Significance of release technology in tissue engineering

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Regenerative medical therapy has been expected to compensate for the therapeutic disadvantages of reconstructive surgery and organ transplantation, as well as offering a new therapeutic strategy. The objective of regenerative medical therapy is to induce the repair of defective tissues based on the natural healing potential of patients. For successful tissue regeneration, it is indispensable to provide cells with a local environment of artificial extracellular matrix where they can proliferate and differentiate efficiently. Tissue engineering is the key to this regeneration environment; release technology often enhances the *in vivo* stability of growth factors and related genes and prolongs the maintenance of biological functions for tissue regeneration.

Role of tissue engineering in regenerative medicine

The surgical therapies that are currently available consist of reconstruction surgery and organ transplantation. Although there is no doubt that these therapies have saved and improved countless lives, they have some clinical limitations. In the case of reconstruction surgery, biomedical devices cannot completely substitute the biological functions of a single tissue or organ and consequently cannot prevent progressive deterioration of the injured tissue and organ. One of the biggest issues for organ transplantation is the shortage of donor tissues or organs. Additionally, the permanent use of immunosuppressive agents to prevent immunological rejection responses often causes side-effects, such as the high possibility of infection, carcinogenesis and virus infection. Therefore, there are several limitations in these two advanced therapies. To resolve these issues, a new therapeutic solution that is clinically mild to patients is required. In these circumstances, a new therapeutic trial, in which disease healing can be achieved based on the natural healing potential of patients, has been explored. This therapy is termed regenerative medicine, where the regeneration of tissues and organs is naturally induced to therapeutically treat diseases by artificially accelerating the proliferation and differentiation of cells. To realize this, it is necessary to provide cells with a local *in vivo* environment of artificial extracellular matrix that is suitable to their proliferation and differentiation. Tissue engineering is one such biomedical engineering form to build up the environment for regeneration induction. The basic concept of tissue engineering was originally introduced by R. Langer and J. Vacanti [1,2]. Several technologies and methodologies have been reported so far in this field [3–9]. If this concept can be used to induce regeneration of defective or lost tissues, this therapy could be realized on the basis of its cell-mediated natural healing potential. For surgical tissue engineering, biomaterials are applied to a defective body tissue to induce tissue regeneration. By contrast, drugs are applied to digest the fibrous tissue of

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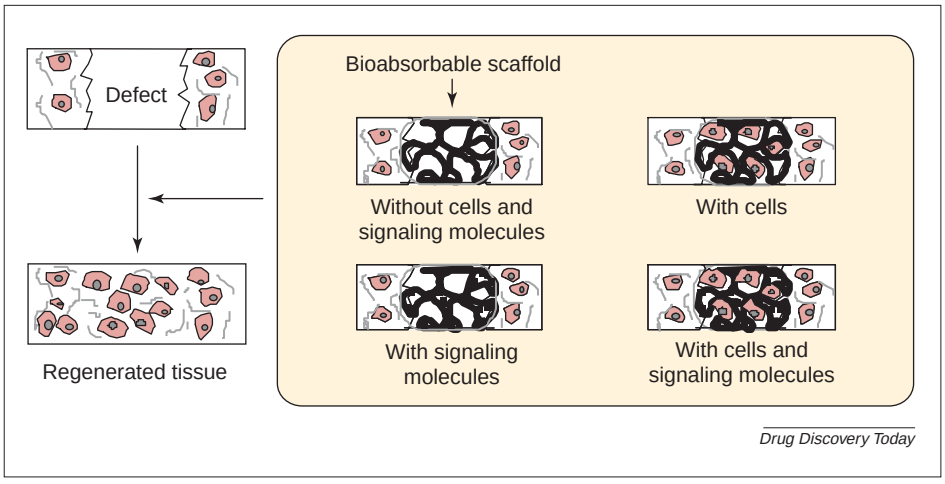

FIGURE 1

The first fundamental technology and methodology with biomaterials for tissue engineering. A 3D scaffold to promote the proliferation and differentiation of cells is prepared from biodegradable biomaterials. The scaffold with or without cells and/or biological signaling molecules (e.g. growth factors, cytokines, chemokines and genes) is applied to a body defect to induce the *in vivo* regeneration of tissues and organs.

chronic diseases, leading to disease therapy based on the regeneration induction potential of the surrounding tissue, defined as 'tissue engineering of internal medicine'.

