Regenerative Medical Therapy for Hard Tissues Based on Tissue Engineering

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Abstract :This paper overviews the present status on therapy of regenerative medicine which is based on tissue engineering. Tissue engineering is a biomedical form which enables cells to promote their proliferation and differentiation, resulting in induction of tissue regeneration. The scaffold of 3-dimensional porous material for cells with or without the controlled release system of growth factor is applied to induce tissue regeneration in vivo. Some data of bone tissue regeneratio are introduced to emphasize significant role of growth factor release technology in the therapy of regenerative medicine bone.

Keywords: tissue engineering, drug delivery system, growth factor, regenerative medical therapy

Basic idea of tissue engineering

When the body tissue or organ is severely injured, largely lost or functionally wrong, it is clinically treated with either reconstruction surgery or organ transplantation at present. However, due to the poor biocompatibility of biomaterials and the shortage of donor tissues or organs, their therapeutic limitations have been clinically recognized. In this circumstance, a new therapeutic trial to induce the regeneration repairing of tissues and organs based on the self-healing potential of patients has been initiated. This is the therapy of regenerative medicine.

To realize the third therapy, there are two approaches: cell therapy and tissue engineering. For the cell-based tissue regeneration, cells of high proliferation and differentiation potentials are required to use, and the research of basic medicine and biology has been intensively performed. However, only by supplying the cells to the site to be regenerated, tissue regeneration cannot be always induced. This is because cells generally interact with the surrounding local environment to live and biologically function in the body. Thus, it is necessary for successful tissue regeneration to create an appropriate environment which enables cells to efficiently proliferate and differentiation, inducing tissue regeneration. It is tissue engineering that is a biomedical form to create this environment for regeneration induction.

For tissue engineering, there are four fundamental technologies. The first technology is cell scaffolding. As the local environment to induce in vivo tissue regeneration, temporary scaffolds for cell attachment and the subsequent proliferation and differentiation have been attempted to create by biodegradable biomaterials. Without any therapeutic treatments, a body defect is often filled with the fibrous tissue. Once such tissue filling takes place in the defect, the regeneration or repairing of right tissue thereat can be no longer expected. For example, it is necessary to protect the space for regeneration induction from the undesired tissue ingrowth. For the regeneration of a large-size or unhealthy tissue defect, it is necessary to use the scaffold combining cells and/or growth factor. In addition to obtain a large number of cells with high proliferation and differentiation potentials clinically available, the technology and methodology to efficiently isolate and proliferate the cells should be developed. On the other hand, only the direct injection of growth factor in the solution form into the regeneration site is often not effective, as the growth factor injected is rapidly diffused out from the site or deactivated. To enhance the in vivo efficacy of growth factor, drug delivery system (DDS) which is the technology or methodology for drug administration, is practically available. For instance, by the controlled release of growth factor, it is highly expected that the biological activity is promoted to realize tissue regeneration. Depending on the site where tissue regeneration is expected, there are two approaches of tissue engineering in vitro and in vivo. However, only by the basic knowledge of cell medicine and biology and cell culture technology currently available, it is quite difficult to artificially set up an environment required for in vitro tissue construction. On the contrary, it is highly expected that in the body, most of biological substances necessary for tissue regeneration are automatically supplied by the host living body. Therefore, in vivo tissue engineering has been mainly performed.

Induction of tissue regeneration based on tissue engineering technologies

In case that the tissue surround a defect is healthy and biologically potential for regeneration, tissue regeneration at the defect is induced only by supplying a cell scaffold. The scaffold is often used with cells and/or growth factor to induce tissue regeneration.

To enhance the in vivo biological activity of growth factor, DDS technologies are required and among them, the controlled release of biologically active growth factors have been achieved to realize the regeneration repairing of various tissues and organs (Table 1). For example, the controlled release with gelatin hydrogels enabled bFGF to induce angiogenesis, which is available for the angiogenic therapy of ischemic diseases and the supply of oxygen and neutrients to cells transplanted for cell therapy. Among them, clinical experiments of an angiogenic therapy for ischemic legs have been started in several university hospitals of Japan while the therapeutic result is good. Gelatin hydrogels also augmented the activity of bFGF, TGF-β1, and BMP-2 for bone regeneration and repairing at the bone defects of rats, rabbits, and monkeys. X-ray diffraction studies revealed that the bone tissue regenerated by the growth factor release had complete integrity in bone physiology. As one example, necessity of bone regeneration in the vascular grafting surgery of cardiac infarction. The bilateral sternum artery is normally used because of the high patency.

