Lymphology 57 (2024) 19-26

Symposium Highlight

PULMONARY LYMPHATICS HISTORY, ANATOMY, AND PATHOPHYSIOLOGY: EMERGING KNOWLEDGE AND A LOOK TO THE FUTURE

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ABSTRACT

Central lymphatic disorders of the lung have not received intense investigation. Lymphatic system physiology is presented in the context of historical developments and basic lung lymphatic anatomy is reviewed followed by emerging characteristics of primary and secondary pathophysiological disturbances of lymphatic involvement in a number of pulmonary diseases including Gorham-Stout disease, pulmonary edema and infections and inflammatory conditions including lymphangioleiomyomatosis (LAM). The future includes potential molecular targeting of lymphangiogenesis or lymphatic vessels for interventional occlusion.

This article is an amalgamation of presentations at the 2023 ISL International Congress of Lymphology, Genoa, Italy in a special symposium on central and regional lymphatic system in health and disease and as part of a Special Symposium on the Lymphatic system of the Heart and Lung in Health and Disease at the 26th International Congress of Lymphology meeting held in Barcelona, Spain, September 2017, which has been updated to 2024.

Keywords: lymphatic history, lymphatic anatomy, lymphatic pathophysiology, lung, lung disease, central lymphatic disorders, lymphopulmonology

HISTORY

Our current understanding of the pulmonary lymphatic system can be traced to the early work of anatomists including Olaus Rudbeck, who in 1653 studied the distribution of lung lymphatics and lymph flow in small animals (1). In the 1700s William Cruikshank (2) and Paolo Mascagni (3) described the deep and superficial components of the pulmonary lymphatics. Early work in the mid to late 1800s by anatomists began to reveal the arrangement of the pulmonary l.ymphatic system, including work by Arnold and Miller using injection techniques to discriminate between the pleural and intrapulmonary lymphovascular network (4). Further studies during this time by Włodarski and Sikorski also added to the growing knowledge of the anatomy by showing that the lymphovascular drainage of the lungs had its own alveolar network (4).

Studies trying to detail the structure of the pulmonary lymphatic system continued into the early 1900s. During this time anatomists made strides in understanding how the pulmonary lymphatic system was arranged, including the discovery that there are no lymph capillaries in the alveolar walls, a finding that

led to much discussion, continuing even to this day (5). Studies using injection techniques to visualize lymphatic vessels continued and in 1912, after injecting the pulmonary lymphatic vessels, Franke noted that the superficial and deep lymph vessels may communicate with each other (6). This arrangement of lymphatic vessels is important and in the 1930s Miller believed that the flow of lymph fluid from the deep vessels to the pleural lymph vessels occurred in one direction due to the presence of valves that point towards the pleura (7). In the 1950s, Machado de Sousa noted that some lymph vessels of the lower lungs pass through the diaphragm and anastomose with vessels in the abdominal cavity or connect to periaortal lymph nodes (4). His findings led to further understanding of how the vast network of lymphatic vessels is connected to the surrounding anatomy, including the abdominal lymphatic vessels and nodes. The connection between the superficial and deep lymphatic vessels was confirmed in 1970 by Lauweryns and Boussauw after demonstrating connections between pleural and deep pulmonary vessels in newborn lungs (4). It was also around this time when Kubik performed serial sectioning of lung tissue and was able to visualize histologically the plexiform network of pulmonary lymphatic vessels (4).

The cumulative work of these anatomists laid the foundation for our current understanding of the pulmonary lymphatic system. Their discoveries not only illuminated the complex network of lymphatic vessels within the lungs but also highlighted the intricate connections between the pulmonary lymphatics and surrounding anatomy. These historical contributions continue to influence modern research, underscoring the importance of the pulmonary lymphatic system in both health and disease.

ANATOMY AND FUNCTION

Efficient pulmonary lymphatic drainage is crucial. It counters accumulation of fluid in the alveolar space which prevents pulmonary edema and maintains optimal conditions for an efficient gas exchange. Extravasation of fluid to the pulmonary interstitial space is constant throughout capillaries and venous reabsorption negligible under most conditions (8). Apart from the obvious necessity of continuous fluid removal by the lymphatic system, the airways are also exposed to constant pathogens and other inflammatory mediators where activation and mobilization of the local immune system in nearby lymph nodes is required. Accordingly, the lymphatic system is highly prevalent in the lungs (9), with the majority of lymphatic vessels draining from one of three following locations: the pleural space, the interlobular septa, and the broncovascular bundles (10).

