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Anatomy of lymph nodes deep cortex in laboratory spices

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Abstract. The lymph nodes are organized lymphoid organs in which lymphocytes are located inside reticular stroma. The lymphoid parenchyma of lymph nodes is divided into separated cell zones, the most developed one is parenchyma in which the deep cortex located. The lymph nodes of small mammals, which are often used for laboratory research, The investigated lymph nodes in this research were Somatic (superficial cervical and axillary) and visceral (hepatic and mediastinal) lymph nodes were selected from mice (n = 5), guinea pigs (n = 5), hamsters (n = 3) and rabbits (n = 5). We used classical histological methods (determination of general histological structure of organs), morphometric (determination of the relative area of individual structural and functional zones), immunohistochemical (determination of location of individual cell populations). It was shown that the deep cortex of the parenchyma of the lymph nodes composed by separate structures «deep cortex units», and some of them are combined into complexes. Each unit is represented by a semicircular structure formed by lymphocytes and reticular fibers. The size of units is approximately the same in all studied animals and does not depend on the size of their bodies. The most developed units of the deep cortex were found in the superficial cervical ganglion, and the largest – in rabbits, where their size reached 3 mm. In all studied animals, units of the deep cortex are located at the same level, along the subcapsular sinus. The most developed component tissue of the studied lymph nodes is the lymphoid parenchyma, in laboratory mice it occupies a significantly larger area than in other animal species. The least developed were the central sections of units in the deep coating crust.

Keywords: lymph nodes; lymphoid parenchyma; structural and functional zones; cell zones; laboratory mice; rabbit; Guinea pigs; hamster.

Анатомія глибокої кори лімфатичних вузлів у лабораторних тварин

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Анотація. Лімфатичні вузли – це компактні лімфоїдні органи, які побудовані з лімфоцитів і тонкої ретикулярної строми. Лімфоїдна паренхіма лімфатичних вузлів розділена на окремі клітинні зони, найбільш розвиненими з яких, являються одиниці глибокої кори. У роботі досліджені лімфатичні вузли дрібних ссавців, яких часто використовують для лабораторних досліджень. Соматичні (поверхневий шийний і пахвовий) і вісцеральні (печінковий та середостінний) лімфатичні вузли відібрані від мишей (n = 5), мурчаків (n = 5), хом'яків (n = 3) і кроликів (n = 5). Використовували класичні гістологічні методи (загальна гістологічна будова органів), морфометричні (визначення відносної площі окремих структурно-функціональних зон), імуногістохімічні (розташування окремих клітинних популяцій). Показано, що глибока кора паренхіми лимфатичеких вузлів складається з окремих структур «одиниць глибокої кори», деякі з яких об'єднані в комплекси. Кожна одиниця це округла структура, утворена лімфоцитами і ретикулярними волокнами. Розмір одиниць приблизно однаковий у всіх досліджених тварин і не залежить від розмірів їх тіла. Найбільш розвиненими одиниці глибокої кори виявлені в поверхневому шийному вузлі, а найбільші – у кроликів, де їх розмір досягав 3 мм. У всіх досліджуваних тварин одиниці глибокої кори розташовані на одному рівні, уздовж підкапсулярного синуса. Найбільш розвиненим тканинним компонентом досліджених лімфатичних вузлів є лімфоїдна паренхіма, у лабораторних мишей вона займає значно більшу площу ніж у інших видів тварин. Найменш розвиненими були центральні ділянки одиниць глибокої кори.

Ключові слова: лімфатичні вузли; лімфоїдна паренхіма; структурно-функціональні зони; клітинні зони; лабораторні миші; кролики; мурчаки; хомяки.

