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The Role of the Mammary Gland in Ensuring Immune Homeostasis of the Fetus and Newborn

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Abstract: This review presents research on structural and functional features of mammary gland parenchymal and stromal components; importance of the mammary gland in the adoptive immunity transfer to a newborn, particularly immune humoral and cellular components transmitted from mother to baby.

Keywords: mammary gland, parenchyma, stroma, adoptive immunity, immunoglobulins, immunocompetent cells.

Apart from the epithelial part, the mammary gland contains connective tissue and immunocompetent cells participating in vital functions of the organ. It is known that cellular components, intercellular ground substance and fibers of the connective tissue play an important role in organs' growth, development and functionality [1, 2, 3, 4]. Physiological renewal of connective tissue and epithelial structures proceed constantly in mammary gland, depending on the period of its vital activity [14, 15]. The main part of gland in immature animals at the early stage of development is made of adipose tissue, and parenchyma begins to predominate over the stroma with the onset of pregnancy and lactation [6].

Parenchyma development is accompanied by the growth of its vascular bed. While in nulliparous females mammary gland vascular network is presented in the form of single plexuses around a few alveolar buds and terminal ducts, in pregnancy and lactation dynamics vessels take form of baskets densely entwining the alveoli [42]. Gland involution is accompanied by a gradual regression of its vascular network [10, 33].

With changes in hormonal levels during puberty the gland “awakens” in the female body, which along with the growth of the glandular tree also leads to the development of loose, unformed connective tissue, replacing regressive adipose tissue [12, 13].

According to I.I. Grachev et al. [3] the fatty tissue of the mammary gland is involved in the plastic provision of lactocytes not only in its morphogenesis, but also in intensive secretion [20]. It is assumed that there are molecular mechanisms of adipocyte influence on gland parenchyma development and regeneration [43].

Data on the dynamics of mammary gland connective tissue cells (fibroblasts, mast cells, eosinophils and lymphocytes) during pregnancy and lactation was unable to be found in analyzed literature, as well as about their influence on the lactocyte activity. There is only one study tracing dynamics of mast cells and eosinophils depending on gland functional state in mice [7]. It states that the number of mast cells increases at the beginning of pregnancy, then decreasing before childbirth increases again in the first 24 hours of lactation and persists during the subsequent period. At the same time, the number of eosinophils is increased throughout the entire period of pregnancy and they are mainly located in the interlobular connective tissue.

Some studies indirectly indicate the influence of fibroblasts and lymphocytes on gland morphogenesis [74, 75]. In a contrary to above, the role of neutrophils in gland secretory cycle has been described in some detail [35, 48]. It has been shown that neutrophil myeloperoxidase inhibits the activity of lactocytes, blocking the transport of amino acids into the cell and secretory product synthesis and removal from them.

An analysis of the literature led us to the conclusion that the mammary gland is cruical in maintaining immune homeostasis of a newborn [12, 13, 19–23, 40, 48–57, 71, 72, 76, 77, 78].

In accordance with the existing biological constancy of immunoglobulins transfer, for certain classes of immunoglobulins high placental permeability determines their low importance in trophic wastes for transmission with maternal milk in neonatal period. Desmochorionic placental structure in ruminants does not allow immunoglobulin transfer from mother to fetus, so the transfer of the latter occurs through colostrum and milk to the newborn [33, 34]. In mammals, however, (particularly in rats, mice, cats and dogs) passive immunity is created both by transplacental transfer of maternal antibodies and antibodies' intake with milk [40, 41]. In humans, however, IgG is transported across the placenta; passive immunity is based on intrauterine transfer of antibodies. However, immunoglobulins from colostrum and milk absorbed by the intestine are very important, since they participate in local intestine immunity creation, forming part of the unified mucosal immune system (EISSO), which includes the intestines, lungs, genital tract, milk and salivary glands [46, 62, 63, 67, 68, 69].

All classes of immunoglobulins are found in human colostrum and breast milk, including secretory immunoglobulin A (SIgA) that determine a specific immune response [56], as well as nonspecific immune defense factors: complement components, lactoferrin, lysozyme, chemotactic factor, factors that suppress the migration of macrophages and stimulate the synthesis of interferron [58]. Milk and colostrum also contain significant amounts of cellular components: macrophages, monocytes, T- and B-lymphocytes, plasma cells, polymorphonuclear leukocytes [58]. It should be noted that colostrum also stimulates the elimination of meconium, thereby promoting the colonization of the neonatal gastrointestinal tract by non-pathogenic bacteria [58,71].

