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25 Lymphatic macrophage crosstalk during neonatal mouse heart regeneration and transition to brotic repair following surgical myocardial infarction

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In adult mice, surgically-induced myocardial infarction MI) activates the cardiac lymphatics, which undergo sprouting angiogenesis, draining interstitial uid and trafficking macrophages to mediastinal lymph nodes MLNs), improving cardiac function.

Given the importance of the adult cardiac lymphatics post-MI, we investigated their role across the neonatal regenerative window". At post-natal day 1 P1) neonatal mice fully regenerate their heart following MI, in a macrophage-dependent manner, whereas equivalent injury at P7 leads to macrophage-driven scarring. We hypothesised that lymphatics respond differently during this window to clear macrophage subtypes depending upon their requirement for regeneration versus fibrotic repair.

The response to injury revealed limited lymphangiogenesis and minimal macrophage clearance from P1 versus P7 infarcted hearts, coincident with maturation of lymphatic endothelial cell LEC) junctions. Unbiased scRNA-Seq datasets from neonatal hearts post-MI demonstrated altered signalling between LECs and macrophages across the regenerative window, most notably of the lymphangiocrine factor Reelin

Finally, in mice lacking the lymphatic endothelial receptor-1 LYVE1), that exhibit impaired transmigration of macrophages to lymphatic vessels, MRI revealed surprising functional impairment in P1 mice post-MI. Given macrophages at P1 are not trafficked, this suggested a distinct role for LYVE1 in tissue-resident TR) macrophages, where it is also expressed. Macrophage-specific deletion of *Lyve* revealed impaired heart regeneration post-MI, characterised by reduced neovascular response and function.

Collectively, we reveal that cardiac lymphatics are developmentally compromised for clearance in early neonates, enabling retention of pro-regenerative macrophages, and that LYVE1 plays an essential role in macrophages to facilitate heart regeneration via the induction of coronary angiogenesis.