In the interstitial space, the highly permeable lymphatic capillaries are kept open by local anchoring filaments, and interstitial fluid is moved into and through the lymphatic system by local gradients. In the lungs, much of this movement is influenced by the pressure changes of respiration. During inspiration, a combination of an increased abdominal pressure and decreased thoracic pressure secures a cephalad gradient for movement of lymphatic fluid. Although it also reduces pressure in the airways, the same forces may help pulmonary lymphatic fluid move from the smaller collecting lymphatic vessels and out into the larger more terminal collecting vessels and the thoracic duct. Expiration increases intrathoracic pressure, and squeezes lymphatic fluid back into the venous system (11). Contractions of the muscle cells surrounding the thoracic duct may assist lymphatic return (12) (*Fig. 1*).

PULMONARY LYMPHATICS AND PARTICIPATION IN VARIOUS DISEASE STATES

Early Historical Work

The pulmonary lymphatic system plays a critical role not only in immune surveillance against inhaled pathogens but also in managing fluid balance during pulmonary diseases. Early studies examining how bacteria are managed by the pulmonary lymphatics showed that while a large number of organisms are phagocytosed by macrophages, some

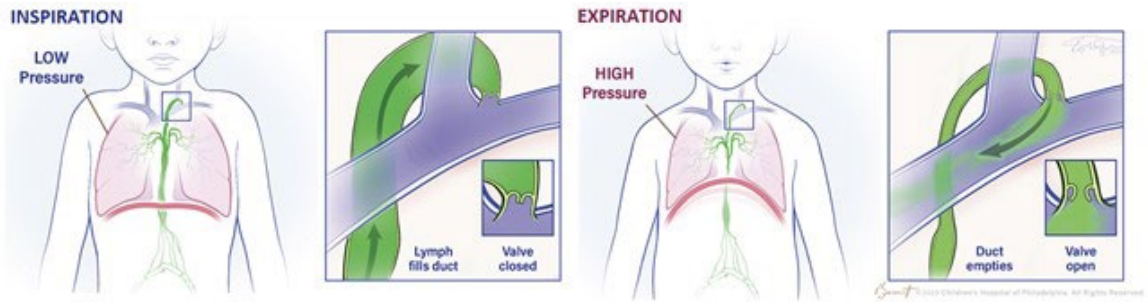

Fig. 1. *Illustrations of changes in lymphatic flow during respiration. During inspiration, pressures decrease in the thoracic cavity allowing lymphatic fluid and venous blood to flow towards the thoracic duct outlet and heart respectively (Left). During expiration, intrathoracic pressure increases while lymphatic valves in the thoracic duct prevent backflow. The lymphatic fluid is squeezed into the venous system. Contractions of the muscle cells surrounding the thoracic duct may assist lymphatic return. Illustrations by Brittany Bennett and Eo Trueblood, courtesy of The Children's Hospital of Philadelphia.*

bacteria pass through the alveoli and enter the lymphatics. Continued work attempting to understand how the pulmonary lymphatic system was involved in various disease states took off in the 1940s with Warren and Drinker's experiments inducing pulmonary hypertension (13). Paine, et al. found pulmonary congestion due to heart valve failures lead to an increase in lymph flow from the lungs (14). This finding was later confirmed by Uhley et al. after induced venous stasis from a left atrium balloon catheter in dogs (15). In the 1950s, Földi studied pulmonary hypertension and pulmonary edema by ligating pulmonary lymph vessels and inducing mitral stenosis in animal models (4). Courtice in the 1950s and 60s also studied lymph flow, quantifying its rate and composition, as well as studying its absorption from alveoli in models of pulmonary edema. In the 1970s, Ortega, et al. also induced pulmonary edema and lymphangiectasia using aortocaval shunts in dogs and found that the pulmonary lymph vessels were insufficient at maintaining fluid balance with increased lymph fluid (16).

