Diagnostics and Therapeutics
https://ojs.luminescience.cn/DT

LUMINESCIENCE
https://luminescience.cn

Mini Review

The lymphatic vasculature associated with the peripheral nervous system: structures and functions

Senrui Li[1], Nan Zhou[*1]

[1] Department of Orthopedics, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450000, Henan Province, China.

*Correspondence: fcczhoun@zzu.edu.cn

Abstract: The lymphatic vasculature is widely considered to be a unidirectional transport system, which can collect excess fluid and metabolic waste in the interstitial space, and mediate immune cell transport, the absorption of certain special substances (such as lipids) and other functions. In clinical and basic research, the lymphatic vasculature appears to have generally received less attention than the blood vascular system. However, recent research on lymphatic vessels has greatly enriched our knowledge and directed our attention to the lymphatic vasculature. Furthermore, lymphatic vessels are not only widely distributed, but also have important functions in the cardiovascular, reproductive, respiratory, digestive, and central nervous systems (CNS), and their dysfunction may be the basis for the pathogenesis of various diseases. In the CNS, the existence and role of lymphatic vessels have been well confirmed and revealed. Although from a traditional point of view, the peripheral nervous system (PNS) is different from the CNS, there have something in common in some structures. We reviewed recent research on lymphatic vessels in the PNS, aiming to confirm the existence and to understand the structures and functions in the physiological and pathological processes of peripheral nerves. This review is intended to help open up a new field of research prospectively.

Keywords: Lymphatic vasculature, Peripheral nervous system, Central nervous system, Lymphatic endothelial cell, Structures and functions

Introduction

While the importance of blood vessels for the nervous system is well known, the lymphatic system is often overlooked. However, with the deepening of research, lymphatic vessels have been found around the nervous system [1]. In fact, it may be associated with a variety of disorders including Alzheimer's disease [2], Parkinson's disease [3], stroke [4], brain/nerve injury [5], and autoimmune neurological disease [6]. Especially in the PNS, there is still much unknown about lymphatic vessels, but their importance is to be assumed. The lymphatic system includes initial lymphatic vessels and collecting lymphatics. The initial lymphatic vessels are mainly distributed at the terminal end of the lymphatic system, also known as capillaries, which are composed of a single layer of lymphatic endothelial cells and have high permeability. This structure is conducive to the passage of excess fluid, metabolic waste, macromolecular substances, immune cells, etc. [7]. The initial lymphatic vessels would gradually converge into secondary collecting lymphatic vessels, and then gradually converge into collecting lymphatic vessels and return to thoracic and right lymphatic ducts until the fluid in the lymphatic vessels flows back into the blood

Received: Mar.22, 2022; Revised: Apr.25, 2022; Accepted: May10, 2022; Published: May13, 2022

DOI: https://doi.org/10.55976/dt.120221606-12

circulation [8]. The collecting lymphatic vessels are covered with a layer of functionally specialized muscle cells (SMCs) that help backflow by constricting, and valves in collecting lymphatic vessels regulate the unidirectional flow of lymph [7, 9]. The contraction of skeletal muscles around the lymphatic vessels is also one of the driving forces for lymphatic propulsion [10]. Lymph nodes are also important structures of the lymphatic system and have a great significance in the study of various inflammatory diseases and tumors [11]. In lymph nodes rapid recruitment of immune cells and activation of immune responses occur. The lymphatic system has multiple functions in the nervous system, including draining cerebrospinal fluid (CSF), collecting waste, providing immune surveillance, and mediating immune responses [1, 8]. However, there are still many mysteries about their distribution, structure in the nervous system, and how they specifically participate in physiological and pathological processes, especially in the PNS. This review aims to reveal the new research field of lymphatic vessels associated with peripheral nerve by exploring the research progress of nerve-related lymphatic vessels in recent years, and to provide ideas for future research.

