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EDITORIAL

CENTRIFUGAL VERSUS CENTRIPETAL ORIGIN(S) OF THE LYMPHATIC SYSTEM: CONTROVERSY (MOSTLY) RESOLVED?

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ABSTRACT

New findings reopen the controversy about centrifugal vs. centripetal origin of the lymphatic system and support that the latter may be the predominant source of lymphatic endothelial cells from mesenchymal lymphangioblasts.

Keywords: lymphatic system development, theories, lymphangioblasts

More than one hundred years ago the controversy over the origin of the lymphatic system/source of lymphatic endothelial cells (LECs) was heavily debated: whether they were derived from venous endothelial cells as early lymphatic sacs (which later involute) around the cardinal vein in a narrow window during embryonic life (1; centrifugal) or from tissue mesenchyme as described by Huntington (2). It was a "dispute which then [early teens of the 20th Century] agitated and took possession of the annual meetings [of the American Society of Anatomy] for several years." Indeed, so utterly did it dominate these meetings that other members not involved in it voiced the threat of secession. To understand how the mere thought of such a drastic protest could arise, we need but be reminded that half a century ago the gathering was small enough for the reading of all the papers in one common or joint program (3). Many lymphologists retained their doubts that a full explanation had been provided because in part it was demeaning to think that lymphatics all arise from veins when the systems maintain strict separation postnatally and only in disease states seem to blur their distinction. Moreover, Kampmeir (3) provided a longitudinal view that evolutionarily, lymphatic like structures functioning to drain interstitial fluid appear long before blood and the blood circulation in higher invertebrates. For the last 20 years, as a new generation of lymphologists has developed, the venous source has become "textbook" (4,5). However, newer techniques, such as genetic knockouts and single cell sequencing of transcriptomes, show convincingly that, in mice, embryonic LECs are predominantly derived from the mesenchyme, specifically the paraxial mesenchyme (PXM).

Stone and Stainier provided strong evidence in 2019 that it was the non-venous source which was most important (6). This conclusion was based primarily on deleting *Prox1* specifically in PXM-derived cells, which resulted in a failure of lymphatic vessel development. Now, in an even more definitive

study involving the collaboration of Stone's group at Oxford and Kiefer's group in Munster (7), the conclusion is massively supported. They performed immunohistochemistry on dozens of mouse embryos from days 8.5, 9.5, and 10.5; isolating cells with various cell markers in a large number of flow-sorting experiments; performing transcriptomes on 19,699 single cells and computationally isolating and re-clustering 2,488 of them. In addition, they used transgenic mice driving fluorescently tagged-Pax3 or Myf5, both expressed in the dermomyotome, induced at day 9 and found in Prox1 positive endothelial cells at day 10.5. They have substantially confirmed a major source of LECs from paraxial mesoderm-derived progenitors (PXM) (7). Most importantly, they used BrdU to identify dividing cells and have shown that the PXM-derived cells make up the vast majority of the LECs in developing lymphatics: 5 times the number provided by the venous route (7).

However, it is important to realize that there may be species differences as well as differences in organ-specific, local development. Wilting, et al (8) showed, using quail/chick chimeras, that the jugular sacs arise from both venous and PXM sources. In zebrafish, two of the facial lymphatics develop from venous sources while a third arises from arises from a migratory angioblast cell near the ventral aorta (9). In both these cases, the venous source predominated as it does in the mouse heart (10) while in locally derived lymphatics in the skin of mice (11), the mesenchymal source predominated. Thus, rather than being a minor contribution as Oliver (5) postulates, except for a narrow window during embryonic life, the centripetal mode appears to predominate, including in visceral and peripheral lymphatic development growth and regeneration. While the lymphology community can consider the matter temporarily resolved, further confirmation of the findings and application of the two theories merit continued exploration.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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