Functional porous hydrogels to study angiogenesis under the effect of controlled release of vascular endothelial growth factor

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1. Introduction

Recovering the physiological functions of degenerated or injured tissues is one of the most critical aspects in tissue engineering and regenerative medicine [1,2]. Vascular integration between the implant and the surrounding tissues is key to achieving this goal. This requires the rapid formation of new capillaries to supply oxygen and the necessary nutrients and to remove waste products from cells [3,4]. In this field angiogenesis, i.e. blood vessel formation from pre-existing ones, plays a pivotal role. It is a very complex phenomenon which is regulated by several biochemical and biophysical factors. Several issues must be addressed in the promotion of angiogenesis in biological matrices such as porous scaffolds and hydrogels. Among these, tight control of the dose and temporal evolution of bioactive signals is fundamental to guide and direct proper cell functions [5]. In particular, for functional angiogenesis pore dimension and the spatial arrangement of bioactive molecules within the matrix play a critical role in blood vessel formation in vitro and vessel invasion in vivo. It is known that the minimum porosity required to regenerate blood vessel is generally considered to be 30–40 μm [6], in order to enable the transport of metabolic components and the induction of endothelial cell invasion. Furthermore, signals presented by the extracellular matrix (ECM), such as soluble macromolecules (e.g. growth factors (GF), chemokines, and cytokines) and insoluble factors (e.g. ECM proteins, glycoaminoglycans, and proteoglycans), also play a major role in tissue regeneration. Accordingly, angiogenic processes are guided by various growth factors whose spatial and temporal presentation is strictly regulated by various ECM components. For example, heparin molecules are known to bind various angiogenic growth factors, such as for vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor beta (TGFβ), through non-covalent and reversible interactions [7]. Such an interplay brings two major benefits: first, bound GFs are less prone to degradation; second, the spatial arrangement of heparin molecules and their binding affinity for GFs provides cells with directional and temporal cues which guide and direct the process of new vessel formation. Cells are very sensitive to both the local concentration of VEGF and to the way it is delivered. High doses of VEGF elicit an evident tissue response, but generally lead to dysfunctional growth. Indeed, undesired...