The lymphatic vasculature system associated with the CNS and autonomic nerve

The glymphatic system of the CNS was first proposed by Iliff in 2012 [12]. The glymphatic system describes a structure powered by arterial pulsations to propel the inflow of surrounding cerebrospinal fluid in the same direction [13]. During this process, CSF mixes with interstitial fluid which is facilitated by the water-channel aquaporin-4 (AQP4) located at the end feet of astrocytes [14]. In addition, fluid entering through the blood-brain barrier can also power the glymphatic system [15, 16]. Eventually, CSF and interstitial fluid pass through the venous system and leave the CNS [17, 18]. The presence of meningeal lymphatics, also considered as the main route of CSF outflow, was first described in 2015 by Louveau A et al. and Aspelund et al. [19, 20]. This study provides a description of a route for meningeal lymphatic drainage to deep cervical lymph nodes (dCLNs). A follow-up study [21] reconfirmed the importance of this passage: In an animal model of experimental allergic encephalomyelitis (EAE), no significant changes were observed in meningeal lymphatic vessels during inflammation. However, when the drainage of meningeal lymphatic vessels to the dCLN was ligated, the pathological changes of EAE were alleviated and disease progression was delayed. This finding demonstrates the importance of the lymphatic system in neuroimmune surveillance and response. Besides, with the deepening of the understanding of meningeal lymphatic vessel function, a series of central neurological disorders, such as Alzheimer's disease, are speculated to be closely related to lymphatic drainage [2]. CNS injury is very common in the clinic, and the vascular damage and epilepsy caused by injury may lead to secondary injury cascades and neurodegeneration [22, 23]. Lymphatic vessels also function in a concussion model, in which they appear to regulate the degree of edema, the degree of microglia activation, and overall neuronal degeneration [5]. Likewise, in different stroke models, disease progression is accompanied by disruption of meningeal lymphatic vessels [4, 24]. Meanwhile, the circadian rhythm of the lymphatic system and spinal lymphatic vessels were observed, suggesting that the functions of the lymphatic system are up-regulated at night, and this phenomenon may be involved in the occurrence and development of certain diseases [25-27]. Research on aging has shown that the lymphatic vessels of the CNS in the elderly may face a decline in function, resulting in an abnormal decrease in the excretion of harmful waste including amyloid, and ultimately causing CNS lesions [28]. Except for the brain and spinal cord, lymphatic markers were also found in the optic nerve (though still controversial). A recent study by Kasi A et al. confirmed the glymphatic system there by imaging the optic nerve of healthy humans and AQP4-deficient mice [29]. Using human tissue from autopsies, an immunohistochemical analysis of optic nerves showed positive lymphatic staining and distribution [30]. However, Trost A et al. raised objections. Through immunofluorescence staining of lymphatic vessel-specific markers in the optic nerve, they found that the positive cells of the two lymphatic-specific antibodies Lyve-1 and Podoplanin did not colocalize, and put forward the view that lymphatic vessels do not exist in the optic nerve [31, 32]. From the above studies, we know that lymphatic vessels are not only exactly present in the CNS, but also have important functions such as draining fluid, metabolic waste, and providing immune monitoring and response. Furthermore, the glymphatic system, meningeal lymphatic vessel imaging, circadian rhythm, and aging studies have demonstrated the richness and diversity of lymphatic vessel functions and structures in the CNS. There may still be many unknown functions and structures to be discovered, which are of great research value.

Autonomic nerves, including sympathetic and parasympathetic nerves, have been detected in the walls of collecting lymphatic vessels [33]. Mignini F et al. found that differences in lymphatic innervation affect lymphatic flow, and that reductions in nerve fibers are observed in aging individuals and contribute to lymphatic dysfunction [34]. The bidirectional regulation of lymphatics and nerves proposed by them caught our attention. Lymphatic vessels may regulate or affect nerve function by removing metabolic waste and providing immune monitoring and response, and nerve innervation of lymphatic vessels could affect their function and efficiency. Whether the same two-way regulation mechanism exists in nerves and

lymphatic vessels in other parts has research value.

The lymphatic vasculature system associated with the PNS

Unlike the CNS, there are significantly fewer studies of lymphatic vessels associated with the PNS, both quantitatively and qualitatively. In the past, it was widely believed that these lymphatic vessels did not even exist due to the sequestration of lymphocytes and antibodies by the blood-brain barrier [35]. We believe that the importance of the main lymphatic vessels or the lymphatic system has not been fully revealed. In addition, compared with the CNS, the lymphatic vessels of the peripheral nerves are more dispersed and have smaller anatomical structures, which may be one of the reasons for the lack of research on the lymphatic vessels of the peripheral nerves. However, in limited studies, we have attempted to uncover the structure and role of a subset of lymphatic vessels in the PNS.