Current Understanding

Reflecting the functions of the system in the lungs, lymphatic involvement in disease typically relates to either failure to prevent interstitial fluid accumulation or consequences of altered inflammation or immune modulation. Fluid accumulation preventing an effective gas-exchange is detrimental. For this reason, multiple protective mechanisms exist including a large lymphatic reserve capacity for removal of fluid and a natural reduction of the oncotic gradient favoring extravasation when proteins are diluted and washed into the lymphatic system at increased filtration (17). In relation, changes in the oncotic gradient are rarely the cause of substantial fluid accumulation. This is typically caused by either a significant increase in capillary hydrostatic pressure (18), as is seen in heart failure, or endothelial injury resulting in a more permeable barrier as observed in severe infections and sepsis (19). Limitations or changes in the lymphatic capacity may be a final relevant contributor to accumulation. The lymphatic capacity is determined by both the number of lymphatic vessels and by the functional pumping capacity of these vessels. Genetic mutations are known to alter lymphatic morphology and function as in seen in pulmonary lymphangiectasis (20), and lymphatic function, like cardiac function, may decline as a consequence of a number of exposures including altered hemo- and lymphodynamics (21-23).

Somewhat unrelated to pulmonary fluid homeostasis, the lymphatic system may also cause accumulation in the case of ruptured lymphatic vessels leaking out into the low-

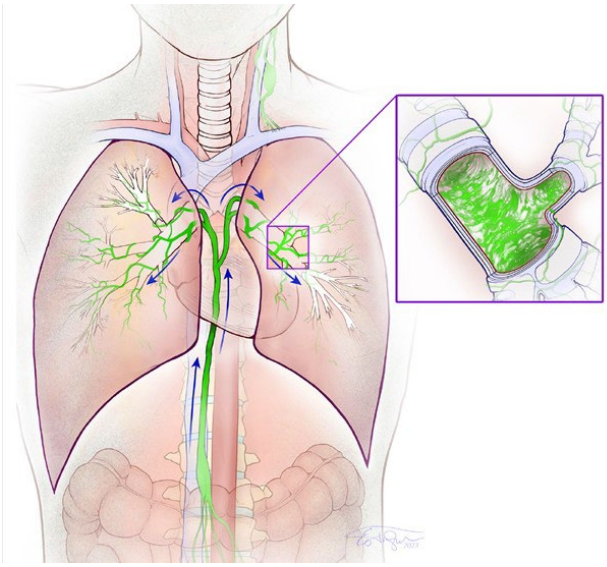

Fig. 2. *Illustration of the thoracic duct in the abdomen and thorax. In chylothorax and plastic bronchitis, lymphatic flow redirects towards the lungs. Here leakage into the thoracic cavity causes chylothorax and leakage into the airways may cause plastic bronchitis (Small image). Illustrations by Eo Trueblood, courtesy of The Children's Hospital of Philadelphia.*

pressure environments of the thoracic cavity or the airways. Chylothorax has numerous causes ranging from inborn to traumatic and entails leakage of lipid-rich lymphatic fluid originating from the intestines out into the thoracic cavity (24-26). Similarly, in plastic bronchitis, lymphatic fluid leaks out into the airways and coagulates (27). These pulmonary lymphatic complications are rare, but frequently encountered in individuals with congenital heart defects or genetic syndromes such as Noonans (28,29) (*Fig. 2*).

Based on these roles, the pulmonary lymphatics have been implicated in a variety of diseases, (many of which have been studied by ISL members). Despite our somewhat limited understanding of the pulmonary lymphatic system in disease pathogenesis, our current understanding is possible because of observations and experimental studies undertaken by numerous early lymphologists, beginning centuries ago. The following are a few of the diseases with known lymphatic involvement, highlighting how the pulmonary lymphatic system plays a role in attenuating or alternatively aggravating infectious and inflammatory conditions. It is our goal in discussing them to promote more research on these and other lung disorders.

Lymphangioleiomyomatosis (LAM)

Lymphangioleiomyomatosis, (LAM) is a disease characterized by cystic destruction of the lungs, kidneys, and lymphatics, causing lymphangioleiomyomas or smooth muscle cell proliferations within lymphatic vessels (30,31). The abnormally proliferating neoplastic LAM cells embed within dilated lymphatic vessel walls. Lymphadenopathy and chylous effusions are commonly seen. In addition, elevated mediators of lymphangiogenesis, vascular endothelial growth factors, VEGF-C and VEGF-D, have been found to be elevated in patients with LAM but it is unclear whether there is a cause and effect relationship or only a secondary association (31,32).

Lymphangitic Carcinomatosis

Lymphangitic carcinomatosis is a rare manifestation of adenocarcinoma, character-

ized by a diffuse infiltration and obstruction of the pulmonary lymphatic system by metastatic tumor cells, most commonly from tumors arising from the breast, lungs, stomach, pancreas, uterus, cervix, and colon. Metastasis of the tumor cells to the lymphatics is thought to follow hematogenous spread to the lungs but could also be derived from thoracic duct delivery of carcinoma cells to systemic veins. All segments of the lymphatic system within the lungs can be involved, including the peripheral, interlobular, and septal lymphatics.

