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Generation of Vascular Smooth Muscle Subtypes

A team led by Dr. Sanjay Sinha has generated origin-specific vascular smooth muscle cells from both human embryonic stem cells and induced pluripotent stem cells.

Key features:

- High quality lineage-specific human cells generated in vivo using chemically defined media for consistency of cell production.
- Highly efficient derivation of almost pure (> 90%), mature & contractile SMC population with no sorting or complex manipulation required pluripotent stem cell origin ensures a consistent and unlimited supply of genetically identical SMC

Potential uses:

- High throughput drug screening for therapeutic and preventive strategies
- 'Disease in a dish' enables investigation of mode of action of drugs
- Bio-engineering of vascular grafts for regenerative medicine

For further information please contact:

Dr Terry Parlett
✉ terry.parlett@enterprise.cam.ac.uk
☎ +44 (0)1223 760337

Cambridge Enterprise Limited, University of Cambridge
The Hauser Forum, 3 Charles Babbage Road, Cambridge CB3 0GT UK
www.enterprise.cam.ac.uk

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Background

Vascular smooth muscle cells (SMCs) and pericytes are the principal cellular components in the walls of larger vessels and capillary beds. They stabilize nascent vessels and are indispensable for the development of a mature and durable vasculature. They are involved in a range of vascular disease including atherosclerosis and aneurysm. Lineage tracking studies have shown that vascular SMCs in different vessels and vascular territories have distinct embryological origins. The diversity of SMC origins may contribute to a number of vascular diseases The current state of the art for derivation of SMCs from human embryonic or induced pluripotent stem cells (hESCs or iPSCs) requires serum and does not encompass the concept of generating SMCs using a lineage-specific approach.

Technology

Here we report a novel chemically defined stepwise method for generating origin-specific SMCs from hESCs and iPSCs via three intermediate lineages – neuroectoderm, lateral plate mesoderm and paraxial mesoderm. Flow cytometric analysis demonstrated that the vascular SMC subtypes could be derived with high efficiency (> 80% $MYH11^+$ and $ACTA2^+$) from all three intermediate lineages (Cheung et al Nature Biotech 2012:30:165-73).

Immunocytochemistry also showed extensive staining for SMC markers (Cheung et al Nature Biotech 2012:30:165-73). In addition, we have shown that the derived SMCs possess contractile function (Figure 1) and participate in blood vessel formation *in vivo* (Figure 2). The derived SMC subtypes are able to recapitulate the unique proliferative and secretory responses to cytokines previously documented in studies using aortic SMCs of distinct origins. We also used this *in vitro* system to predict the responses of different SMC subtypes to an inflammatory mediator, and validated the results using rat aortic SMCs of distinct origins. The findings reveal that origin-specific SMCs exhibit differential activation of matrix metalloproteinases and tissue inhibitor of metalloproteinase. Hence, our SMC subtypes could potentially be used to study origin-dependent disease susceptibility, the mode of action of drugs in vascular diseases and also serve as a source of therapeutic cells for vascular regenerative medicine.

Key advantages of this system include a human relevant system, robust production of unlimited amounts of genetically consistent SMC and scalability for high throughput formats. In addition, SMC generated from patient-derived iPSC could be used for personalised medicine.

References

Christine Cheung et al. (2012) Generation of human vascular smooth muscle subtypes provides insight into embryological origin-dependent disease susceptibility.

Commercialisation

We are seeking a commercial partner for licensing, collaboration and development of this technology, protected by patent application PCT/GB2012/051334

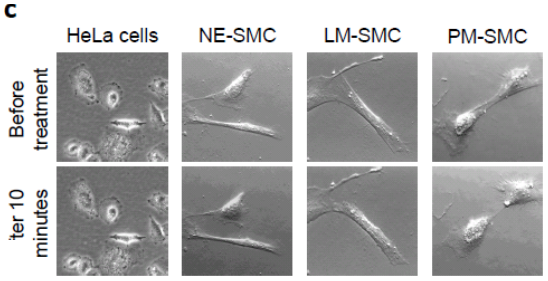

Figure 1. *In vitro* functional characterization: SMC subtypes display contractile ability in response to carbachol treatment. There was a 10-20% change of surface area in contracting cells. NE: neuroectoderm-derived; LM: lateral mesoderm-derived; PM: paraxial mesoderm-derived. HeLa cells: negative controls.

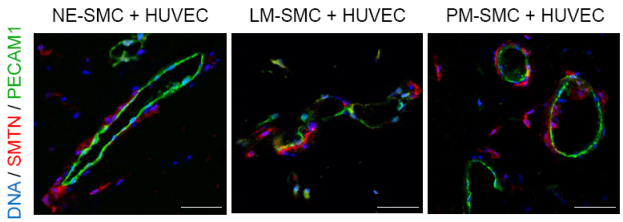

Figure 2. *In vivo* functional characterization. Matrigel plugs embedded with SMCs and HUVECs were implanted subcutaneously into immunodeficient mice. Two weeks later, plugs were harvested and histological sections were immunostained. Luminal structures made up of HUVECs (green) were observed; SMCs (red) were recruited to occupy peri-endothelial region, reminiscent of their biological niche.