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Perspective

Significance of Cardiac Lymphatic Vasculature and its Development

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DESCRIPTION

The blood and lymphatic vascular systems make up the two complementary vasculatures that make up the circulatory system of animals. This fluid and macromolecule extravasation causes an on-going accumilation of extracellular fluids and a rise in interstitial pressure. The lymphatic vasculature, an open circulatory system that returns fluids and cells from organs to the blood circulation, maintains tissue fluid balance. In addition to controlling the homeostasis of interstitial fluid, lymphatic vessels play crucial roles in the immune response by removing pathogens, antigens, and immune cells from tissues and transporting them to local lymph nodes before returning extravagated fluid and solutes to blood circulation. A vast lymphatic network in the heart contributes to appropriate cardiac function under steady-state conditions as well as myocardial recovery after injury.

A growing number of studies have confirmed the lineage heterogeneity of cardiac lymphatics during development and their critical function in fibrotic repair following Myocardial Infarction (MI) in both non-regenerative and regenerative animal models, such as adult mice and zebrafish.

These findings offer considerable promise for current efforts to develop cardiovascular disease therapeutics, identifying lymphatic arteries as a possible therapeutic target for reducing myocardial oedema and modulating the immunological response after MI. In this study, the most recent developments in the study of cardiac lymphatic heterogeneity in mice and zebrafish are highlighted with a focus on the formation, shape, and function of the cardiac lymphatic vasculature.

The immunomodulatory role of the cardiac lymphatics and their functional interaction with immune cells during the fibrotic repair process following injury in the adult mammalian heart, as well as during cardiovascular tissue restoration and regeneration in neonatal mice and in adult zebrafish, are also discussed. The lymphatic vessels are being studied in current preclinical research as a possible therapeutic target in acute MI. The cardiac lymphatics run alongside the blood vessel network and share many of the functional characteristics of the systemic lymphatic vasculature, notably the maintenance of interstitial fluid pressure homeostasis and immune response control. Disruption of these systems can result in serious health issues; for example, a 3.5% rise in myocardial fluids can result in a 40%decrease in cardiac output. Lymphatic vessels are lined with an oak-leaf-shaped monolayer of Lymphatic Endothelial Cells (LECs) and are divided into three compartments: Initial lymphatics, pre-collector lymphatics, and collector lymphatics. Surprisingly, the location of lymphatic capillaries and collection vessel pathways in the heart are not totally preserved between species. Only the subepicardial layer of the zebrafish has the cardiac lymphatics, which empty into large collecting arteries in the outflow tract and link to the face lymphatic vasculature. Zebrafish cardiac lymphatic vessels come from both venous and non-venous (angioblast) sources, much like mouse cardiac lymphatics do. Specifically, facial lymphatic vessels that develop from sprouts of the cardinal vein and primary head sinus (lymphangiogenesis) as well as from a population of lymphangioblasts (lymphvasculogenesis) first establish the cardiac lymphatic endothelium on the outflow tract, or bulbus arteriosus. At around 3-4 Weeks Post-Fertilization (WPF), this process occurs relatively late in development but before the start of the coronary vasculature. However, in juvenile zebrafish, the proliferation of cardiac lymphatic capillaries over the ventricle occurs around following the establishment of the coronary vasculature.

In the following weeks, the bulbus arteriosus lymphatic vessels sprout towards the ventricle, adjacent to the major coronary vessels, and continue to grow along the base-to-apex axis in a mechanism similar to the growth of the cardiac lymphatics in mice. Interestingly, hearts with a CXC-chemokine receptor type 4 (Cxcr4a) loss have significant ventricular lymphatic defects, although the bulbus arteriosus lymphatics are normal. This implies that the lymphatics must travel down the ventricle in the presence of a mature coronary tree, with putative coronary artery-derived signals (such CXC-chemokine ligand 12 (Cxcl12a)) encouraging this developing process. In addition to sprouting lymphatics, it has been noted that isolated LEC clusters of unknown origin link to and add to the cardiac lymphatic vasculature. The cardiac lymphatics, like the systemic lymphatic vessels, depend on Vegfr3-Vegfc signalling for growth, and genetic models have a strong lymphangiogenic phenotype.

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