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The concept of *in vivo* airway tissue engineering

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ABSTRACT

We investigated whether decellularized pig tracheas could regenerate *in vivo*, without being recellularized before transplantation, using the own body as bioreactor. Decellularized pig tracheal scaffolds were intraoperative conditioned with mononuclear cells and growth and differentiation factors. During the postoperative period, the in situ regeneration was boosted by administering bioactive molecules to promote peripheral mobilization and differentiation of stem/progenitor cells and ultimately the regenerative process. Results revealed, after 2 weeks, a nearly normal trachea, with respiratory epithelium and a double-banded cartilage but without any mechanical differences compared to the native tissue. The growth factor administration resulted in a mobilization of progenitor and stem cells into the peripheral circulation and in an up-regulation of anti-apoptotic genes. Isolated stem/progenitor cells could be differentiated *in vitro* into several cell types, proving their multipotency. We provide evidence that the own body can be used as bioreactor to promote *in vivo* tissue engineering replacement. Moreover, we demonstrated the beneficial effect of additional pharmaceutical intervention for an improved engraftment of the transplant.

1. Introduction

Although the vast majority of benign and malignant diseases of the trachea can be surgically cured, a safe and conventional surgical reconstruction is not always possible and these patients are treated with palliation alone [1]. Airway tissue engineering has proven its capability to repair tracheal defects of extensive length (>6 cm) in animals and in humans [2,3], by using decellularized natural scaffolds reseeded with stem cell-derived chondrocytes and respiratory cells *via* a bioreactor. This approach generates scaffolds that maintain their extracellular matrix (ECM), induce *in vivo* neoangiogenesis, and provide epithelial cell engraftment. Equally important, decellularized tracheal scaffolds have almost all characteristics of a native trachea, such as longitudinal flexibility, lateral rigidity, non-immunogenicity, air- and liquid tightness, biocompatibility, and least but not last, are resistant to bacterial colonization [3–6]. Although this regenerative approach outrivals previously published methods [7,8], it also requires extensive GMP laboratory facilities, *in vitro* cell culture and manipulation, specific manpower and know-how, and high costs which significantly limit its clinical translation worldwide.

To bypass this hurdles, and based on our initial reverse translational experience [9] we developed a new concept, the combined *in vivo* and in situ tissue engineering, which has passed the preclinical stage in a number of tissues such as skin and bone regeneration and is currently being evaluated in a human multicenter clinical trial [10]. This concept bases on the use of the own body as a natural bioreactor at a normotopic in situ positioning of the transplant. This reduces contamination risks, significantly shortens the processing time and costs, and combines the peritransplantation administration of bioactive molecules [11] to (*e.g.* granulocyte-colony stimulating factor) mobilize mesenchymal and

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