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Cover story

Engineered cell/matrix platform for hypoxia-induced angiogenesis

The importance of angiogenesis, the process of growing a new network of blood vessels, has been well recognized. Stimulating angiogenesis is of paramount importance in various biological processes, e.g., therapeutic vascularization of ischemic tissues, as well as utilization of engineered tissues of clinically relevant dimensions. Indeed, delayed or inadequate vascularization is one of the major factors leading to tissue infarction and poor graft survival. While previous research has primarily focused on delivering single (or a few) growth factors (at the gene or protein level), these strategies have proven ineffective or hard to control in practice. It would be therefore more clinically useful and effective to use engineered implants that behave similarly to biological tissues in stimulating angiogenesis.

Recently, Hadjipanayi and colleagues described an approach for stimulating physiological angiogenic factor cascades by engineering local cell-hypoxia within a nano-fibrillar collagen material [1]. The rational of this approach is based on the fact that the full sequence of signals leading to new blood vessel formation, under physiological (e.g., embryogenesis) or pathological (e.g., carcinogenesis) conditions, is a response to tissue hypoxia through upregulation of angiogenic factor cascades. For this reason, the authors had hypothesized that controlled initiation of this mechanism for therapeutic/engineered angiogenesis must rely on precisely localized hypoxia. Cell-mediated hypoxia was engineered using human dermal fibroblasts, to generate local populations of Hypoxia-Induced Signaling (HIS) cells. Such HIS cell depots essentially acted as self-regulating factory units, releasing angiogenic factor proteins which induced directional endothelial cell (EC) migration and tubule formation in a spatially defined assay system. Furthermore, depots of HIS cells that were positioned in the core of 3D collagen construct directed host vessel in-growth deep into subcutaneous implants by 1 week, which was accompanied by improved deep implant oxygenation. The findings of this first study established the angiogenic potential of HIS cells, applicable to in vitro tissue modeling and implant vascularization. Utilization of this approach for development of predictable angiogenic therapies, however, presented certain limitations. Its reliance on implanting living cells into a target tissue meant that precisely controlling the levels of factors delivered, and the extent of resulting angiogenesis, would be difficult (if not impossible), due to the unpredictability of cell behavior/survival in vivo. The limited long term stability of living cell depots, as well as safety considerations relating to implantation of living cells, represented additional obstacles for immediate clinical translation of this strategy to the bedside. These concerns led the authors to focus their efforts on engineering an implantable device for on-demand delivery of hypoxia-induced angiogenic signaling, without the need to implant living cells.

In the study by the same group published in this issue [2] the authors used the identical basic strategy, namely pre-conditioning human dermal fibroblast-seeded dense-collagen depots under cell-generated physiological hypoxia, in order to up-regulate production of key angiogenic factors, but hypothesized that angiogenic factor proteins would be retained within the nano-porous collagen matrix, after cells were killed by freezing the depots. The authors showed that angiogenic factor delivery from hypoxia pre-conditioned, non-viable depots rapidly induced an angiogenic response within endothelial cell-seeded constructs in vitro. In vivo study showed that implanted acellular 3D constructs incorporating such angiogenic depots in their core were infiltrated with perfused vessels by 1 week. The depot-free control implants were minimally perfused during the same time period. The findings of this study highlight for the first time the feasibility of making hypoxia-induced angiogenesis a device-based reality. Depending on the application, engineered implants of different sizes/shapes and angiogenic factor composition/concentration can be prepared. Such non-viable, stable angiogenic depots, of tunable cell/matrix composition, could provide a new platform for developing cost effective, engineered angiogenic therapies to improve local tissue perfusion.

References

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