Introduction

Lymph nodes – organs of secondary lymphatic system, helps to protect and maintain the fluid environment of the body by producing and filtering their fluid tissue (lymph), with the help of their antigen recipient sites, -dependent proliferation of T- and B-lymphocytes and antibody synthesis. Lymph nodes consist of stromal and parenchymal components. The parenchyma, in turn, is represented by functional units separated structurally – compartments or lymphatic lobules (Willard-Mack, 2006; Sainte-Marie, 2010). Each lobule (compartment) has an irregular oval shape, its expanded summit is directed to the marginal (subcapsular) sinus, and the narrowed par of it is directly related to the cranial cords and directed to the portal sinus (Willard-Mack, 2006). The basis of each lymphoid lobule (compartment) is a unit of the deep cortex – the site of clonal T-lymphocytes proliferation. They are surrounded by an interfollicular zone on the summit and each side, are the basis of which lymph nodes are formed – proliferation zones of B-lymphocytes. The very important unit of the deep cortex consists of the main part - the center of the unit (the site of localization and proliferation of T-lymphocytes) and the periphery which called also «transit zone», containing veins with endothelium to provide the processes of lymphocyte migration into the parenchyma (Ruddle, 2016; Ager, 2017). In quantitative terms, the proliferation zones of of T-lymphocytes in the lymphatic lobules are the most developed, reaching 25–40 % of the total volume of the lymph node parenchyma (Gavrilin et al., 2017). It is also known that it extends from the moment of lymph nodes ontogenesis till the end of prenatal period in cattle, in which the most developed zones are the interfollicular zone, paracortical and cranial cords. And among the clonal proliferation zones, T-lymphocytes dependent zones prevail, the relative volume of which is 5–7.5 times higher than the volume of B-dependent zones (Gavrilin et al., 2018). Throughout the post natal period, the structure and especially the cytoarchitectonics of units of the deep cortex are very labile, due to the active processes of lymphocytes recirculation (through the wall of veins with high endothelium) and antigen-presenting cells (Kim et al., 2012; Platt & Randolph, 2013; Butler et al., 2016).

The histology of the deep cortex of the mouse lymph node has recently been clarified by a three-dimensional study (Zhu et al., 2019). Recent discoveries on the deep cortex as well as previous data on the peripheral cortex of the organ (Brown et al., 2018). The recent study found that the deep cortex of a rat node consists of one or more basic elements, called «units» of the deep cortex, some of which are variably merged into «complexes» deep cortex (Kim et al., 2016; Gavrilin & Gibert, 2016). A unit is a semi-rounded structure, contiguous to the peripheral cortex and swollen in the cord. Each unit is centered on the opening of an afferent lymphatic vessel, and the topography of the deep cortex of a node is correlated with the pattern of the opening distribution of its afferent lymphatics. In addition, each unit can be distinguished into a center and a periphery, each carrying distinct morpholoical characteristics and having somewhat different functions. herefore, the purpose of this article is to determine the structural features of the units of the deep cortex parenchyma of the lymph nodes in various species of small mammals, usually used for laboratory researches.

Material and methods

Our research was based on somatic lymph nodes: superficial cervical and axillary and visceral: mediastinal and hepatic, selected from five Swiss mice aged 10 weeks, five guinea pigs aged 8 weeks, three hamsters aged 8 weeks and finally five rabbits aged 5 months, the sum of studied animals «from which we sampled organs» is eighteen (n = 18), the total sum of sampled lymph nodes is ninety (90), which have been dissected in a segmental plane, perpendicular to their hilum's. The selected samples were fixed in a 10 % solution of neutral buffered formalin.

A part of the fixed fragments of sampled lymph nodes was embedded in paraffin in order to make thin sections (3–5 microns), for further hematoxylin and eosin staining The remaining fragments were used to make sections using a microtome cryostat.

To obtain sections with the microtome cryostat, the frozen sections were impregnated with silver nitrate and potassium permanganate in an acetic acid medium, temperature 45 degrees Celsius for a duration of 20 minutes of time according to (Gibbings & Jakubzick, 2018).

The histological sections stained with hematoxylin & eosin were examined, the morphometry and the microphotography was made with an optical microscope Bresser LCD 8.9 cm (3.5), 50-500×, 2000 (digital), this allowed us to visualize the different areas of the parenchyma as well as the sinuses, follicles and stroma of the lymph nodes. Other histological sections of frozen tissues of rabbit lymph nodes underwent staining with the intervention of proteins expressed prominently on silicone, stained for fibronectin and laminin-1, soaked in a china anchor solution for 24 hours at 1:100 ppm. In the histological sections impregnated with silver nitrate, the percentage of the relative area of the lymphatic sinuses of the stroma (capsule, trabeculae) and of the lymphoid parenchyma was determined. The total relative area of the parenchyma areas, namely the area of the cortical or inter-follicular plateau and the paracortical cords, the units of the deep cortex and the follicles including the presence of B-lymphocytes and medullar cords, including the accumulation of plasma cells was calculated by the state of the art precision calculation method of statistic R.