In general, we believe that lymphatic vessels and the lymphatic system also play an important role in waste removal and immune monitoring in the PNS. Notably, peripheral nerves can innervate the lymphatic system. Multiple previous studies have shown that the popliteal lymph node (popLN) receives direct innervation from the sciatic nerve [36-38]. Chen et al. found that in sciatic nerve injury, denervation of the popLN (sciatic nerve transection) can cause lymph node expansion, which is manifested by a significant increase in the number of B cells, CD4+T cells, and CD8+T cells [39]. The authors describe this phenomenon as a pro-inflammatory response. Interestingly, this process does not rely on the LN to receive signals or cytokines in the lymph or blood, which the authors believe is directly under neural regulation. Peripheral nerves can directly regulate the lymphatic system under some physiological and pathological conditions to activate the lymphatic system to recruit immune cells. Conversely, functioning of the lymphatic system also affects the peripheral nerves. In the PNS, lymphocytes (including macrophages, T cells, B cells, etc.) can participate in many physiological and pathological processes including phagocytosis, immune monitoring and response, and repair after nerve injury. On the other hand, the transport of lymphocytes is one of the main functions of the lymphatic system, especially macrophages/monocytes, dendritic cells, T and B lymphocytes [40-42], which are closely related to the physiopathological processes of the PNS. A review by Mietto et al. [43] shows that non-neuronal cells, including immune cells, are important for nerve regeneration. In a study of sciatic nerve injury in mice, Bombeiro AL et al. [44] found that the frequency of pro-inflammatory Th1 and Th17 cell subsets increased in subjects 7 days after injury and remained unchanged 21 days after injury. In contrast, when lymphocytes (including B cells, CD4+T cells, CD8+T cells, etc.) extracted from the spleen of mice 21 days after injury were injected into mice 3 days after injury, exogenous lymphocytes could be observed in the diseased tissue 1 hour after injection. The experimental group performed better than the control group in neurological recovery and function 21 days after injury.

Conversely, the lymphatic system can also exaggerate immune response and deterioration of neuronal function. Myelin degeneration results in macrophage aggregation, T lymphocyte infiltration, major histocompatibility complex (MHC) class II antigen expression, and immunoglobulin G (IgG) deposition in neural membranes, which jointly lead to nerve edema, which affects nerve regeneration [45, 46]. Analyzing the above studies, we believe that in peripheral nerve injury, the immune environment is important and resides in a delicate balance. Although the evidence is not direct, we can still find that the lymphatic system is involved in this balance, including the recruitment and transport of immune cells, the uptake of broken cells and tissues, etc. Therefore, we believe that interfering with this balance by modulating the lymphatic system is a potential target that may improve the current poor prognosis of peripheral nerve injury. Meng FW et al. [47] confirmed the existence of lymphatic endothelial cell-specific markers in the sciatic nerve by immunohistochemistry in a sciatic nerve crush injury model and showed different states at different time points after injury. At 7 post-injury days, a significant increase in Lyve-1 distribution and passing through the interneural space was observed, and there was no difference in Lyve-1 expression between the control group and 14 days post-injury. Also, co-localization of Prox1 with Lyve-1 was observed, which is indicative of lymphangiogenesis under inflammatory conditions. The above studies reveal changes of lymphatic vessels during repair of peripheral nerve injury, indirectly confirming that the proliferation of lymphatic vessels is involved in the biological processes of nerve injury repair. However, the specific mechanism remains to be studied. Besides, Masahide et al. [48] studied the distribution and fine structure of lymphatic vessels associated with nerves by immunohistochemistry in the murine craniofacial region, and claimed that the lymphatic system associated with the cranial nerves provides the pathway for transport of cerebrospinal fluid, tissue fluid, and free cells involved in immune response and tumor metastasis in the craniofacial region. Volpi et al. [49] examined biopsied sural nerves from patients with CIDP (chronic inflammatory demyelinating polyneuropathy), vasculitic neuropathy and non-inflammatory axonal neuropathy, and lymphatic capillaries were found in the sural epineurium by immunostaining of D2-40 and CD31 in frozen sections of tissue.

