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Searching for patterns in chaos: Mapping the changing vascular landscape in liver fibrosis

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SHORT SUMMARY:

Endothelial cells (EC) are known to be one of the most diverse cell types of the body. Their distinct transcriptomic, proteomic and metabolic characteristics enable the formation of unique organotypic vascular networks. In response to fibrosis, EC can rapidly change their properties. Even though these changes are well documented at a transcriptomic level, the proteomic changes that occur are less well studied. To address this knowledge gap, we used a murine model of liver fibrosis to follow the stages of progressive fibrogenesis and resolution and assess their impact on endothelial

plasticity. We developed an integrated approach combining immunofluorescence microscopy and full spectrum flow cytometry (FSFC) to describe 14 EC clusters and performed in-depth analysis detailing their abundance, localisation and phenotype. We identified novel fibrosis-associated EC (FA-EC) populations with traits of endothelial-to-mesenchymal transition (EndMT). These FA-EC populations have distinctive immune regulatory roles and directly translate to the progression and outcome of patients with liver disease.

SHORT BIO:

Dr Dufton has a PhD from Queen Mary University of London and undertaken post-doctoral positions at McMaster University in Canada and Imperial College in London. In 2019 he returned to Queen Mary University of London where he is a Senior Lecturer in Inflammations Sciences with a focus on the adaptability and plasticity of blood vessels. His research looks to understand how endothelial cells heterogeneity plays a fundamental roles in health and chronic disease pathogenesis. His lab has developed novel imaging approaches to identify fibrosis-associated endothelial phenotypes, including distinct endothelial-to-mesenchymal transition (EndMT) sub-populations, with the aim to develop new diagnostic and therapeutic approaches to tackle progressive fibrotic diseases. Link to webpage Centre for Microvascular Research: https://www.centre-for-microvascular-research.com/dufton-lab

RELEVANT PUBLICATIONS:

1. Cytokine-Mediated Degradation of the Transcription Factor ERG Impacts the Pulmonary Vascular Response to Systemic Inflammatory Challenge. Christopher M. Schafer, Silvia Martin-Almedina, Katarzyna Kurylowicz, Neil Dufton, Lourdes Osuna-Almagro, Meng-Ling Wu, Charmain F. Johnson, Aarti V. Shah, Dorian O. Haskard, Andrianna Buxton, Erika Willis, Kate Wheeler, Sean Turner, Magdalena Chlebicz, Rizaldy P. Scott, Susan Kovats, Audrey Cleuren, Graeme M. Birdsey, Anna M. Randi, Courtney T. Griffin. ATVB Aug. 2023

2. Placental Inflammation Leads to Abnormal Embryonic Heart Development. Eleanor Ward, Serena Bert, Silvia Fanti, Kerri M Malone, Robert T Maughan, Christina Gkantsinikoudi, Fabrice Prin, Lia Karina Volpato, Anna Paula Piovezan, Gerard J Graham, Neil Dufton, Mauro Perretti, Federica M Marelli-Berg, Suchita Nadkarni. Circulation Mar. 2023.

3. Cooperative ETS Transcription Factors Enforce Adult Endothelial Cell Physiology and Cardiovascular Homeostasis. Gomez-Salinero J, Itkin T, Badwe C, Lin Y, Houghton S, Kunar B, Birdsey G, Kalna V, Dufton N, Peghaire C, Yokoyama M, Wingo M, Li G, Xiang JZ, Hsu Y, Redmond D, Schreiner R, Randi AM, Rafii S. Nature CVR. Oct 2022.

4. Novel application of live imaging to determine the functional cell biology of Endothelial-to-mesenchymal transition (EndMT) within a Liver-on-a-chip platform. J Whiteford, S Arokiasamy, CL Thompson and NP Dufton*. In Vitro Models Sept. 2022.

5. Dynamic regulation of canonical TGFß signalling by endothelial transcription factor ERG protects from liver fibrogenesis. Dufton N, Peghaire C, Osuna-Almagro L, Raimondi C, Kalna V, Chuahan A, Webb G, Yang Y, Birdsey G, Lalor P, Mason J, Adams D and Randi AM – Nature Communications Oct. 2017.