d depicts a possible mechanism of intrableb formation. Occasionally, stellate-shaped MRCs exhibited mitosis (Figure 4e), supporting the viability of MRCs.

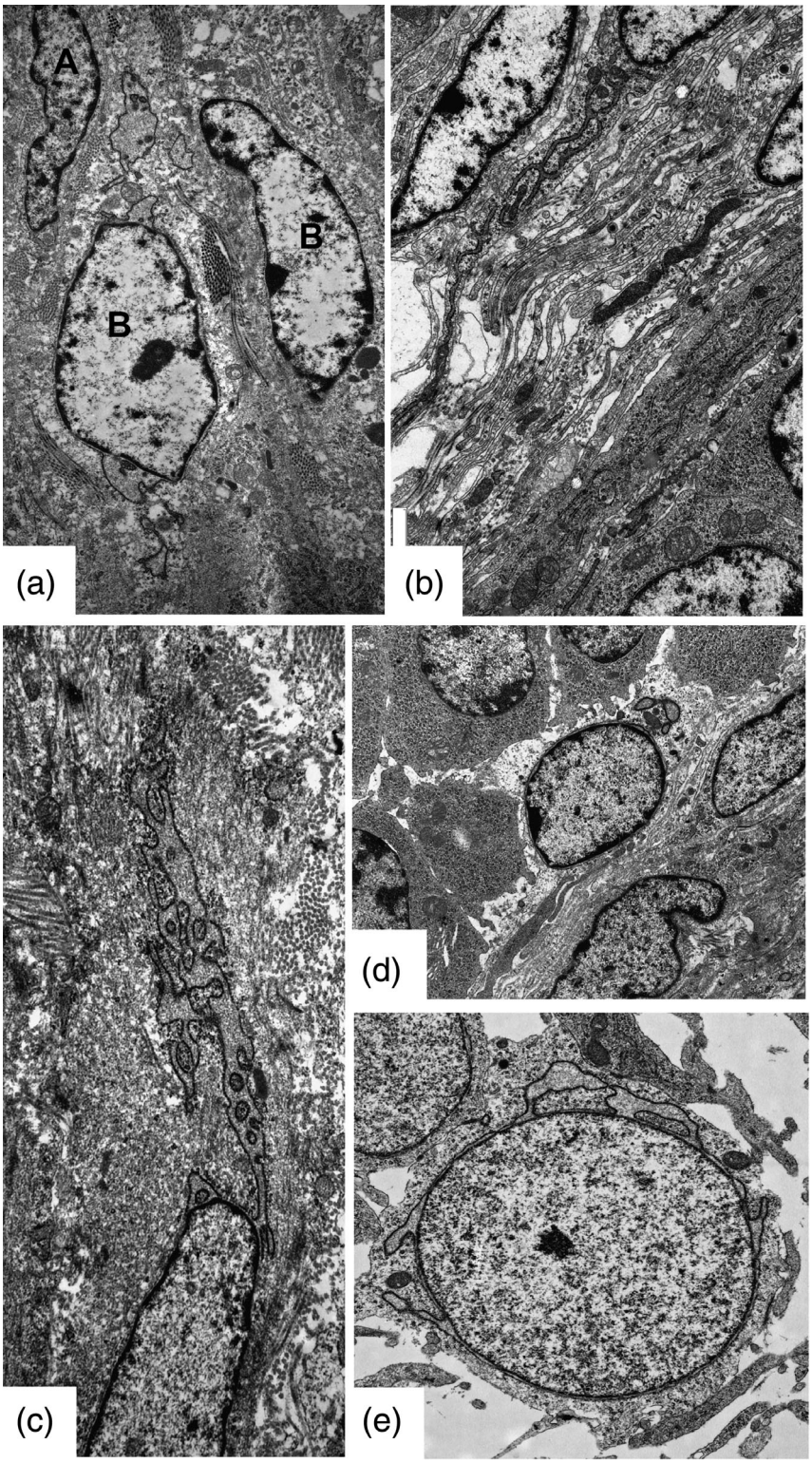

FIGURE 6 (a) Two kinds of cells can be observed in the connective tissue: A highly elongated, electron dense fibroblast (a) and a less elongated, low electron dense cell with "bag"-like granular endoplasmic reticulum (GER) formations (b). Mag. 15×. (b) In 2-day-old chicken, the fibroblasts and mesenchymal reticular cell (MRC) progenitors form highly elongated cell processes, which are organized in lamellated pattern in the interfollicular connective tissue (ICT). Mag. 15×. (c) Within the fibroblast, the GER also arises from dilation of perinuclear space. Mag. 15×. (d) At the border of the cortex and ICT, topographically transitory cells occur between MRC and fibroblast. Several cell processes of these cells enter the cortex, while others cover the cortical surface. Mag. 12×. (e) Ten-day-old embryo. The low electron dense, vesicle-like nucleus produces multiple blebs in the bursal mesenchyme. Mag. 15×