Gorham Stout Disease

Gorham Stout known as "disappearing bone disease," is a rare disease associated with lymphangiomatosis, the development of abnormally thin-walled ectopic lymphatic vessels. The disease is characterized by osteolysis of bones with lymphatic infiltration and fibrosis. Osteopenia develops, and fractures and disabilities are common in these patients. Chylous reflux, including chylothorax and chylous ascites, is often present when there is involvement of the thorax or abdomen, and is a major cause of morbidity and mortality in these patients. The etiology of this disorder is not well understood and more research is needed to understand the inciting cause and pathomechanisms.

Pulmonary Edema

Pulmonary edema is another example of a condition in which the pulmonary lymphatic vessels play an important role in mitigating the amount of fluid within the lungs by several-fold increases in lymph drainage. The two main types of pulmonary edema, cardiogenic edema due to increased pulmonary capillary pressures from left heart failure, and non-cardiogenic edema due to increased permeability of the endothelial cell barrier (as in acute respiratory distress syndrome or sepsis), causes increased lung lymph fluid formation. Pulmonary edema results when the pulmonary capillary filtration of the lung produces more fluid than the pulmonary lymphatic vessels can transport. This leads to distension of the peribronchial lymphatic vessels to help drain the excess lymph fluid out of the congested lungs. Early lymphologists, including Paine, Földi, and Uhley (4,14,15) found increased transport of lymph fluid out of the lungs in right heart overload in experimental studies (4).

Infectious and Inflammatory Conditions

The pulmonary lymphatics are important for mitigating airway wall remodeling that occurs in response to infectious and inflammatory conditions such as in asthma and chronic obstructive pulmonary disease (COPD) (31,33). It has been shown that the airway epithelial and inflammatory cells are sources of VEGF-C and VEGF–D which induce lymphangiogenesis leading to a decrease of inflammation and edema. However, the exact contributions of pro- and anti-lymphangiogenic factors are not fully understood in these diseases (31,33). In COPD, increased lymphatic vessel density and increased number of lymphoid follicles have been identified, with recent animal models showing that impaired lymphatic function may precede and contribute to the disease's pathogenesis. These findings suggest that lymphatic dysfunction is an early event in these diseases, potentially offering a new avenue for therapeutic intervention (34). A study using mice infected with Mycoplasma pulmonis elucidated the pathogenesis of airway lymphatic and blood vessel remodeling via VEGF-C and VEGF-D through VEGF-3 (32,35). In 2014, Behr and Waters explored the nature of tuberculosis as a lymphatic disease, with the lungs (or gut) as the portal of entry and exit of the mycobacterium (36). Interestingly in the 1920s and 1930s, microdiverticuli with formation of new lymphatics were observed in pulmonary tuberculosis (4). Not to mention, lymphangitic spread of tuberculosis is common (4).

Recent work studying the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown the virus causes endothelial cell dysfunction with endotheliitis and cell death in the lung and other organs (37). The authors did not specifically study lymphatic endothelial cells. However, if these same

findings are not also found in lymphatic endothelial cells, it is likely that widespread damage to the vascular endothelial cells causes downstream secondary effects on the lymphatic system. In addition, a severe inflammatory response (cytokine storm) to this virus by the immune system can have detrimental effects leading to increased fluid in the lungs and cell death. (38).

CONCLUSION

Over the last decades there has been remarkable progress in identifying and characterizing lymphatic vessels and understanding their function in health and disease. Along with new methods of investigation, new knowledge of lymphatic involvement in a number of larger pulmonary diseases is slowly emerging. Although outside the scope of this brief summary, the lymphatic system is now being described as having a more active and disease-modifying role (39). Both chronic obstructive lung disease and interstial lung disease have been shown to display signs of increased lymphangiogenesis and increased lymphatic vessel density, with changes correlating with disease severity (40,41). In sarcoidosis and tuberculosis, granulomas typically develop in close relation to the lymphatic system hinting a central role for the system in disease development and progression (42,43). Although diverging in their results, studies also attribute a role for the lymphatic system in relation to lung transplantation and potential organ rejection (44,45). Finally, molecular targeting of lymphangiogenesis or lymphatic vessels for interventional occlusion have been introduced. Although the understanding of the role of the lymphatic system in many pulmonary diseases still leaves much to be desired, additional future therapeutic targets related to the lymphatic system seem highly likely and all studies underline the need for more knowledge into the field of pulmonary lymphatics.