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However, in spite of successful vascular graft, the repairing of sternum is often delayed, and much worse the infection at the resection area sometimes takes place, while healing of the surrounding soft tissue is also delayed. This is because is blood supply poor to the area of front chest due to surgical elimination of the nutrient artery. As one trial to tackle the incomplete bone and wound healings following the grafting surgery of cardiac infarction, application of the hydrogel incorporating bFGF for the controlled release was effective in inducing bone regeneration as well as angiogenesis. By use of the release hydrogel, BMP-2 regenerated bone in the monkey skull defect even at the dose as low as that of rabbit and rat defects, in marked contrast to BMP-2 in the solution form. This hydrogel system of controlled release not only can release one single growth factor, but also two types of growth factors at the same time or in different time profiles or concentrations. Synergistic effects on the bone regeneration and angiogenesis were achieved by the dual controlled release of bFGF and TGF-b1 and βFGF and HGF, respectively. Combination of growth factor release with stem cell allowed them to enhance their osteogenetic activity.

As tissue engineering is still in infancy, it will take much more time until to come to full blooming. Several research approaches have been tried to design and prepare the scaffold for cell proliferation and differentiation. However, comparing with the scaffolding research, little has been reported on the DDS research aiming at tissue regeneration as well as organ substitution. There are technologies of DDS other than the controlled release which can be applied for growth factor-based tissue engineering: the prolongation of life-time period, absorption improvement, and targeting. The DDS technology is also available to create the non-viral vector for gene transfection. The nonviral vector system will enhance the efficacy of gene therapy, while it facilitates to prepare gene-engineered cells which are indispensable to achieve successful cell therapy for tissue regeneration. Substantial collaborations among different research fields are required to reach scientific and technological maturity in tissue engineering, losing no time in realizing regenerative medical therapy.

Table 1. Our approaches of tissue and organ regeneration based on the controlled release of growth factors from biodegradable hydrogels.

Materials	Growth factor	Animals	Effect	Objective
Acidic gelatin (PI 5.0)	bFGF	Mouse, Rat, and Dog	Angiogenesis	Transplantation of Langerhans islands for diabetes therapy
		Rat	〃	Transplantation of hepatocytes for therapy of enzyme deficiency disease
		Rat	〃	Transplantation of renal epithelial cells
		Rat and Dog	〃	Transplantation of cardiomyocytes
		Rat and Guinea pig	〃	Promoted repairing of skin dermal layer
		Rat and Pig	〃	Treatment of cardiac infarction
		Rabbit	〃	Treatment of lower limb ischemia
		Rat, Dog, and Monkey	Osteogenesis and Angiogenesis	Repairing sternum and connective tissue
		Rat, Rabbit, and Monkey	Osteogenesis	Repairing of skull bone
		Rat, Rabbit, Dog, and Monkey	〃	Repairing of long bone
		Mouse	Adipogenesis	Repairing of breast and soft tissue reconstruction
		Mouse	Angiogenesis and activation of hair follicle tissue	Promotion of hair growth
		Dog	Periodontium repair	Repairing of periodontium
		Dog	Peripheral nerve repair	Nerve repairing
		Dog	Osteogenesis	Repairing of mandiblular bone
	TGF-β1	Rabbit and Monkey	〃	Repairing of skull, long, and mandiblular bone
		Goat	Chondrogenesis	Repairing of tracheal cartilages
	HGF	Mouse	Angiogenesis and activation of hair follicle tissue	Promotion of hair growth
		Rat. Pig	Angiogenesis and inhibition of apoptosis	Treatment of dilated cardiomyopathy
	bFGF/TGF-β1	Rabbit	Osteogenesis	Repairing of skull bone
	CTGF	Rabbit	Chondrogenesis	Repairing of articular cartilage
Basic gelatin (PI 9.0)	BMP-2	Rat, Dog, and Monkey	Osteogenesis	Repairing of skull and mandiblular bone
		Dog	Chondrogenesis	Repairing of tracheal cartilage
Collagen	TGF-β1	Rabbit	Osteogenesis	Repairing of skull bone
	VEGF	Pig	Angiogenesis	Treatment of myocardiac infarction
		Rabbit	〃	Promotion of engraftment of soft tisue grafts
		Rabbit	Osteogenesis	Osteogenesis for spinal fusion
		Mouse	Angionesis and activation of hair follicle tissue	Promotion of hair growth

bFGF:basic fibroblast growth factor TGF-β1: transforming growth factor β1 HGF: hepatocyte growth factor CTGF:connective tissue growth factor
BMP-2:bone morphogenetic protein 2 VEGF:vascular endothelial growth factor