Title
Using three-dimensional imaging to study how kidney lymphatic vessels develop

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Authors
Daniyal J Jafree[1,2], Dale Moulding[1], Maria Kolatsi-Joannou[1], Nuria Perretta Tejedor[1], Karen L Price[1], Simon-Walker Samuel[3], Paul R Riley[4], Adrian S Woolf[5], Peter J Scambler[1], David A Long[1]

[1] Developmental Biology and Cancer Programme, UCL Great Ormond Street Institute of Child Health, University College London, London, UK
[2] MB/PhD Programme, Faculty of Medical Sciences, University College London, London, UK
[3] Centre for Advanced Biomedical Imaging, Division of Medicine, University College London, London, UK
[4] Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK
[5] School of Biological Sciences, Faculty of Biology Medicine and Health, University of Manchester, Manchester UK

Abstract
Kidney development is a complex process, involving the interaction of a variety of cell types which establish the function of the mature organ. One cell receiving relatively little attention is the lymphatic cell, which assemble into vessels to help clear dying cells, tissue fluid and toxins from organs. Kidney lymphatics are difficult to study owing to limitations in imaging technology, and so little is known about how lymphatics form or what role they play in the developing kidney.

We overcame these limitations by developing a technique for wholemount immunolabelling, optical clearing and 3D imaging of mouse and human embryonic kidneys down to the resolution of a single cell. Computational techniques were then used to segment and generate 3D lymphatic models and quantify the dynamics of lymphatic growth during kidney development.

We found that lymphatics first emerged as a ring-like cellular plexus in the hilum of the developing mouse kidney at embryonic day (E)14.5. As the mouse kidney matures through to E18.5, the lymphatics develop into lumenised vessels, wrap around the base of the nascent renal pelvis and branch towards the cortex alongside renal arterioles. We also found a population of cellular clusters expressing lymphatic markers growing adjacent to the lymphatic plexus, proliferating and increasing in number as kidney development progressed. Analysis of human embryonic kidneys between 10 and 12 post-conceptional weeks revealed an analogous appearance of both lymphatic vessels and clusters.

In summary, we implement a strategy for 3D imaging to reveal the dynamics and spatial relationships of lymphatics in the developing kidney. The lymphatic cell clusters in both mouse and human kidneys may represent an evolutionarily conserved lymphatic progenitor, as has recently been described in other organs.