The most important local immunity component is IgA. (SIgA) and IgM [4, 8, 9]. β2A-globulin serum predominates in milk and has unique characteristics due to the presence of a polypeptide called the secretory component, which was found by its isolation and further study [9]. It is known that the dimeric polypeptide SIgA predominating in secretions can be synthesized locally in the mucous membrane of organs by plasma cells (Pcl) in adult mammals [66]. Dimeric immunoglobulin A on epithelial cells' (ECL) membrane binds to the secretory component (SC) and is transported in vesicles through ECL into the intestinal lumen as SIgA [31]. Specialized SIgA molecules' presence in secretions explains the establishment of specific long-term immunological resistance of mucous membranes to infections, which also manifests in antibodies' absence in blood serum [69]. The mechanism of dimeric IgA transition produced locally by PCL into mammary gland secretion has not been precisely established. However, by intestine analogy, Bienenstock et al. suggest that IgA is transported across cells, namely through the basal and intercellular membranes in vesicles. Dimeric IgA has a high affinity for SC, which is synthesized by ECL and binds to basal and intercellular membranes, thereby acting as a receptor for dimeric IgA. Referring IgM it was found that rats have a weak affinity for SC, so a small amount of this immunoglobulin is transported during liver perfusion. However, there is a high affinity for SC in humans and the opposite picture is observed [27].

Colostrum and milk of mammals also contain antibodies of hematogenous origin, in addition to locally secreted Ig and these antibodies pass from blood serum into milk without any changes [37]. And surprisingly, their concentration in colostrum is much higher than in blood serum [41]. In particular, study on gammaglobulins' concentration in cow milk showed that it was 5 times higher than in blood serum [42, 46].

It has been established that mammary gland produces secretory immunoglobulin A, which is confirmed by the frequent secretory component detection in an unbound state in cow milk. It has also been proven that cow milk IgG is mainly of hematogenous origin and is almost entirely transferred into milk by blood, while IgA is secreted in mammary gland and colostrum IgM is partially transported from the serum and is also synthesized locally [67]. However, in ruminants IgG content prevails over the IgA content in milk, since IgA is more easily transported to the alveoli epithelium of mammary glands, where a large number of Fc receptors are found. The number of receptors for IgG is increased in the intestinal cells of calves accordingly, which together ensures the protection of newborns from intestinal infections [65].

Secretory immunoglobulin A is produced in the mammary gland; the secretory component is often found in an unbound cow milk. If IgG in cows is almost entirely transferred into milk from the blood, and IgA is produced locally, then IgM in colostrum consists of a mixture of molecules, some of which are transported from the serum, and others are synthesized locally [53].

In many mammalian species (in rats, mice and rabbits and also in humans) the main immunoglobulin in colostrum is IgA although only traces of it are detected in the blood of pregnant females. The experiment established that Pcl are rare in nulliparous mice, but their number increases significantly during pregnancy. On the first day after birth during the colostrum period of lactation a moderate increase in the number of IgM and IgG-producing cells was shown in female mice, which was accompanied by a 150-fold increase in the number of IgA-secreting cells, and a 6-fold increase in the weight of the mammary gland, whereas cessation or artificial lactation interruption helps to reduce the number of IgA-producing cells and atrophy epithelial tissue of the glands. Hormonal regulation of this process is assumed, and pituitary prolactin plays an important role in it [67].

Significant quantities of SIgA are detected in colostrum, milk and all external in women's exocretes. Typically, its content increases before childbirth. During the colostrum period of lactation its concentration reaches 20-40 mcg/ml, in contrast to only 1 mcg/ml in milk. It has been proven that during the first week of lactation colostrum IgA is of hematogenous origin, while from the 2nd week it is secreted mainly in the gland itself [42]. With further lactation the amount of milk secreted by gland increases, so the decrease in IgA concentration is compensated by the amount of milk consumed by a newborn. Therefore, with normal breastfeeding, the child receives almost the same amount of SIgA. SIgA provided with the milk of nursing mothers is able to bind receptors of oral mucosa cells of newborns [46]. SIgA receptors' distribution density in the saliva of premature infants is lower than that of full-term infants, which may be one of the reasons for the insufficiency of natural immunity. IgG consists of serum-derived IgG1 and IgG2 produced locally by the mammary gland. IgD immunoglobulins are also detected in colostrum having an immunoprotective effect when entering the newborn’s body.

During the study of antibodies' presence in colostrum and milk from of various mammals, it was found that the content of antibodies depends on the evolution of placental permeability. If there is no direct transfer of IgG antibodies from the mother’s blood to the fetal blood through the placenta, it is compensated by their increased content in mammary gland secretions. Therefore, in primates and humans, where maternal IgG antibodies are transmitted transplacentally to the offspring, SIgA has local bactericidal activity and becomes the main immunological component of colostrum and milk. But it should be noted that the content of antibodies in colostrum and milk is subject to large changes in different representatives of mammals.

Much less attention has been paid to the cellular components of milk in studies of maternal-neonatal immune transmission during lactation. Lymphocytes and macrophages are constant components of colostrum and milk in many animal species, including humans [47].

It has been established that the number of leukocytes in cow milk is subject to large individual fluctuations [48]. Their number directly depends on the stage of lactation and time of day, it

ranges from 0.5 to 1 million cells in 1 ml of milk on average. Among the cellular components, epithelial cells, macrophages and lymphocytes dominate the number of eosinophils, which is insignificant [10].

In rat milk the number of leukocytes ranges from 2 to 15 million/ml, of which 75% are macrophages, 23% are small and large lymphocytes and 2% are neutrophils [18, 19]. Studies using a radioactive label introduction have shown the migration of maternal milk lymphocytes from the intestine into Peyer's patches and lymph nodes of rat pups and their ensuring bacterial resistance of the newborn [18, 19]. However, there is also an opposite data indicating the functional inferiority of lymphocytes supplied with mother's milk [21].