If regenerative medical therapy is realized, it will enable us to produce new therapeutic methods, as well as increasing the therapeutic choice of clinicians, which consequently brings about large therapeutic benefits for patients who have not received clinically effective therapies. However, this new therapy cannot always substitute conventional clinical therapies, reconstructive surgery and organ transplantation, and has advantages and disadvantages. One of the advantages is the ability to accelerate the natural healing of body injury through promoted angiogenesis or the infiltration and recruitment of key cells at the injured site. This will enable patients to shorten the healing period even under inflammation and infection conditions. Conventional therapy is not always effective in healing wounds of patients who are aged or suffer from other diseases, such as diabetes and hyperlipemia, because the number of key cells is small and the potential for proliferation and differentiation is low. In this case, it is possible that combination with regenerative medicine improves the therapeutic efficacy. A disadvantage of this therapy is that, generally, at least a few days are required to induce cell-based tissue regeneration, therefore, it cannot be expected that regenerative medicine alone will achieve the rapid healing of wounds or diseases.

Fundamental technology and methodology of tissue engineering

There are three key factors that comprise body tissue: (i) cells, (ii) the extracellular matrix (ECM) for cell proliferation and differentiation (natural scaffold) and (iii) growth factors. There are four fundamental technologies or methodologies that are necessary for tissue engineering. The first key technology is the preparation of an artificial scaffold of cells for proliferation and differentiation for tissue regeneration (Figure 1). ECM is not only a physical support for the cells but it also provides a natural environment for cell proliferation and differentiation or morphogenesis, which contributes to tissue regeneration and organogenesis [10]. Generally, it is difficult to naturally regenerate and repair a large-size tissue defect by only supplying cells to the defective site because, in addition to the cells, the ECM is also lost. Therefore, to induce tissue regeneration at the defective site, one way is to artificially build an environment for cells that can induce tissue regeneration by providing a scaffold of artificial ECM, which initially assists cell attachment and subsequent proliferation and differentiation. It is expected that cells residing around the scaffold infiltrate the scaffold and proliferate and differentiate therein if the artificial ECM is biologically compatible.

When the tissue around the defect does not have the inherent potential to regenerate, tissue regeneration cannot always be expected if only the scaffold is supplied. The scaffold should be used in combination with cells and/or signaling molecules (e.g. growth factors, cytokines, chemokines and genes) that have the potential to accelerate tissue regeneration. Cells with a high potential for proliferation and differentiation are prepared and applied to a tissue defect to induce tissue regeneration therein. Although there are cases where growth factor is required to promote tissue regeneration, the direct injection of growth factor in solution into the site to be regenerated is generally not effective because the growth factor rapidly diffuses from the injected site and is enzymatically digested or deactivated. To enable the growth factor to exert its biological function efficiently, a new technology is required.

This comes in the form of the second key technology of tissue engineering – the drug delivery system (DDS) (Figure 2). Although every technology is available for tissue engineering, so far only the release technology has been applied to growth factors and genes for the induction of tissue regeneration. For example, the controlled release of growth factor at the site of action over an extended period of time is achieved by incorporating that factor into an appropriate carrier. It is also possible that the growth factor is protected against proteolysis when incorporated in the release carrier, for prolonged retention of activity *in vivo*. The release carrier should be degraded in the body because it is not required after the growth factor is released. In addition to controlled release, the DDS includes stabilization and prolongation of half-life, acceleration of absorption and targeting.

Over time, DDS has been improved as a technology to enhance the *in vivo* efficacy of therapeutic drugs. Therefore,