At the current stage, we have to admit that the research on peripheral nerve-related lymphatic vessels is still in its infancy, and most studies involve only preliminary identification and functional research, and have received little attention. There are still many doubts: are lymphatic

vessels present around peripheral nerves in both physiological and pathological conditions? Are there differences in the distribution and structure of lymphatic vessels beside peripheral nerves in different regions? What physiological or pathological processes of peripheral nerves are lymphatic vessels involved in? Will the intervention of lymphatic vessels (such as promoting/inhibiting the generation of lymphatic vessels, ligating lymphatic vessels, changing the drainage path of lymphatic vessels, etc.) affect the biological processes and functions of peripheral nerves under normal physiological and pathological conditions? This needs further research to provide more evidence. However, due to the extensive distribution of lymphatic vessels and the diversity of their functions, based on the existing research results, we believe in the existence of peripheral nerve-related lymphatic vessels and recognize their value.

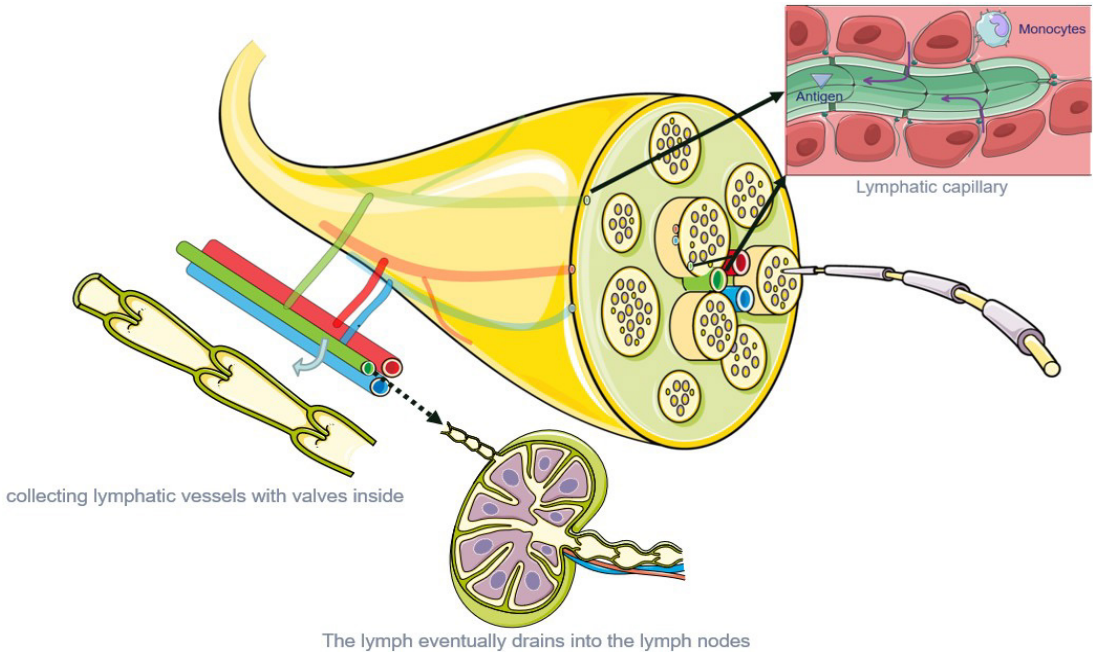

Figure 1. The lymphatic vessels associated with the PNS. Lymphatic vessels and blood vessels are widely distributed in the adventitia, peritoneum, and interstitium of peripheral nerves. The lymphatic vessels are shown in the green tubular structures in the figure, red for arteries and blue for veins. Due to insufficient research, the distribution and structure of lymphatic vessels in the picture are based on existing research and conjectures, which may deviate from the actual situation and are for reference only. This picture is an open-source material edited and painted by the author. Our thanks to the material providing website: https://smart.servier.com/.