Results

From the results obtained from our research, we deduced that the lymphatic system in the laboratory animals that we used, that there is a relationship between the lymphatic vessel and the lymph node, we noted that the system superficial lymphatic could be divided into lymphatic territories.

The center of the deep cortex units and the follicles of the peripheral cortex, both of which contained little fiber, appeared dark because most of their densely packed nuclei were blackened. On the other hand, the periphery of the units, the extra-follicular area of the peripheral cortex and the medullar cords were of a lighter shade. In the latter structures, the presence of abundant reticular fibers inhibited the darkening of almost all the nuclei, thereby producing their lighter shade.

Impregnation with silver nitrate has therefore proved to be more effective than standard staining techniques in order to allow us to define more clearly the units, in particular the units constituting a complex. In addition, each unit includes a center and a periphery, the density of the small lymphocyte population being higher in the former than in the latter (Fig. 1).

The lymphocyte population in the center of a unit was sometimes unevenly distributed, producing a mottled appearance. The periphery of the units also contained a network of reticular fibers and a high concentration of post-capillary venules. Finally, the lymphatic sinuses were detected at the periphery of the units.

In each of the species studied, the units of the deep cortex were generally larger in the cervical nodes than in those from other anatomical locations. However, this difference in size was less marked than that observed in white mice. The largest units, observed in rabbits, reached almost 3 mm in thickness.

Surprisingly, in larger species, such as rabbits and guinea pigs, the units were smaller, rarely exceeding 1 micron in thickness. Compared to the size of a node, these units were relatively so small that they were not easily detected at first sight (Fig. 2).

In fact, in rabbits, unlike the other species studied, the units were not much larger than the follicles in the overlying peripheral cortex, which made the units even less obvious, the deep cortex occupied

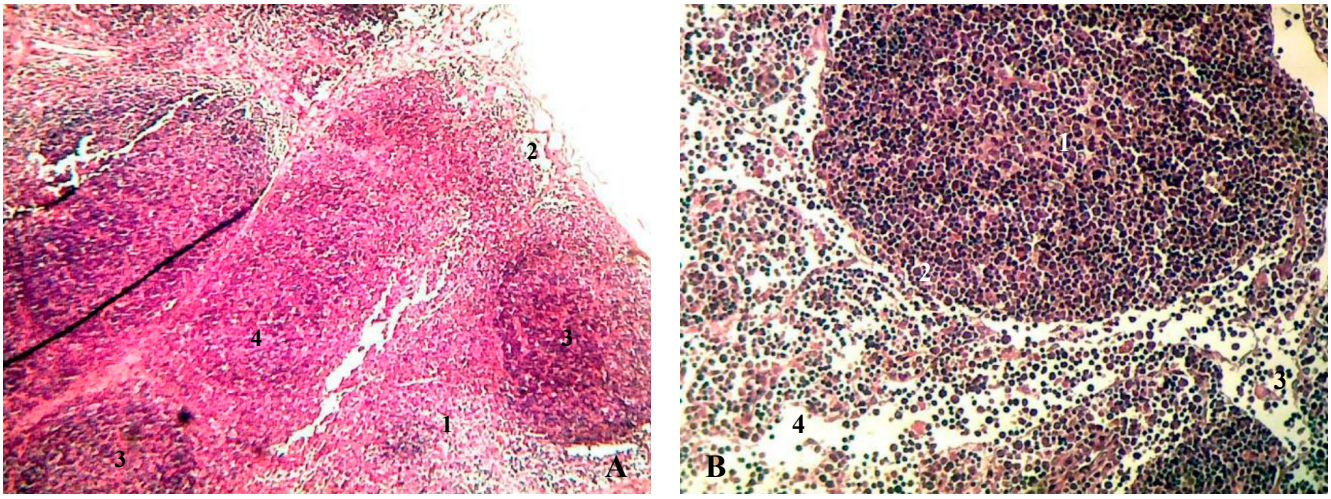

Fig. 1. Histological section of the axillary lymph node of the rabbit. Hematoxylin & eosin, A – × 40: 1 – paracortical zone, 2 – cortical sinus, 3 - follicles, 4 – deep cortex units; B – × 100: 1 – follicular center, 2 – mantle, 3 – inter follicular sinus, 4 – medulla.

a volume much less important more knots in smaller species like white mice and hamsters. In the largest species, most of the volume of a node was therefore made up of the medulla, in particular of the medullar sinuses (Fig. 2).