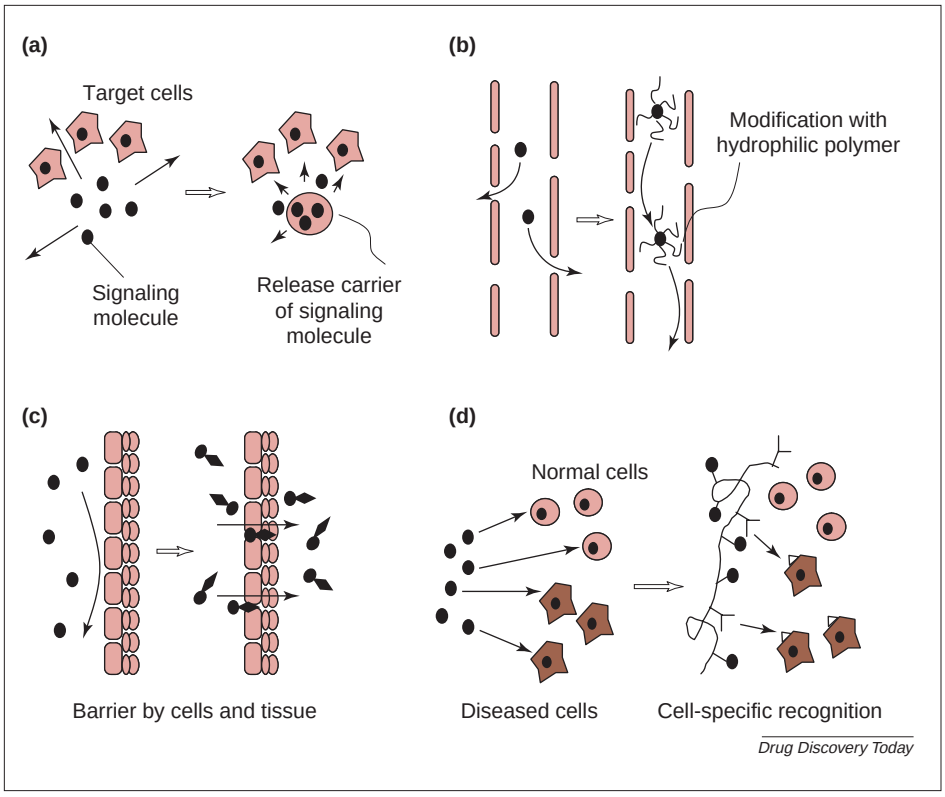

FIGURE 2

The second fundamental technology and methodology with biomaterials for tissue engineering. A drug delivery system (DDS) is a technology that enables biological signaling molecules to enhance *in vivo* therapeutic efficacy by combination with biomaterials. All four DDS objectives, **(a)** controlled release, **(b)** stabilization and life-time prolongation, **(c)** absorption acceleration and **(d)** targeting, are applicable for the regeneration of tissues and organs, which is induced by signaling molecules with *in vivo* instability.

few researchers have applied this DDS to the field of regenerative medicine. Drugs for regenerative medicine include proteins and genes that are effective in promoting the proliferation and differentiation of cells for the induction of tissue and organ regeneration. Biological signaling molecules are generally unstable *in vivo*, therefore, it is necessary to administer them to enhance their *in vivo* biological activity. DDS is a promising technology for this purpose but, as always, each technology has its own advantages and disadvantages (Table 1). Cells with high proliferation and differentiation potentials, so-called stem cells, are important to induce tissue regeneration. However, one of the problems is the shortage of cells that are clinically available. Therefore, it is necessary to increase the number of stem cells to a level that is clinically acceptable. For this purpose, cell isolation and *in vitro* cell culture are required.

The third technology is the efficient isolation and proliferation of cells (Figure 3), which are activated by providing a 3D substrate as the artificial ECM. The cell scaffold mentioned previously can be used as the substrate for cell culture. From the viewpoint of the supply of nutrients and oxygen, the research and development of cell culture methods and bioreactors are required.

The fourth key technology is a physical barrier to protect transplanted cells and the area to be regenerated from immunological attack and fibroblast infiltration, respectively (Figure 4). When a body defect is generated, the defect space is generally occupied rapidly with the fibrous tissue produced by fibroblasts, which are ubiquitously present in the body and can proliferate rapidly. This is one of the typical wound healing processes to temporarily fill and emergently repair the body defect. However, once this in-growth of fibrous tissue into the space to be regenerated takes place, the regeneration and repairing of a target tissue at the space can no longer be expected. To prevent tissue in-growth, a barrier membrane to secure a space for tissue regeneration is required. In addition to tissue regeneration, there is an approach where cells with biological functions, such as metabolism and biological substance secretion, are used to substitute the functions of the injured organ. For this cell-based organ substitution, functional cells are encapsulated in a hydrogel membrane to prevent them from immunological attack by antibodies and host cells. The immuno-isolated cells are implanted to enable substitution of the functions of injured organs. This immuno-isolation membrane to protect transplanted cells from biological attack by humoral and cellular components is one of the barrier methods. This combination of cell scaffold, barrier and DDS technologies to create an environment for the proliferation and differentiation of cells to induce tissue regeneration is known collectively as tissue engineering.

Tissue regeneration based on DDS technologies

Tissue engineering for clinical regenerative medicine can be classified as either *in vitro* or *in vivo* depending on the site where tissue regeneration or organ substitution is performed. I*n vitro* tissue engineering involves tissue reconstruction by cell culture methods and organ substitution with functional cells – termed bioartificial hybrid organ. If a tissue can be reconstructed *in vitro* in factories or laboratories on a large scale, it can be supplied to patients when required. However, it is difficult to reproduce the *in vivo* event completely *in vitro* by using present knowledge of biology and medicine or cell culture technologies. At present, it is difficult to complete *in vitro* tissue engineering because it is impossible to artificially arrange a biological environment for cell-based tissue reconstruction. In addition, oxygen limitation often causes difficulty in the *in vivo* growth of large tissue. Another application of *in vitro* tissue engineering is the substitution of organ functions by the use of allo- or xeno-geneic cells. The cells are combined and used with an immuno-isolation membrane for organ substitution, the target organs are the liver and pancreas.