3.3 | Communication between the cortex and medulla

Communication between the cortex and medulla occurs via cell migration through the CM border. The direction of migration cannot be determined on the static transmission micrograph, but the cytological structure of migrating cells occasionally hinted at lymphocytes. During IBIDEMV infection, the migration of macrophage-like cells (Mal) into the cortex markedly increased (Figure 5). The MRC covered the cortical surface of the CMBL (Figure 5a) and surrounded the migrating cells at the gap of the BL (Figure 5b).

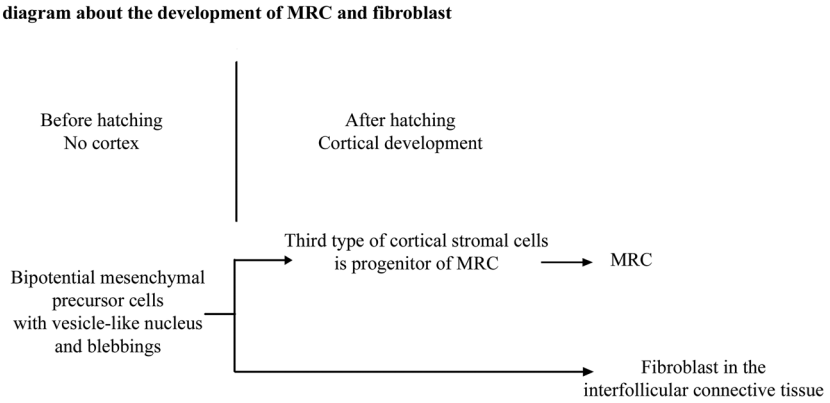

FIGURE 7 Schematic diagram depicting the development of mesenchymal reticular cell (MRC) and fibroblast

3.4 | Macrophage

The irregularly shaped nucleus differs from the round or ovoid-shaped nucleus of the MRC. Moreover, the bulky cytoplasm and nucleus were not as translucent as those of the MRC. The Ma cytoplasm showed apoptotic cells and an unusual bag-like GER (Figure 5c). The cell membranes among the Mas were frequently indistinct, and in some places they were clearly absent, creating multinucleated giant cells (Figure 5c).

3.5 | Histologically undefinable cell

Histological classification of the third type of cortical stromal cells is uncertain, but certain cytological features suggest that they are young, immature MRCs (Figure 5d). Tentatively, the cell has been named a progenitor of mesenchymal reticular cells (pMRCs). The pMRC had a lesser translucence and bulky cytoplasm, which produced extensions. In addition, the cytoplasm contained a large number of small vesicles and "bag-like" GER (Figure 5d).

3.6 | Interfollicular and subepithelial connective tissues

The connective tissue of the BF receives blood and lymphatic vessels, and connects the bursal parenchyma (follicle as well as surface epithelium) to the circular smooth muscle layer. The contraction of smooth muscles may contribute to the relocation of intrabursal lymphocytes. In interfollicular connective tissue (ICT), two types of cells could be distinguished: a highly elongated fibrocyte-like cell and a translucent, less elongated MRC-like cell (Figure 6a). In 2-day-old birds, both types of cells produced GER by blebbing (Figure 6a,c) and long, very slim (0.05–0.10 μ) cell processes, which formed a lamellated pattern among the growing follicular cortex (Figure 6b). MRC-like cells were located at the border of the cortex and ICT, but these cells did not form a complete layer (Figure 6d). In the 10-day-old embryo, cells with large, vesicle-like nuclei already produced blebs (Figure 6e), which are possibly precursor cells of MRCs and fibroblasts of ICT. The bleb formation and "bag-like" GER in both cell types may prove their common origin (Figure 7).

