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Historical overview of lymphangiogenesis

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The investigation of the lymphatic system has a very long and intriguing history, with several medical figures which brought important contributions. Work on the lymphatic system began in the 17th century, and by the beginning of the 19th century the anatomy of most of the lymphatic system had been described. This system is an essential component of the immune system, as well as vital to the maintenance of fluid homeostasis within the body. In this review article, I summarize the most important contributions to this field, until to the discovery of a specific lymphangiogenic factor, namely vascular endothelial growth factor-c (VEGF-C) (summarizing figure).

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First descriptions of the lymphatic vessels

The first description of the lymphatic vessels was published in 1627 by Gaspare Aselli, professor of anatomy and surgery in Pavia, Italy (Figure 1). He observed thin, white vessels distributed within the mesentery and above the upper intestinal wall [1]. Aselli named his findings 'venae albae aut lacteae', 'venae' from their similarity to veins; 'albae' to distinguish them from vessels carrying blood; and 'lacteae', for the milk-like fluid they contained. In 1651, Jean Pecquet discovered the thoracic duct and its entry into the left subclavian vein, which for the first time described the correct route of the lymphatic fluid entry into blood circulation. He established that gut lacteals containing the milk-like lymph empty into the cisterna chyli to be conveyed to the thoracic duct and not to the liver, as erroneously assessed by Aselli and other anatomists before him [2].

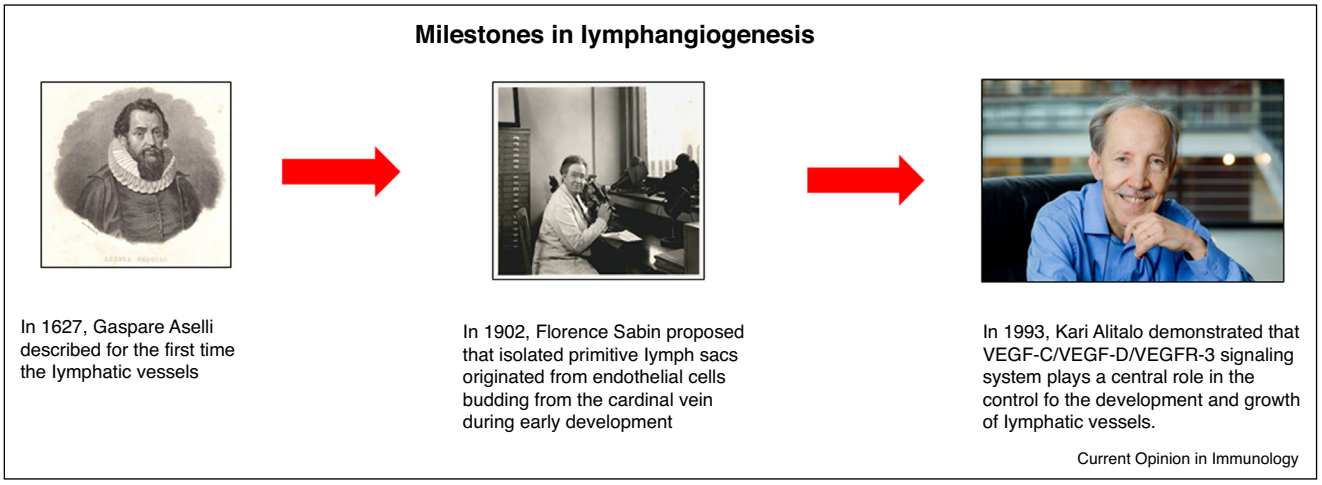
The main difference between blood vascular and lymphatic endothelial cells resides in the fact that lymphatics develop much later. In the human, lymphatic primordia have been found in 6–7-week-old embryos, 3–4 weeks after the development of the first blood vessels [3].

Florence Sabin, an American anatomist, proposed that isolated primitive lymph sacs originated from endothelial cells budding from the cardinal vein during early development after India ink injection experiments in embryonic pig [4••,5,6]. She believed that the lymphatics are formed by a process of sprouting from the large central veins and that these sprouts demonstrate almost immediately their own lymphatic character. Using the injection method in the pig embryo, Sabin showed that, starting from the region of each primitive sacs, there is in the skin a gradually increasing zone of injectable lymphatics which may cover the whole body (Figure 2). The India ink injection did not show up any isolated lymphatics, suggesting that growth is towards the periphery by the sprouting of pre-existing endothelium in the surrounding tissues and organs, where local capillaries are formed (the centrifugal model). The lymphatic vasculature is generated by centrifugal sprouting of lymphatic vessels from the lymph sacs.