From a quantitative point of view, whatever the type of structure of the intra-nodal lymphatic channel, the most developed tissue component of the lymph nodes of animals of all species is the lymphoid parenchyma, the relative surface of which in the somatic nodes reaches 48 to 52 % and in the visceral nodes 35 to 39 %. It has also been clarified that in the lymph node of white mice, the relative surface of the parenchyma is higher than in the other lymph nodes of the other animals studied. Also, the relative area of the stroma including the capsule and trabeculae in the examined lymph nodes does not exceed 14 % in the somatic lymph nodes and 21 % in the visceral lymph nodes; the components of the stroma are better developed in the visceral lymph nodes of the Rabbit.

For the description of the statistical data, it was found that the maximum area occupied by the capsule is found in the hepatic visceral lymph node of 12.01 ± 0.97 %, while it is minimal in the axillary somatic lymph node, equal to 5,56 ± 0.31 %, for the trabeculae, it is almost the same results for the two types of lymph node, and somatic and visceral, it does not exceed 9.48 ± 0.77 %. On the other hand, the para cortical zone is maximum in the axillary somatic lymph nodes and of 17.56 ± 0.46 %, this percentage is minimum in the hepatic visceral lymph node, of 09.13 ± 0.52 %. Concerning the active follicles, the surface they occupy reaches 2.45 ± 0.41 % and 2.41 ± 0.17 % in the axillary and mediastinal lymph nodes simultaneously, while there is a slight increase in this rate for the inactive follicles, it reaches a sum of 3.57 ± 0.01 % in the hepatic visceral lymph node (Fig. 3).

The amount of medullar substance was found with a rate of 39.77 ± 0.73 % in the cervical somatic lymph node, which is

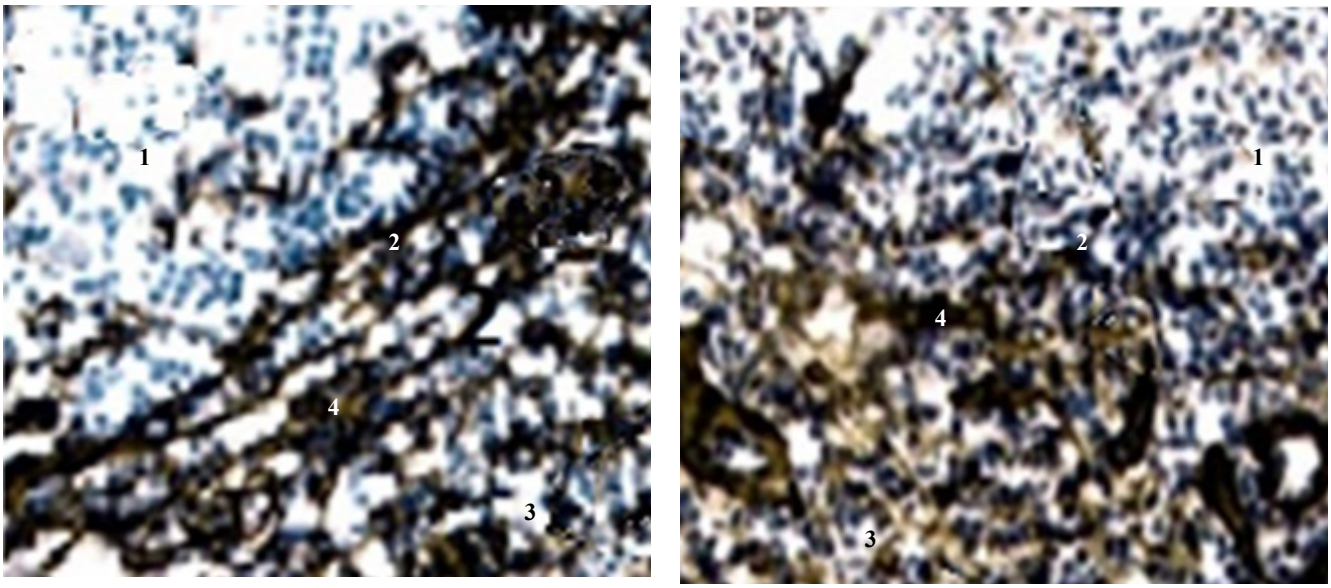

Fig. 2. Histological section of the hepatic lymph node of the hamster: 1 – follicle, 2 – mantle, 3 – para-cortical zone, 4 – peri-follicular zone. Silver nitrate staining, × 100.

