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Review

The potential role of telocytes in Tissue Engineering and Regenerative Medicine

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ABSTRACT

Research and ideas for potential applications in the field of Tissue Engineering (TE) and Regenerative Medicine (RM) have been constantly increasing over recent years, basically driven by the fundamental human dream of repairing and regenerating lost tissue and organ functions. The basic idea of TE is to combine cells with putative stem cell properties with extracellular matrix components, growth factors and supporting matrices to achieve independently growing tissue. As a side effect, in the past years, more insights have been gained into cell–cell interaction and how to manipulate cell behavior. However, to date the ideal cell source has still to be found. Apart from commonly known various stem cell sources, telocytes (TC) have recently attracted increasing attention because they might play a potential role for TE and RM. It becomes increasingly evident that TC provide a regenerative potential and act in cellular communication through their network-forming telopodes. While TE in vitro experiments can be the first step, the key for elucidating their regenerative role will be the investigation of the interaction of TC with the surrounding tissue. For later clinical applications further steps have to include an upscaling process of vascularization of engineered tissue. Arteriovenous loop models to vascularize such constructs provide an ideal platform for preclinical testing of future therapeutic concepts in RM. The following review article should give an overview of what is known so far about the potential role of TC in TE and RM.

Contents

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1. Tissue Engineering and Regenerative Medicine

Regenerative Medicine (RM) is an interdisciplinary field of research and clinical application focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and aging [1]. It uses a combination of several technological approaches that transforms it beyond traditional transplantation and replacement therapies. These approaches may include the use of soluble molecules, stem and progenitor cell therapy, Tissue Engineering (TE) and the reprogramming of cell and tissue types using gene therapy [2].

The concept of RM however, has its roots deep in the ancient world. Since prehistoric times, mankind has been searching for regeneration and immortality. The myth of Prometheus, who stole the fire – a symbol of civilization and technology – from Mount Olympus and gave it to mankind [3], is often regarded as symbolic of RM. As a punishment, Hephaistos chained him to the Caucasian Mountains, where an eagle send by Zeus tearing at his liver every day. His liver regenerate every day until he was released by Hercules who killed the eagle and unchained him [3]. Thus, the Ancient Greeks were obviously aware of the regenerating capacity of the liver, hence they named it 'hepar', meaning to "repair oneself". Since prehistoric times, mankind has been searching for regeneration and immortality. The dream to master regeneration is one primordial ambition like flying or communicating over distances. Man cannot rest until he has reached that goal [4].

The term "Tissue Engineering" was officially appointed for the whole field in 1987 and the whole area of TE was excited by the progress in skin cell culture propagations in the 1980s and 1990s, fostered by publications on "living skin equivalents" [5]. Years later, the idea came about to construct custom-made scaffolds for cell loading in an effort to overcome organ shortage for transplantation. The first conference on the "Engineering of Living Tissue" was held in 1988 in California, where a definition for the new field was given: "Tissue Engineering is the application of the principles and methods of engineering and the life sciences toward the fundamental understanding of structure/function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve functions" [6].

Two years later, when the BBC broadcast images around the world of a mouse from Charles Vacanti's laboratory with a tissue-engineered ear 'growing' on its back, this aroused huge public interest in new biotechnological advances [4]. However, despite fundamental efforts and progress in standardizing cell culture techniques and developing customized biomaterials to substitute for lost organ functions, the initial enthusiastic prospect of soon being able to grow individual replacement parts and organs in the laboratory was hampered by numerous obstacles. The translation of laboratory achievements into clinical scenarios has thus far not proved successful. This is partly due to the three-dimensional structure of organs and tissue that necessitates a microvascular network to allow for sufficient blood flow and oxygenation of cells to keep them viable, even in the middle of any given construct [7,8].

2. Basic Tissue Engineering concepts and techniques

Tissue Engineering may well be regarded as a truly interdisciplinary field that aims to overcome disadvantages of existing therapeutic concepts, by developing strategies for tissue replacement based on the combination of scaffolds, cells and growth factors. It therefore definitely represents an important research field due to the great demand for optimization of treatment strategies of tissue defects and the limited current treatment options for many diseases [8,9] (Fig. 1).

Basically TE approaches often start with an *in vitro* step, in which cell isolates are expanded or differentiated and, in the next step, are seeded on scaffolds and implanted, e.g., in combination with growth factors *in vivo* [10,11]. Particularly in the generation and implantation of large tissue-engineered constructs in clinically relevant size, there is still the problem of a sufficient blood supply. This lack represents a serious obstacle for successful clinical application. Immediately after transplantation, the supply of cells with oxygen, nutrients, and the removal of carbon dioxide and metabolites will occur only by diffusion from the environment until an adequate vascular network has formed. Mainly in large volume constructs and in poorly vascularized recipient beds, insufficient vascularization is considered as the main limiting factor for survival and integration of the tissue-engineered construct into the defect [12]. The survival of the implanted cells depends on the local vascularization network, as well as on the period of time in which a functional vascular supply can be developed. Centrally located areas in particular are often not adequately supplied with oxygen and nutrients [11,13].

Two fundamentally different types of vascular networks can be discerned (Fig. 2):

(a) In subcutaneous scaffold implantations, blood vessels from the surrounding tissue penetrate into the implanted construct, spreading from the periphery toward the center (*extrinsic vascularization*). With the explantation of an extrinsically vascularized construct, it will suddenly be cut off from the blood supply. The high number of small supplying vessels cannot be connected to the local vascular system in the defect site. Consequently, the construct will no longer be adequately supplied with blood.
(b) In contrast, the existence of a defined vascular axis within the construct (e.g., an arteriovenous (AV) loop), from which small vessels can sprout out from the center to the periphery, is called *intrinsic axial vascularization*. If this axially vascularized construct is separated and transplanted microsurgically to a defect site, it can immediately be connected to the local blood supply by microvascular anastomosis, so its blood supply will be independent of local conditions at the recipient site [13,14].

Based on this finding, Erol and Sira developed a method in the animal model of the rat that describes the induction of an intrinsic axial vascularization from a microsurgically generated arteriovenous shunt [15]. This model was later refined by others by implantation of an AV loop into an isolation chamber. It was shown that intrinsic, axially vascularized fibrous tissue can thus be generated [16,17]. So far, only axially vascularized tissue of a maximum of 1 ccm could be generated in various small animal models. In recent years, the AV loop model has been modified and upscaled to a large animal by our research group in order to evaluate the vascularization properties of large volume constructs and to generate axially vascularized tissue in clinically relevant dimensions [18]. *De novo* formation of axially vascularized tissue could previously be demonstrated in the sheep model [19]. A β-tricalcium phosphate/hydroxyapatite (β-TCP/HA) bone matrix and clinically approved processed bovine cancellous bone could be fully vascularized with newly formed capillaries arising from the AV loop [20,21]. To engineer independently axially vascularized bone tissue in the sheep AV loop model, mesenchymal stem cells (MSC) without and with recombinant human bone morphogenetic protein-2 (rhBMP-2) were harvested and directly auto-transplanted in the sheep, in combination with β-TCP/HA granules. Twelve weeks after explantation, histological and immunohistochemical evaluation revealed newly formed bone in both groups. An increased amount of bone area was obtained, using directly auto-transplanted MSC with rhBMP-2 stimulation. Osteoblastic and osteoclastic cells were