CONFLICT OF INTEREST

The authors declares that no financial conflict of interest exists.

ACKNOWLEDGMENTS

Supported by NIH #T35 HL07479, Short-Term Training: Students in Health Professional Schools and NHLBI R25 HL108837, Short-Term Training to Increase the Diversity Pipeline in Heart/Lung/Blood Research (SD).

REFERENCES

1. Natale, G, G Bocci, D Ribatti: Scholars and scientists in the history of the lymphatic system. J. Anat. 231 (2017), 417-429.
2. Cruikshank, W: The Anatomy of the Absorbing Vessels of the Human Body. G. Nicol, London, 1786.
3. Mascagni, P: Vasorum lymphaticorum corporis humani historia et ichnographia. Senis Pazzini Carli. Pazzini Carli, Siena, 1787.
4. Földi, M, JR Casley-Smith (Eds.): Lymphangiology. FK Schattauer, Stuttgart, 1983.
5. Weber, E, F Sozio, A Borghini, et al: Pulmonary lymphatic vessel morphology: A review. Ann. Anat. 218 (2018), 110-117.
6. Franke, K: [I, ber die Lymphgefisse der Lunge, zugleich ein Beitrag zur Erkiarung der Baucherscheinungen bei Pneumonie.] Dtsch. Z. Chir., 119, 1912.
7. Yoffey, JM, CK Drinker, FC Courtice: Lymphatics, lymph and lymphoid tissue (No. 2). Harvard University Press, Cambridge, 1956.
8. Levick, JR, CC Michel: Microvascular fluid exchange and the revised Starling principle. Cardiovasc. Res. 87 (2010), 198-210.
9. Oliver, G, J Kipnis, GJ Randolph, et al: The lymphatic vasculature in the 21st century: Novel functional roles in homeostasis and disease. Cell 182 (2020), 270-296.
10. Weber, E, F Sozio, A Borghini, et al: Pulmonary lymphatic vessel morphology: A review. Ann. Anat. 218 (2018), 110-117.
11. Dori, Y, J Mazurek, E Birati, et al: Ascites in animals with right heart failure: Correlation with lymphatic dysfunction. J. Am. Heart Assoc. 12 (2023), e026984.
12. Kelly, B, CL Smith, M Saravanan, et al: Spontaneous contractions of the human thoracic duct-Important for securing lymphatic return during positive pressure ventilation? Physiol. Rep. 10 (2022), e15258.
13. Warren, MF, CK Drinker: The flow of lymph from the lungs of the dog. Am. J. Physiol. 136 (1942), 207-221.
14. Paine R, HR Butcher, JR Smith, et al:

