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FSTL3 enhances the function of endothelial cells derived from ips cells by facilitating b-catenin nuclear translocation through inhibition of gsk3b activity

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Topic(s):
Basic Science - Vascular Diseases: Gene Therapy, Cell Therapy

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S51

Funding Acknowledgements:
BBSRC, BHF

The fight against vascular disease requires functional endothelial cells (ECs) which could be provided by differentiation of induced Pluripotent Stem Cells (iPS Cells) in great numbers for use in the clinic. However, the great promise of the generated ECs (iPS-ECs) in therapy is often restricted due to the challenge in iPS-ECs preserving their phenotype and function. We identified that Follistatin-Like 3 (FSTL3) is highly expressed in iPS-ECs, and, as such, we sought to clarify its possible role in retaining and improving iPS-ECs function and phenotype, which are crucial in increasing the cells’ potential as a therapeutic tool.

We overexpressed FSTL3 in iPS-ECs and found that FSTL3 could induce and enhance endothelial features by facilitating β-catenin nuclear translocation through inhibition of GSK3β activity and induction of endothelin-1. The angiogenic potential of FSTL3 was also confirmed both in vitro and in vivo. When iPS-ECs overexpressing FSTL3 were subcutaneously injected in mice or implanted into ischemic mouse hindlimbs, they were shown to induce significant angiogenesis and recovery from ischemia by regenerating vasculature and blood flow, respectively.

This study, for the first time, demonstrates that FSTL3 can greatly enhance the function and maturity of iPS-ECs. It advances our understanding of iPS-ECs and identifies a novel pathway that can be applied in cell therapy. This novel differentiation approach could therefore help improve efficiency and generation of therapeutically relevant numbers of ECs for use in patient-specific cell-based therapies. In addition, it can be particularly useful towards the treatment of vascular diseases instigated by EC dysfunction.