Leukocytes in maternal colostrum are represented mainly by macrophages, monocytes and lymphocytes and their number is 1.5–4 million/ml. In milk, however, macrophages' percentage decreases somewhat and both T- and B-lymphocytes are detected among lymphocytes [30]. Milk macrophages retain the ability for amoeboid movements and phagocytosis and take part in the synthesis of lysozyme, lactoferrin, complement and other bactericidal products. Monocytes fully possess Ia antigens and serve as antigen-presenting cells [31]. Female colostrum leukocytes are capable of producing lymphokines, MIF, as well as a mediator that stimulates B lymphocyte differentiation of into IgA-secreting cells. The T cell population of human colostrum consists of helper and cytotoxin suppressor cell phenotypes [36]. Colostral lymphocytes have individual sensitivity in specific agents' presence, indicating their ability to express T-cell immune reactivity [1]. It has been proven that among rats and mice the newborn acquires immunity to skin allografts and graft versus host [4, 10]. There are isolated reports of the T-helper functions transfer from mother to child through colostrum and milk, but they are not sufficiently evidenced [49].

Thus, there are sufficient works devoted on immunological properties of colostrum and milk. At the same time, structural mechanisms determining the immunobiological significance of milk in its synthesis and secretion process in the gland itself remain practically unclear.

It is known that lymphocytes cover a small but important cellular component of the lactating mammary gland in rodents and contribute to antibodies' formation in their exocretes. The number of lymphocytes and their subpopulations varies depending on the animal species and lactation stages [30]. Besides lymphocytes producing cytoplasmic immunoglobulin A predominate [31]. It has been experimentally shown that "gut-associated lymphoid tissue" (AGLT) contains a significant number of SIgA+ cell precursors for mice mammary glands. These precursors can migrate as circulating lymphoblasts and have affinities for different tissues.

In contrast, other authors deny the possibility that a large number of donor SIgA+ progenitors from mesenteric lymph nodes (MLNs) can accumulate in rat mammary gland, although these cells migrate to the small intestine of the recipient. Similar results were obtained by other authors in rats and mice [55]. They show that the mammary gland contains a significant number of its own SIgA+ cells with the adoptive administration of SIgA+. Lymphoblasts do not accumulate in breast tissue. SIgA+ B cells accumulate naturally in the mammary gland only a few days after the migration of T lymphocytes into the gland (T-inducers predominanting). It has been suggested that distinctive feature of the small intestine and the mammary gland in rats are inductive microenvironment and the mammary gland predisposition to T-dependent clonal expansion of B cells preceding their final differentiation into breast cells [57]. Identical data were obtained using the method of labeled T lymphoblast adoptive administration [41, 42].

With the help of labeled cells, it was revealed that B and T lymphoblasts from MDR and lymphoblasts from peripheral lymph nodes quite intensively enter the mammary gland throughout lactation [39]. In the gland B-lymphoblasts are mainly localized in connective tissue as precursors of PCL, but they can migrate to the secretory epithelium and then enter milk. It has been shown that about 16% of all mammary gland T-lymphocytes are located in the connective tissue and only 24% of them are concentrated intraepithelially. The relative T-lymphocytes

predominance in the connective tissue presumably indicates their role in antibody synthesis induction or local protection of the gland, and low T-lymphocyte content within the alveolar epithelium is apparently due to fairly rapid intraepithelial transition of these cells. To date, there is a large number of studies devoted to mammary gland ultrastructure [3, 6, 27]. The analysis showed that they studied in details submicroscopic organization of secretory and myoepithelial cells [19, 20, 29, 36, 38]. However, ultrastructural identification of stromal and intraepithelial "light" cells remains problematic [40]. There are the most conflicting opinions on this issue [40, 55]. For example, in an ultrastructural study on rat lactating mammary glands intraepithelial "light" cells are perceived as large lymphocytes [60]. Other authors indicate that besides the "light" cells there are positive dendritic cells, which are different from Ia macrophages and similar to Langerhans cells [7]. According to the authors these cells have a large pale cytoplasm containing many mitochondria with well-developed cristae, short RER profiles and membrane-coated lipid particles [26]. They are also characterized by the presence of long microtubules and many microfilaments. Outgrowths of the cytoplasmic membrane with bulbous ends are discovered along the periphery of the cells.

It is known that dendritic Langerhans cells form an important component of immune defense [26]. They are mainly found in lymphoid organs, but also have a generalized distribution in almost all organs in the connective tissue [12]. Some authors believe that these cells are constantly present during lactation and perform the most important function in antigen presentation [12].

According to existing literature morphofunctional characteristics issues of mammary gland terminal secretory sections and their changes in its life have been well covered by now. Specific features of gland development and functioning during pregnancy and lactation and various phases of mammary gland secretory cycle in mammals are also covered quite well. There are reports indicating the role of the mammary glands in maintaining newborn immune homeostasis in postnatal ontogenesis.

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