Observations on the role of pulmonary congestion in the production of edema of the lungs. J. Lab. Clin. Med. 36 (1950), 288-296.
15. Uhley HN, SE Leeds, JJ Sampson, et al: Right duct lymph flow in experimental heart failure following acute elevation of left atrial pressure. Circ. Res. 20 (1967), 306-310.
16. Maier, HC: The pulmonary and pleural lymphatics: A challenge to the thoracic explorer. The Journal of Thoracic and Cardiovascular Surgery 52 (1966), 155-163.
17. Clark, AL, JGF Cleland: Causes and treatment of oedema in patients with heart failure. Nat. Rev. Cardiol. 10 (2013), 156-170.
18. Guyton, AC, AW Lindsey: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ. Res. 7 (1959), 649-57.
19. Schmidt, EP, Y Yang, WJ Janssen, et al: The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis. Nat. Med. 18 (2012), 1217-1223.
20. Bellini, C, F Boccardo, C Campisi, et al: Pulmonary lymphangiectasia. Lymphology. 38 (2005), 111-121.
21. Mohanakumar, S, N Telinius, B Kelly, et al: Morphology and function of the lymphatic vasculature in patients with a fontan circulation. Circ. Cardiovasc. Imaging 12 (2019), e008074.
22. Rossitto, G, S Mary, C McAllister, et al: Reduced lymphatic reserve in heart failure with preserved ejection fraction. J. Am. Coll. Cardiol. 76 (2020), 2817-2829.
23. Mohanakumar, S, B Kelly, ALR Turquetto, et al: Functional lymphatic reserve capacity is depressed in patients with a Fontan circulation. Physiol. Rep. 9 (2021), e14862.
24. Tutor, JD: Chylothorax in infants and children. Pediatrics 133 (2014), 722.
25. Savla, JJ, M Itkin, JW Rossano, et al: Post-operative chylothorax in patients with congenital heart disease. J. Am. Coll. Cardiol. 69 (2017), 2410-2422.
26. Resch, B, YG Sever, F Reiterer: Congenital chylothorax of the newborn: A systematic analysis of published cases between 1990 and 2018. Respiration 101 (2022), 84-96.
27. Dori, Y, MS Keller, JJ Rome, et al: Percutaneous lymphatic embolization of abnormal pulmonary lymphatic flow as treatment of plastic bronchitis in patients with congenital heart disease. Circulation 133 (2016), 1160-1170.
28. Joyce, S, K Gordon, G Brice, et al: The lymphatic phenotype in Noonan and Cardiofaciocutaneous syndrome. Eur. J. Hum. Genet. 24 (2016), 690-696.
29. Kelly, B, S Mohanakumar VE Hjortdal: Diagnosis and management of lymphatic disorders in congenital heart disease. Curr. Cardiol. Rep. 22 (2020), 164.
30. Glasgow, CG, S El-Chemaly, J Moss, et al: Lymphatics in lymphangioleiomyomatosis and idiopathic pulmonary fibrosis. Eur. Respir. Rev. 21 (2012), 196-206.
31. Glasgow, CG, A Taveira-DaSilva, G Pacheco-Rodriguez: Involvement of lymphatics in lymphangioleiomyomatosis. Lymphat. Res. Biol. 7 (2009), 221-228.
31. El-Chemaly, S, SJ Levine, J Moss: Lymphatics in lung disease. Ann. N.Y. Acad. Sci. 1131 (2008), 195-202.
33. Stump, B, Y Cui, P Kidambi, et al: Lymphatic changes in respiratory diseases: More than just remodeling of the lung? Am. J. Resp. Cell. Mol. 57 (2017), 272-279.
34. Trivedi, A, HO Reed: The lymphatic vasculature in lung function and respiratory disease. Front. Med. (2023), 1118583.
36. Behr, MA, WR Waters: Is tuberculosis a lymphatic disease with a pulmonary portal? Lancet Infect. Dis. 14 (2014), 250-255.
35. McDonald, DM: Angiogenesis and remodeling of airway vasculature in chronic inflammation. Am. J. Resp. Crit. Care 164 (2001), S39-S45.
37. Varga, Z, AJ Flammer, P Steiger, et al: Endothelial cell infection and endotheliitis in COVID-19. Lancet 395 (2020), 1417-1418.
38. Witte, M, S Daley: SARS-CoV-2/COVID-19, lymphatic vessels, lymph, and lymphology. Lymphology 53 (2021), 97-98.
39. Trivedi, A, HO Reed: The lymphatic vasculature in lung function and respiratory disease. Front. Med. 10 (2023), 1118583.
40. Lara, AR, GP Cosgrove, WJ Janssen, et al: Increased lymphatic vessel length is associated with the fibroblast reticulum and disease severity in usual interstitial pneumonia and nonspecific interstitial pneumonia. Chest 142 (2012), 1569-1576.
41. Hardavella, G, EG Tzortzaki, V Siozopoulou, et al: Lymphangiogenesis in COPD: Another link in the pathogenesis of the disease. Respir. Med. 106 (2012), 687-693.
42. Patterson, KC, CJ Queval, MG Gutierrez: Granulomatous inflammation in tuberculosis and sarcoidosis: Does the lymphatic system contribute to disease? Bioessays 41 (2019),

e1900086.
43. Kambouchner, M, D Pirici, JF Uhl, et al: Lymphatic and blood microvasculature organisation in pulmonary sarcoid granulomas. Eur. Respir. J. 37 (2011), 835-840.
44. Dashkevich, A, C Heilmann, G Kayser, et al: Lymph angiogenesis after lung transplantation and relation to acute organ rejection in humans. Ann. Thorac. Surg. 90 (2010), 406-411.
45. Cui, Y, K Liu, ME Monzon-Medina, et al: Therapeutic lymphangiogenesis ameliorates established acute lung allograft rejection. J. Clin. Invest. 125 (2015), 4255-4268.

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