Conclusion

The role of lymphatic vessels and the lymphatic system in peripheral nerves may be more important than previously assumed, although much is still unknown. We speculate that in peripheral nerves, lymphatic vessels and nerves are performing a bidirectional regulation. The structural and functional integrity of lymphatic vessels ensures peripheral nerve homeostasis. On the other hand, nerves can directly regulate the lymphatic system and even activate immune response and the recruitment of immune cells. Lymphatic vessels may be involved in various pathological processes including repair after nerve injury, autoimmune diseases, and aging. Uncovering the specific mechanisms involved can deepen our understanding of these diseases and may even improve disease outcomes by modulating lymphatic system action.

Author Contributions

N Zhou conceived the project and edited and approved the final version of the manuscript. SR Li searched the literature, designed the figures, and wrote the manuscript.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Breslin JW, Yang Y, Scallan JP, et al. Lymphatic Vessel Network Structure and Physiology. *Comprehensive Physiology.* 2018;9(1):207-299. Available from: doi: 10.1002/cphy.c180015

[2] Da Mesquita S, Louveau A, Vaccari A, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature*. 2018;560(7717):185-191. Available from: doi: 10.1038/s41586-018-0368-8.

[3] Zou W, Pu T, Feng W, et al. Blocking meningeal lymphatic drainage aggravates Parkinson's disease-like pathology in mice overexpressing mutated α-synuclein. *Translational neurodegeneration*. 2019;8:7. Available from: doi: 10.1186/s40035-019-0147-y.

[4] Yanev P, Poinsatte K, Hominick D, et al. Impaired meningeal lymphatic vessel development worsens stroke outcome. *Journal of Cerebral Blood Flow & Metabolism*. 2020;40(2):263-275. Available from: doi: 10.1177/0271678X18822921.

[5] Bolte AC, Dutta AB, Hurt ME, et al. Meningeal lymphatic dysfunction exacerbates traumatic brain injury pathogenesis. *Nature Communications*. 2020;11(1):4524. Available from: doi: 10.1038/s41467-020-18113-4.

[6] van Zwam M, Huizinga R, Heijmans N, et al. Surgical excision of CNS-draining lymph nodes reduces relapse severity in chronic-relapsing experimental autoimmune encephalomyelitis. *Journal of pathology and translational medicine*. 2009;217(4):543-51. Available from: doi: 10.1002/path.2476.

[7] Baluk P, Fuxe J, Hashizume H, et al. Functionally specialized junctions between endothelial cells of lymphatic vessels. *Journal of Experimental Medicine*. 2007;204(10):2349-62. Available from: doi: 10.1084/jem.20062596.

[8] Oliver G, Kipnis J, Randolph GJ, Harvey NL. The Lymphatic Vasculature in the 21(st) Century: Novel Functional Roles in Homeostasis and Disease. *Cell*. 2020;182(2):270-296. Available from: doi: 10.1016/j.cell.2020.06.039.

[9] Muthuchamy M, Zawieja D. Molecular regulation of lymphatic contractility. *Annals of the New York Academy of Sciences*. 2008;1131:89-99. Available from: doi: 10.1196/annals.1413.008.

[10] Alitalo K. The lymphatic vasculature in disease. *Nature Medicine*. 2011;17(11):1371-80. Available from: doi: 10.1038/nm.2545.

[11] Willard-Mack CL. Normal structure, function, and histology of lymph nodes. *Toxicologic Pathology*. 2006;34(5):409-24. Available from: doi: 10.1080/01926230600867727.

[12] Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Science Traditional Medicine*. 2012;4(147):147ra111. Available from: doi: 10.1126/scitranslmed.3003748.

[13] Iliff JJ, Wang M, Zeppenfeld DM, et al. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *Journal of neuroscience and rehabilitation*. 2013;33(46):18190-9. Available from: doi: 10.1523/JNEUROSCI.1592-13.2013.

[14] Mestre H, Tithof J, Du T, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nature Communications*. 2018;9(1):4878. Available from: doi: 10.1038/s41467-018-07318-3.

[15] Damkier HH, Brown PD, Praetorius J. Cerebrospinal fluid secretion by the choroid plexus. *Physiological Reviews*. 2013;93(4):1847-92. Available from: doi: 10.1152/physrev.00004.2013.