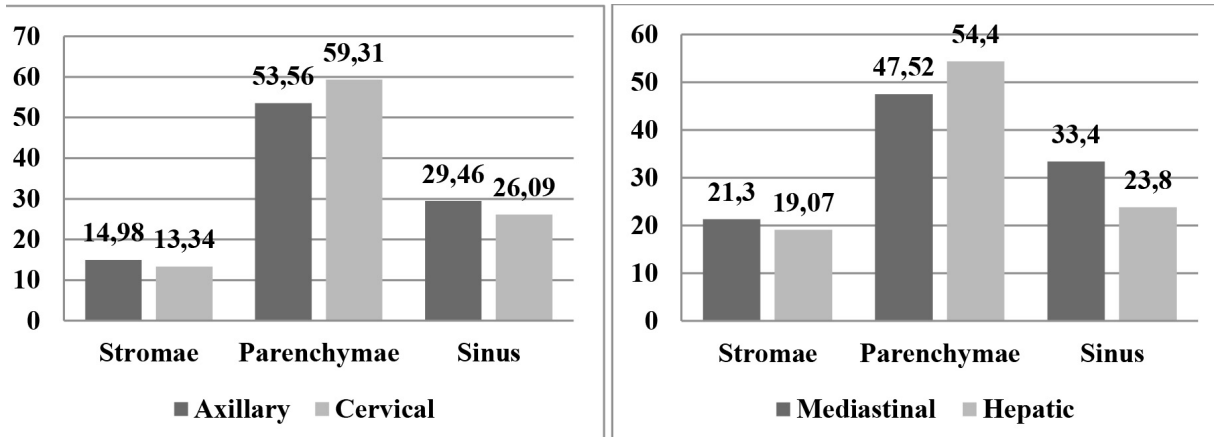

Fig. 3. The ratio of tissue components and sinuses of some somatic and visceral lymph nodes of laboratory animals (M ± m), n = 5, %.

maximum, while it is minimum in the 33.41 ± 0.76 % in the mediastinal lymph node. The value of the quantity of the sub capsular sinuses was almost identical, of 9.09 ± 1.22 % for the axillary somatic lymph node and of 7.04 ± 0.75 % for the cervical somatic lymph node, as regards the lymph nodes visceral lymphatic values are 8.81 ± 0.88 %, 6.29 ± 0.67 %, for the mediastinal and hepatic lymph nodes simultaneously. Data found for the inter follicular sinuses, sums of 1.05 ± 0.54 % for the axillary lymph node, 7.22 ± 0.91 % for the cervical lymph node, a sum of 11.53 ± 1.03 % for the mediastinal lymph node and finally a small found sum of 5.07 ± 0.84 % in the hepatic lymph node. Elucidated medullar sinuses; occupy variable percentages, it is maximum in the mediastinal lymph node, of 13.06 ± 0.91 %, minimum of 9.32 ± 0.83 % in the axillary lymph node. For the other cervical and hepatic lymph nodes, these sums are 11.83 ± 0.77 % and 12.44 ± 0.74 % simultaneously (Table).

For all the animals, it was noticed that the capsule presented a pronounced hilar thickening, as well as the capsular trabeculae, less developed which penetrate into the parenchyma of the nodes, where they form a series of branches. The trabeculae of the hilum region are slightly thick and are located mainly among the medullar cord. In the hamster lymph nodes on a segmented section of the lymph node subunit, the intra-nodal lymphatic canal has a larger relative area than in the corresponding organs of other animals.

It was noted that the sub capsular sinus was without obvious limits, extends in the hilar sinus, covering the parenchyma of the lymph nodes, whose presence of the afferent lymphatic vessels open directly in the marginal sinus, from where the peri-trabecular sinuses and the cortical intermediate sinuses, which continue into the medullar sinuses, which are the sources of efferent lymphatic vessels.

In all lymph nodes of the animal species we studied, showed the superficial cortex was concentrated along the lymphatic collectors exclusively. The main structural component of the arch is the inter-follicular area or cortical plateau located under the marginal sinus, where there are many high endothelium venules through which lymphocytes migrate through the wall of the nodes.

For the anchor staining technique, the fibronectin and laminin-1 factors fixing on the structure of the lymphatic vessels are visualized with the HEV, thus the appearance of follicles swimming in three dimensional structures, thus the inter follicular sinuses and cortical trabeculae are very clear in the results (Fig. 4).

