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A Review of Researches on Preneuralized TEBG

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ABSTRACT

Tissue Engineering Bone Graft (TEBG) provides an ideal way to repair large bone defect, with the blood supply and innervation become the two constraints of tissue engineering bone development. In recent years, neurobiology has attracted more and more attention. The nerves, especially the sensory nerves, have a positive effect in bone reconstruction and bone repair. It is promising to add nerves in TEBG. This article reviews the researches on the construction of preneuralized TEBG and on mechanisms of preneuralized TEBG promoting bone defect repair.

Keywords: Preneuralized TEBG; Bone Repair

Introduction

Large bone defects caused by trauma, infection, tumor resection have brought huge economic pressure to society [1]. Tissue Engineered Bone Graft (TEBG) and regenerative medicine provide an ideal tool for the treatment of bone defects. However, in the development of TEBG, it is restricted by the two factors of blood supply and innervation [2], which is reflected in the fact that when the bone defect reaches a critical size, the blood supply and nerve growth cannot reach the central area of the tissue engineering bone, which directly leads to the failure of TEBG. Many studies have focused on vascularized tissue engineered bone but have not been successfully applied in clinics due to many defects [3].

Sensory nerves and their secreted neuropeptides play an important role in bone repair [4]. Bone repair is impaired after capsaicin selectively damage unmyelinated sensory neurons [5]. It is feasible to apply peripheral nerves to tissue engineering. Kang HW et al. embedded the common peroneal nerve into tissue engineering muscles and found that nerve implantation can effectively promote integration of the constructs [6]. Based on the above researches, Pei GX .et al propose the concept of preneuralized tissue engineered bone (Preneuratized TEBG), implanted sensory nerves into TEBG to repair large bone defects, and found that sensory nerves can effectively promote bone defect repair [7]. This article reviews the advances in preneuralized TEBG research.

Construction of Preneuralized TEBG

Preparation of TEBG: Bone Marrow Stem Cells (BMSC) were obtained and cultured to P3 generation. Using β-TCP as a scaffold material, the scaffold has a porous structure with side grooves on one side, a porosity of 65%, and a pore diameter of 400 μm. The sterile scaffold was soaked in PBS for 1 day before use and soaked in serum-free medium for 1 day. Subsequently, the P3 generation BMSC was compounded with the scaffold, and the TEBG was obtained.

Preneuralized TEBG Repair Large Bone Defect: The experimental animals were anesthetized and prepared for skin disinfection. Fix the prone position on the operating table and expose the outside of the thigh. An incision is made above the knee joint along the longitudinal axis of the femur. The muscles are bluntly separated, and the femur is fully exposed. The inner fixed plate was placed on the outer side of the middle part of the femur, the position of the bone defect was marked, the steel plate was removed, and a bone defect was made along the marked position.

Incision was made on the medial inguinal region, the saphenous nerve and femoral vein bundle were exposed, the blood vessel was removed to obtain a complete saphenous nerve, the saphenous nerve was disconnected, and introduced into the lateral groove through the muscle space into the TEBG, and then the TEBG was inserted into the bone defect, and the muscle was wrapped and fixed. The model is completed.

Preneuralized TEBG Promotes Bone Repair

Sensory nerves promote the repair of large bone defects in TEBG, which is manifested in the increase of blood vessel formation, nerve ingrowth and new bone formation, and the accelerated degradation of materials.

New Bone Formation and Material Degradation: Jiang Y et al. [8] evaluated material degradation and new bone formation by X-ray. It was found that at 8 weeks after surgery, the scaffold degradation of the preneuralized TEBG group was faster than that of the control group, and more scaffold were integrated with the osteotomy end in the preneuralized TEBG group; 12 weeks after surgery, the scaffold degradation was still faster in preneuralized TEBG group than the control group, and the new bone formation was significantly increased with the sensory nerve implantation.

Angiogenesis: In the absence of blood, the distance between cells to maintain survival and nutrient diffusion is 100-200 μm [9], so blood supply is extremely important in tissue engineering products. Fan Junjun et al. [10] used ink perfusion to observe the formation of new blood vessels. It was found that 12 weeks after surgery, the angiogenesis was increased in preneuralized TEBG group than that of the control group, and the blood vessel morphology was intact and more mature than the control group.

Nerve Ingrowth: During the healing process of bone graft repair bone defect, nerve growth in the graft is important for bone to complete the bone creep replacement healing process. Wu Y et al. observed the growth of nerve fibers by injection of fluorescent nerve tracer (Dil) [11]. It was found that 4 weeks after surgery, the pre-implanted sensory nerves were observed to grow into the pores of the scaffold. The sensory nerves were labeled with CGRP, and the protein GAP43 expressed during nerve repair was detected, too. It was found that the expression of CGRP and GAP43 in the preneuralized TEBG group was increased than that of the control group at 4/8/12 weeks after surgery.

The Mechanism of Sensory Nerves Promoting Bone Defect Repair

Sensory Nerve Secreted Neuropeptides on Bone Repair

After sensory nerve implantation, the neuropeptides CGRP, NPY [12], SP [13] and its receptors CGRP1R, NPY1R [11] increased in TEBG. Increased neuropeptides have a regulation on bone cells. For example, SP can promote osteogenic differentiation and hemangioblastic differentiation of BMSCs, thereby promoting new bone formation [14].

Sensory Nerves Maintain BMSC Stemness

The role of the saphenous nerve implanted in preneuratized TEBG may be due to sensory axons or Schwann cells surrounding the axons. Zhang Shuaishuai et al. co-cultured sensory neurons and BMSC [15] in vitro, and found that sensory nerves maintain the stemness of BMSCs by secreting SP. This function is achieved by AMPK / mTOR signaling pathway, which enhances the autophagy of BMSCs. Above all, sensory nerves regulate many processes related to bone repair and ultimately promote new bone formation, further indicating the promising application of preneuralized TEBG for bone repair. However, the preneurlized TEBG is still in the stage of animal experiment, and its clinical application needs further researches.

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