[16] Klarica M, Radoš M, Orešković D. The Movement of Cerebrospinal Fluid and Its Relationship with Substances Behavior in Cerebrospinal and Interstitial Fluid. *Neuroscience*. 2019;414:28-48. Available from: doi: 10.1016/j.neuroscience.2019.06.032.

[17] Cserr HF. Role of secretion and bulk flow of brain interstitial fluid in brain volume regulation. *Annals of the New York Academy of Sciences*. 1988;529:9-20. Available from: doi: 10.1111/j.1749-6632.1988.tb51415.x.

[18] Abbott NJ. Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology. *Neurochemistry International*. 2004;45(4):545-52. Available from: doi: 10.1016/j.neuint.2003.11.006.

[19] Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015;523(7560):337-41. Available from: doi: 10.1038/nature14432.

[20] Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *The Journal of experimental medicine*. 2015;212(7):991-999. Available from: doi: 10.1084/jem.20142290.

[21] Louveau A, Herz J, Alme MN, et al. CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nature neuroscience*. 2018;21(10):1380-1391. Available from: doi: 10.1038/s41593-018-0227-9.

[22] Logsdon AF, Lucke-Wold BP, Turner RC, et al. A mouse Model of Focal Vascular Injury Induces Astrocyte Reactivity, Tau Oligomers, and Aberrant Behavior. *Archives of neuroscience*. 2017;4(2):e44254. Available from: doi: 10.5812/archneurosci.44254.

[23] Small C, Dagra A, Martinez M, et al. Examining the role of astrogliosis and JNK signaling in post-traumatic epilepsy. *Egyptian Journal of Neurosurgery*. 2022;37:1. Available from: doi: 10.1186/s41984-021-00141-x.

[24] Chen J, He J, Ni R, et al. Cerebrovascular Injuries Induce Lymphatic Invasion into Brain Parenchyma to Guide Vascular Regeneration in Zebrafish. *Developmental Cell*. 2019;49(5):697-710.e5. Available from: doi: 10.1016/j.devcel.2019.03.022.

[25] Xie L, Kang H, Xu Q, et al. Sleep drives metabolitem clearance from the adult brain. *Science*. 2013;342(6156):373-7. Available from: doi: 10.1126/science.1241224.

[26] Hablitz LM, Vinitsky HS, Sun Q, et al. Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia. *Science Advances*. 2019;5(2):eaav5447. Available from: doi: 10.1126/sciadv.aav5447.

[27] Ma Q, Decker Y, Müller A, et al. Clearance of cerebrospinal fluid from the sacral spine through lymphatic vessels. *Journal of Experimental Medicine*. 2019;216(11):2492-2502. Available from: doi: 10.1084/jem.20190351.

[28] Patel TK, Habimana-Griffin L, Gao X, et al. Dural lymphatics regulate clearance of extracellular tau from the CNS. *Molecular Neurodegeneration*. 2019;14(1):11. Available from: doi: 10.1186/s13024-019-0312-x.

[29] Kasi A, Liu C, Faiq MA, et al. Glymphatic imaging and modulation of the optic nerve. *Neural Regeneration Reserach*. 2022;17(5):937-947. Available from: doi: 10.4103/1673-5374.324829.

[30] Damasceno R, Barbosa J, Cortez L, et al. Orbital lymphatic vessels: immunohistochemical detection in the lacrimal gland, optic nerve, fat tissue, and extrinsic oculomotor muscles. *Arquivos Brasileiros de Oftalmologia*. 2021;84(3):209-213. Available from: doi: 10.5935/0004-2749.20210035.

[31] Trost A, Bruckner D, Kaser-Eichberger A, et al. Lymphatic and vascular markers in an optic nerve crush model in rat. *Experimental Eye Research*. 2017;159:30-39. Available from: doi: 10.1016/j.exer.2017.03.003.

[32] Trost A, Runge C, Bruckner D, et al. Lymphatic markers in the human optic nerve. *Experimental Eye Research*. 2018;173:113-120. Available from: doi: 10.1016/j.exer.2018.05.001.

[33] D'Andrea V, Panarese A, Taurone S, et al. Human Lymphatic Mesenteric Vessels: Morphology and Possible Function of Aminergic and NPY-ergic Nerve Fibers. *Lymphatic Research and Biology*. 2015;13(3):170-5. Available from: doi: 10.1089/lrb.2015.0018.