We also visualized the deep cortex in the lymph nodes of the guinea pig which is located under the cortical plateau and has a clear structure in the form of spherical units of the deep cortex, which are separated from each other by intermediate sinuses peri- trabecular and cortical. The deep cortex units form the basis of the structural and functional units of the lymph node parenchyma. In the rabbit's lymph nodes, the lymph nodes are found along the marginal sinus in the inter-follicular area, as well as in the para-cortical cords at the periphery of the deep cortex units. As a result, the medullar substance in the lymph nodes in all animals is relatively high. It is also located in the form of rings in the deep sections of the parenchyma. The medullar cords in the rabbit's lymph nodes are thickened and very developed; the hilar thickening of the capsule is well expressed. Sections of the medullar cord amalgamated with each other, forming common fields which are the sources of efferent lymphatic vessels. In all of the lymph nodes studied, the units of the deep cortex are represented by single-level clusters.

A quantitative morphometric analysis of the dynamics of the relative volume of the structural components in the parenchyma of the lymph nodes with a different type of structure from inter follicular lymphatic canal revealed that in the nodes of all species of animals, the central areas of the units of the deep cortex are the least developed. The medullar cords in the hamster's lymph nodes are developed. Unlike the central areas of the deep cortex units,

Table. The ratio of tissue components and sinuses of some somatic and visceral lymph nodes of the laboratory animals, % (M ± m, n = 5)

Lymph nodes	Stromae		Parenchym				Sinus		
	capsulae	trabeculae	para-cortical	actif follicles	inactif follicles	medular	sub capsular	inter follicular	medular
Axillary	5.56 ± 0.31	9.42 ± 0.78	13.62 ± 0.37	2.45 ± 0.41	1.07 ± 0.01	36.42 ± 0.62	9.09 ± 1.22	11.05 ± 0.54	9.32 ± 0.83
Cervical	6.13 ± 0.72	7.21 ± 0.91	17.56 ± 0.46	1.56 ± 0.09	0.42 ± 0.01	39.77 ± 0.73	7.04 ± 0.75	7.22 ± 0.91	11.83 ± 0.77
Mediastinal	11.82 ± 0.43	9.48 ± 0.77	09.18 ± 0.63	2.41 ± 0.17	2.52 ± 0.01	33.41 ± 0.76	8.81 ± 0.88	11.53 ± 1.03	13.06 ± 0.91
Hepatic	12.01 ± 0.97	7.06 ± 0.67	09.13 ± 0.52	2.83 ± 0.11	3.57 ± 0.01	38.87 ± 0.59	6.29 ± 0.67	5.07 ± 0.84	12.44 ± 0.74

