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Cover story

Vascularization in 3D bioprinted scaffolds

Vascularization of tissue-engineered constructs is one of the most important challenges in regenerative medicine. Without sufficient blood supply, oxygen and metabolic needs are not met, which can lead to the central necrosis of constructs. The scaffold size may be limited by the diffusion distance that nutrients can travel in the used material, and such distance may be only several cell layers thick. A possible solution to this problem could be to induce pre-vascularization in the implanted construct so that an efficient vascularization process can be stimulated. Grafts with new blood vessels that can connect to the host vasculature are likely to enhance the quantity and quality of newly formed tissues.

Many research groups have investigated strategies to enhance the pre-vascularization of tissue engineered constructs. A viable option is to provide the construct with (pre)vasculogenic cells or factors. Late outgrowth endothelial progenitor cells (EPCs), also known as endothelial colony forming cells (ECFCs), are suitable to pre-vascularize tissue engineered constructs. EPCs have a high capacity for proliferation and vessel formation in vitro and in vivo. Vascular endothelial growth factor (VEGF) is a potent angiogenic and vasculogenic growth factor that is a key regulator of physiological vessel formation. VEGF degrades rapidly in the blood with a half-life of less than an hour, making its tissue engineering application difficult. To alleviate this problem, a number of delivery systems have been developed for the sustained release of VEGF over an expanded period of time for days. Gelatin is one of the widely used natural polymers for sustained delivery of bioactive proteins from microparticle formulations. Gelatin in the form of microparticles [1] or gels [2] has been frequently used to deliver various growth factors. Gelatin microparticles (GMPs) allow the incorporation of growth factors by diffusional loading, thereby preventing potentially harmful chemical reactions. GMPs can be easily incorporated into hydrogel plugs or 3D bioprinted constructs. This technology enables the production of a new generation of scaffolds with a predefined architecture and predefined regions of pre-vascularization in the scaffold. The 3D bioprinting also allows the introduction of predefined scaffold porosity, which appears to improve the in vivo performance by lowering the diffusion distance for oxygen and nutrients [3].

The study by Professor Jacqueline Alblas and her group in this issue describes the unique convergence of 3D bioprinting and controlled release technologies for tissue engineering applications [4]. The Alblas team selected VEGF-loaded GMPs based on their release profile and biological activity when incorporated in Matrigel. Mixtures of different ratios of Matrigel and alginate were tested for their printability as well as for the vasculogenic ability of the incorporated EPCs. The 3D printed constructs contained two regions, an empty control region and a region containing the slow release GMPs loaded with VEGF. After implantation in vivo, it was noted that the porous bioprinted constructs degraded faster than the Matrigel plugs. Quantification of the blood perfused vessels revealed that slow release of VEGF led to a significant increase in vessel formation when compared with fast release of VEGF, or the control group without growth factor. In the 3D bioprinted scaffolds, the two distinct regions could still be discriminated after explantation. The control regions (without GMP or VEGF) contained hardly any vessels, while the regions with slowly released VEGF produced more vessel formation. The study clearly demonstrated the advantage of controlled release over bolus injection in forming blood vessels. The bioprinted constructs also showed that the predefined localization of VEGF for prolonged release was feasible and effective.

It is also important to consider the maturation of the vessels by pericyte contact to establish long-term stability. VEGF is known to negatively regulate pericytes, but the application of a finite amount of VEGF is expected to allow the return of pericytes to the pre-vascularized region for a stable vascular network. Recent progress in 3D printing technology allows the fabrication of tissue engineering constructs in almost all shapes and densities. The work by the Alblas team on 3D bioprinting based on mixtures of Matrigel and alginate permits the generation of constructs with regional differences in the type and concentrations of bioactive molecules. This, in turn, allows the development of new tissue engineering scaffolds with a high degree of biomimicry. This study has made one step forward in fulfilling our dream of producing tissue engineered organs that can be used clinically.

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