[34] Mignini F, Sabbatini M, Coppola L, Cavallotti C. Analysis of nerve supply pattern in human lymphatic vessels of young and old men. *Lymphatic Research and Biology*. 2012;10(4):189-97. Available from: doi: 10.1089/lrb.2012.0013.

[35] Schwartz M, Sela BA, Eshhar N. Antibodies to gangliosides and myelin autoantigens are produced in mice following sciatic nerve injury. *Journal of Neurochemistry*. 1982;38(5):1192-1195. Available from: doi: 10.1111/j.1471-4159.1982.tb07890.x.

[36] Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S. Noradrenergic and peptidergic innervation of lymphoid tissue. *Journal of Immunology*. 1985;135(2 Suppl):755s-765s. Available from: PMID: 2861231.

[37] Felten DL, Felten SY, Bellinger DL, et al. Noradrenergic sympathetic neural interactions with the immune system: structure and function. *Immunological Reviews*. 1987;100:225-60. Available from: doi: 10.1111/j.1600-065x.1987.tb00534.x.

[38] Sloan EK, Capitanio JP, Tarara RP, et al. Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. *The Journal of Neuroscience*. 2007;27(33):8857-65. Available from: doi: 10.1523/JNEUROSCI.1247-07.2007.

[39] Chen CS, Weber J, Holtkamp SJ, et al. Loss of direct adrenergic innervation after peripheral nerve injury causes lymph node expansion through IFN-γ. *Journal of Experimental Medicine*. 2021;218(8):e20202377. Available from: doi: 10.1084/jem.20202377.

[40] Caillaud M, Richard L, Vallat JM, et al. Peripheral nerve regeneration and intraneural revascularization. *Neural Regeneration Research*. 2019;14(1):24-33. Available from: doi: 10.4103/1673-5374.243699.

[41] Wong BW. Lymphatic vessels in solid organ transplantation and immunobiology. *American journal of transplantation*. 2020;20(8):1992-2000. Available from: doi: 10.1111/ajt.15806.

[42] Kataru RP, Lee YG, Koh GY. Interactions of immune cells and lymphatic vessels. *Advances in anatomy, embryology, and cell biology*. 2014;214:107-118. Available from: doi: 10.1007/978-3-7091-1646-3_9.

[43] Siqueira MB, Klauss M, Blanco M. Neurotrauma and Inflammation: CNS and PNS Responses. *Mediators of inflammation*. 2015;2015:1-14. Available from: doi: 10.1155/2015/251204.

[44] Bombeiro AL, Lima B, Bonfanti AP, et al. Improved mouse sciatic nerve regeneration following lymphocyte cell therapy. *Molecular Immunology*. 2020;121:81-91. Available from: doi: 10.1016/j.molimm.2020.03.003.

[45] Willison H, Stoll G, Toyka KV, et al. Autoimmunity and inflammation in the peripheral nervous system. *Trends in neurosciences*. 2002;25(3):127-9. Available from: doi: 10.1016/s0166-2236(00)02120-2.

[46] Stüve O, Zettl U. Neuroinflammation of the central and peripheral nervous system: an update. *Clinical and Experimental Immunology*. 2014;175(3):333-5. Available from: doi: 10.1111/cei.12260.

[47] Meng FW, Jing XN, Song GH, et al. Prox1 induces new lymphatic vessel formation and promotes nerve reconstruction in a mouse model of sciatic nerve crush injury. *Journal of Anatomy*. 2020;237(5):933-940. Available from: doi: 10.1111/joa.13247.

[48] Furukawa M, Shimoda H, Kajiwara T, et al. Topographic study on nerve-associated lymphatic vessels in the murine craniofacial region by immunohistochemistry and electron microscopy. *Biomedical Research*. 2008;29(6):289-296. Available from: doi: 10.2220/biomedres.29.289.

[49] Volpi N, Guarna M, Lorenzoni P, et al. Characterization of lymphatic vessels in human peripheral neuropathies. *Italian Journal of Anatomy and Embryology*. 2013;117(2):12. Available from: https://oajournals.fupress.net/index.php/ijae/article/view/4198.