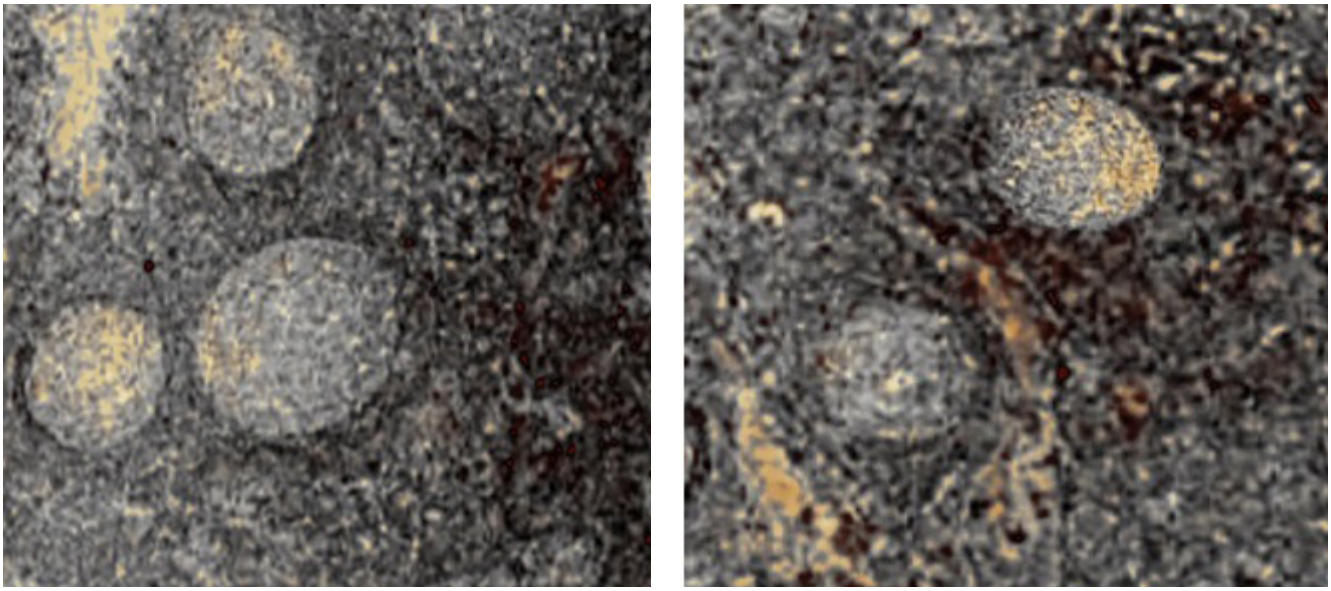

Fig. 4. Shows follicles impregnated swimming in three dimensional structures. Histological section of the mediastinal lymph node of the rabbit. Stained with fibronectin and laminin, and soaked in a china anchor solution, × 40.

the medullar cords are less developed in the rabbit's lymph nodes and their combined relative volume, greater than the corresponding indicator.

Discussion

The present study revealed that the lymph nodes of the animals we studied consist of the main parenchyma structures of the universal system of cracks or peri-trabecular lymphatic sinuses, intermediate and medullar cortex, in a similar way to that of the rat, the deep cortex of mouse and hamster nodes, which are the species currently used in experimental immunology, is made up of units often fused into complexes. This conclusion also applies to the deep cortex of the knots of the guinea pig and the rabbit which are used for experimentation on the process of recirculation of lymphocytes (Le et al., 2016). A similar pattern of variations in the concentration of lymphocytes also the presence of particular sinuses at the periphery of the units. The relationship between the units of the deep cortex and the afferent lymphatic system has not been verified here because it would have required considerable additional three-dimensional reconstruction (Li et al., 2018). However, since all the other morphological characteristics of the units are comparable to those of the rat, it is likely that each unit is also linked to the openings of an afferent lymphatic as in mice, these researches were identified by the authors (Senthilkumar et al., 2019). The absolute size of the units was roughly comparable across the different species, not varying in proportion to the size of the animal nodes. The reason may be that there is an optimal size for a unit, which roughly corresponds to that observed in smaller species such as rats and mice. Larger units could be unfavorable to the organism since the migration of lymphocytes takes place through the thickness of the units, this has been studied by researchers (Belotta et al., 2019).

Examination of the architecture of the rabbit lymph node parenchyma shows the nodal cortex resembles a curved arch towards the hilum of the afferent lymphatic vessels, which is characterized by a uniform layered structure. The outer layer of the cortex of hamster nodes is represented by a single cortical plateau, and the inner layer is represented by a sphere-shaped unit of the deep cortex. In the guinea pig lymph nodes, the cortex is in the form of a characteristic pronounced mat, the latter appearing as a flattened ring on the sides of which is the capsular trabecula, hence the formation of units of the deep cortex of specific structure, researchers have established the same results (Senthilkumar, et al., 2019).

The lymphoid parenchyma as a whole is more developed in the lymph nodes of the animals which were the subject of our studies, contained specialized cellular zones of the parenchyma, the most developed are the zones of proliferation of T lymphocytes in the central zones of the units of the deep cortex, the medullar zones rich in plasma cells, and finally the para-cortical cords which are rich in B lymphocytes, compare with data from (Carvalho et al., 2018) who found the same data.

Conclusion

The absolute size of the units was roughly comparable in the different species, not varying in a proportional way to the size of the animals or the nodes as mentioned below, leads to the hypothesis that what makes this difference is cell composition and speed of immune process. Thus, the nature of the structure and location of the main cumulative distribution link (lymphatic collector) in the mammalian lymph nodes significantly affects both the structure of the intra lymph channel -nodal and histoarchitectonic of the lymphoid parenchyma as a whole, determining their species specificity. The general principles of localization of the main specialized areas, while in the parenchyma of nodes of different types are universal. The areas of clonal proliferation of T and B lymphocytes are formed in the immediate vicinity of the lymphatic collectors, and the areas of plasma accumulation and antibody synthesis at the opposite pole at the level of the hila's of the lymph nodes.

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