Therapeutic angiogenesis induced by human umbilical cord tissue-derived mesenchymal stromal cells in a murine model of hindlimb ischemia

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Abstract

Background

Mesenchymal stem cells derived from human umbilical cord tissue, termed UCX®, have the potential to promote a full range of events leading to tissue regeneration and homeostasis. The main goal of this work was to investigate UCX® action in experimentally induced hindlimb ischemia (HLI).

Methods

UCX®, obtained by using a proprietary technology developed by ECBio (Amadora, Portugal), were delivered via intramuscular injection to C57BL/6 females after unilateral HLI induction. Perfusion recovery, capillary and collateral density increase were evaluated by laser doppler, CD31 immunohistochemistry and diaphonisation, respectively. The activation state of endothelial cells (ECs) was analysed after EC isolation by laser capture microdissection microscopy followed by RNA extraction, cDNA synthesis and quantitative RT-PCR analysis. The UCX®-conditioned medium was analysed on Gallios flow cytometer. The capacity of UCX® in promoting tubulogenesis and EC migration was assessed by matrigel tubule formation and wound-healing assay, respectively.

Results

We demonstrated that UCX® enhance angiogenesis in vitro via a paracrine effect. Importantly, after HLI induction, UCX® improve blood perfusion by stimulating angiogenesis and arteriogenesis. This is achieved through a new mechanism in which durable and simultaneous upregulation of transforming growth factor β2, angiopoietin 2, fibroblast growth factor 2, and hepatocyte growth factor, in endothelial cells is induced by UCX®.

Conclusions

In conclusion, our data demonstrate that UCX® improve the angiogenic potency of endothelial cells in the murine ischemic limb suggesting the potential of UCX® as a new therapeutic tool for critical limb ischemia.

Keywords:

UCX®, Mesenchymal stem cells, Angiogenesis, Arteriogenesis, Critical limb ischemia, Endothelial cells, Hindlimb ischemia