4 | DISCUSSION

The most remarkable transmission electron microscopic finding in MRCs is the multiple blebbing of the nuclear envelope. In addition to nuclear membrane "anomaly or malformation," the alterations in cytoplasmic organelles (inner structure of mitochondria, lack of cis and trans faces of Golgi complex, and the absence of smooth endoplasmic reticulum) exhibit the unique feature of MRCs, which may be supported by the early, embryonic appearance of blebbing in the bursal mesenchymal cells. These mesenchymal cells could be common bipotent precursors of MRCs and fibroblasts of the bursal connective tissue. The special cytological features of MRC raise the question of whether the cytology of MRC represents a developmentally primitive stage or whether the nuclear and cytoplasmic alterations are premature signs of degeneration, which may contribute to early bursal involution. Only some speculations can be made regarding these questions. The bursal mesenchyme develops from the tail bud, which forms the caudal end of the neural tube, sacral neural crest, and the caudal somites. During gastrulation, primitive streak cells create three basic germ layers, from which organ rudiments develop. However, the tail bud does not undergo gastrulation (no formation of the three germ layers). In the tail bud, organ rudiments or anlage develop directly without separation of the epi-, meso-, and endoderm. The unique cytological features and GER formation observed in MRC may be explained

by this developmental process. It is possible that the cytological structure of MRC is ontogenetically normal but evolutionarily represents a primitive or ancestral stage. If this interpretation is adopted for the "unique" cytological structure of MRC, it may be assumed that GER formation from blebbing of the nuclear envelope is phylogenetically normal and preserved in the MRC.

In MRCs, the inner structure of the mitochondria is indistinct. The association of "malformed" mitochondria with blebs is a common phenomenon, which can be either solely topographical or performs some kind of functional role. The inner mitochondrial structure of MRC is highly similar to that of "petite mutants" of yeast. The outer mitochondrial membrane of yeast is normal, while the inner membrane is poorly developed and does not form cristae. These yeast mutants do not possess functional mitochondria because mitochondrial protein synthesis is more or less defunct (Alberts et al., 1983). The morphological similarity between the mitochondria of yeast cells and MRC may be associated with protein synthesis deletion or other functional malformations in MRC, which require further biochemical analysis.

The MRCs not only create a 3D cellular network in the follicular cortex, but also form a continuous layer beneath the CMBL. During cell migration between the cortex and medulla, MRCs may participate in the temporary closing of the gap in CMBL. There is no histologically identified border line between the outer surface of the cortex and the ICT, unlike at the inner surface of the cortex. However, the common origin of MRCs and fibroblasts may be maintained in a common ME for the cortex and ICT (Figure 5b). This statement may be supported by the strict balance between the volume of the cortex and ICT. Bursal growth is a drawback of ICT, while in the case of IBIDEMV infection, the cortex shrinks and ICT spreads. These observations suggest that the two compartments (the cortex and ICT) may share a common ME.

Among cortical macrophages, the cell membranes may be fused to form multinucleated giant cells. This finding may be supported by megakaryocyte formation from monocytes in mammalian bone marrow, and the fusion of epithelioid cells of monocyte origin during infection of *Mycobacterium tuberculosis*, resulting in Langhans giant cell. These observations indicate that monocytes are capable of forming giant cells in normal as well as disease conditions. In the case of tuberculosis, the giant cell formation is a concomitant histological finding of a bacterial infection, whereas the multinucleated giant cell formation in macrophages of follicular cortex is normal, such as with regard to megakaryocytes. Surprisingly, these Mas contain bag-like GER similar to the MRCs. The presence of such a bag-like GER is uncommon in cells of hematopoietic stem cell origin. In the follicular cortex, the giant cell formation from macrophages of monocyte origin and "bag"-like GER may also be related to development from the tail bud.

In the middle of the incubation period (10 days of embryogenesis), some bursal mesenchymal cells with large vesicle-like nuclei showed bleb formation (Figure 6e). During the formation of the cortex, blebbing is present in both MRCs and fibroblasts of ICT, which suggests that MRCs and fibroblasts have common precursors (Figure 7). From this common precursor, it is possible that the third type of cortical stromal cell is a transitory form between vesicle-like cells and MRCs, and is actually a progenitor of MRC, while the fibroblast develops directly from the cell of the vesicle-like nucleus (Figure 6).

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AUTHOR CONTRIBUTIONS

Balázs Felföldi: Methodology (equal). **Zsófia Benyeda:** Methodology (equal). **Nándor Nagy:** Resources (equal). **Tamás Kovács:** Visualization (equal).

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