Clark [7] observed that pointed projections extend, at various intervals and of varying lengths, from the walls of the lymphatics, while the tip ends in one or more pointed processes. This living tip is always changing and the nuclear thickening in the wall of the capillary is perpetually altering shape and position (Figure 3).

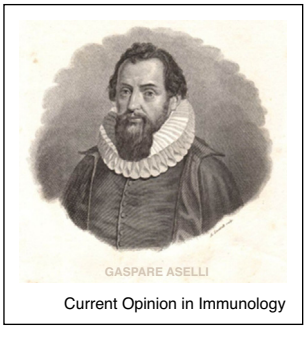
In studies on mammalian embryos, Sabin [8] demonstrated that there are eight lymph sacs; three paired, the jugular, subclavian and posterior lymph sacs, and two unpaired the *Cisterna chyli* and the retroperitoneal (mesenterial) lymph sac. Lymph sac is invaded by lymphatic endothelial cells and connective tissue and its lumen thereby becomes divided into sinuses. Lymph sac are venous derivatives that grow by sprouting into all parts of the body, except for the central nervous system and the bone marrow, free of lymphatics. Lymph sacs later will give rise to primary lymph nodes.

Both Lewis and Hoyer [9,10] agreed with Sabin on the venous derivation of the lymphatic system. However, Lewis believed that the early lymphatic primordia were formed by long series of isolated, but initially venous branches.



Alternatively to Sabin, Huntington, McClure, and Kampmeier [11–13] suggested that the primitive lymphatic vessels arise in the mesenchyme from putative lymphangioblasts (independent on the veins) by confluence of 'lymphatic clefts', fuse with the lymph sacs by centripetal growth and secondarily established venous connections (the centripetal model). Their observations were based upon the study of wax reconstructions of work performed in cat embryos. This theory is in line with findings by Schneider *et al.* [14], who demonstrated through the quail-chick chimera system that lymphangioblasts are present in the avian wing bud before the emergence of the jugulo-axillary lymph sacs. They grafted paraxial mesoderm of 2-day-old quail embryo into the shoulder region of 3-day-old chick embryo, and studied the integration of lymphangioblasts into the jugulo-axillary lymph sac. Then, the host embryo was re-incubated until day 6.5. From their morphological and molecular characteristics, the jugular lymph sac was clearly distinguished from the jugular vein. In all specimen quail endothelial cells integrating into the endothelial lining of chick vessels were observed.

Figure 1

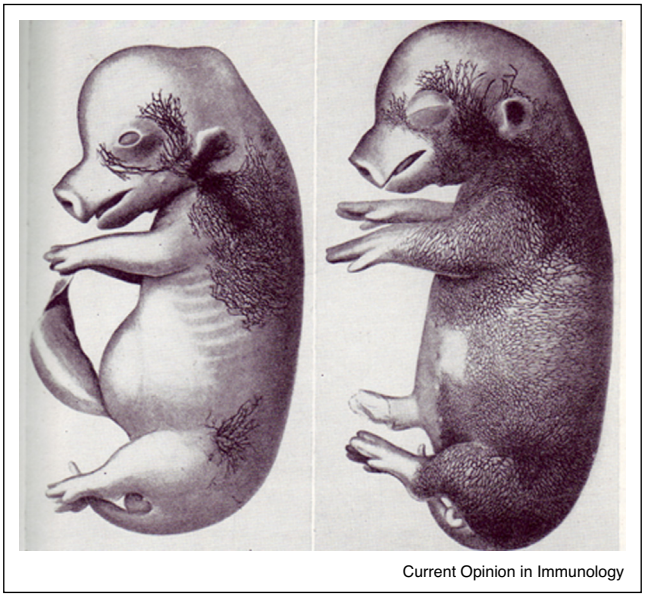


A portrait of the Italian anatomist Gaspare Aselli.
Source: Reproduced from Ref. [53].

In 1932, Clark and Clark [15••] used the ear chamber technique in the rabbit to observe the growth of lymphatic vessels, and showed at higher magnification that the lymphatic capillary wall was composed by a thin endothelium with an evident nuclear thickening. Bellman and Odén [16] documented via contrast microlymphangiography the time course and extent of newly formed lymphatics in circumferential wounds of the rabbit ear, including lymphatic bridging through newly formed scar tissue [17].

Studies of avian development indicate that independent lymphangioblasts might contribute to the formation of

Figure 2



The growth of the lymphatic vessels of the embryo of the pig depicted by India ink injection. Starting from the region of each of the primitive sacs, the skin shows a gradually increasing zone of injectable lymphatics which eventually covers the whole body.
Source: Reproduced from Ref. [53].