TABLE 1

DDS technologies of biological signaling molecules available for the therapy of regenerative medicine

Technology	Material and methodology	Benefit	Disadvantage
Controlled release	Release carrier	Easy fabrication Mass productability	Poor regulation of release profile Activity loss of molecules
	Microfuidic system	Good regulation of release profile	Need power source to work *In vivo* remaining
Stabilization (life-time prolongation)	Carrier	Easy fabrication Mass productability	Poor stabilization efficiency Activity loss of molecules
Gene transfection (absorption acceleration)	Nonviral carrier	Easy fabrication Mass productability	Low transfection efficiency
	Viral carrier	High transfection efficiency	Antigenicity Toxicity Size limitation of genes used
Targeting	Carrier	Easy fabrication Mass productability	Poor targetability Activity loss of molecules
	Natural carrier (cells)	High targetability	Preparation complexicity

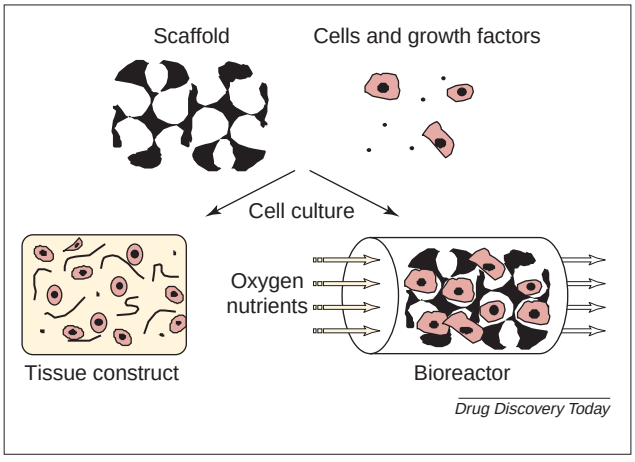

FIGURE 3

The third fundamental technology and methodology with biomaterials for tissue engineering. A 3D scaffold of biomaterials for cell attachment and proliferation is combined with cell culture devices (e.g. a bioreactor) to efficiently isolate and proliferate stem cells. A tissue construct is prepared by several cell culture technologies with cells and the scaffold for *in vitro* tissue engineering.

Distinct from *in vitro* tissue engineering, *in vivo* tissue engineering has the advantage of cell-induced tissue regeneration. It is probable that most biological components that are essential for tissue regeneration, such as growth factors and cytokines to accelerate the proliferation and differentiation of cells, as well as stem and progenitor cells of high proliferation and differentiation potentials, are supplied by the host. Therefore, almost all the approaches of tissue engineering have been performed *in vivo* with or without biodegradable scaffolds. There are several examples where *in vivo* tissue regeneration is achieved by the use of cell scaffolds or in combination with cells [11].

As described previously, if patients are young and healthy and the tissue to be repaired has a high potential to induce regeneration, active and immature cells infiltrate the matrix of biodegradable scaffold implanted from the surrounding healthy tissue, resulting in the formation of new tissue. However, additional means are required if patients are aged and/or suffer from other diseases, such as diabetes and hyperlipemia, and if the regeneration potential of tissue is low as a result of, for example, a low concentration of cells and growth factors. The simplest method is to supply a growth factor to the site of regeneration for cell differentiation and proliferation in a controllable fashion. As described previously, with a growth factor of *in vivo* instability it is necessary to make use of DDS technology. Recent research into tissue regeneration using a combination of growth factors with DDS carriers have indicated that a carrier is necessary to enable the growth factor to exert its biological activity for *in vivo* tissue regeneration. However, although the significance of DDS in tissue regeneration is claimed, the controlled release of growth factor has not been studied extensively. Recently, instead of the growth factor protein, the gene encoding the growth factor has been injected into the body to promote tissue regeneration around the injected site [12].

There are two future directions in the use of gene therapy for basic research. The first direction is conventional gene therapy, whereby plasmid DNA and adenoviruses are injected directly. However, to improve the efficacy of gene transfection, DDS technologies are required. Angiogenesis [13] and bone tissue regeneration [12] have been attempted by using corresponding growth factor genes. If the injected gene is transfected into cells at the site of regeneration, the cells will secrete growth factor for a certain period of time, resulting in promoted tissue regeneration. It should be noted that this approach is one where proteins released from gene-transfected cells are used to induce tissue regeneration. The second direction is to genetically activate cells by gene transfection for enhanced efficacy. There are some cases where transplantation of stem cells alone does not induce a clinically acceptable therapeutic effect. A promising and practical way of breaking through this

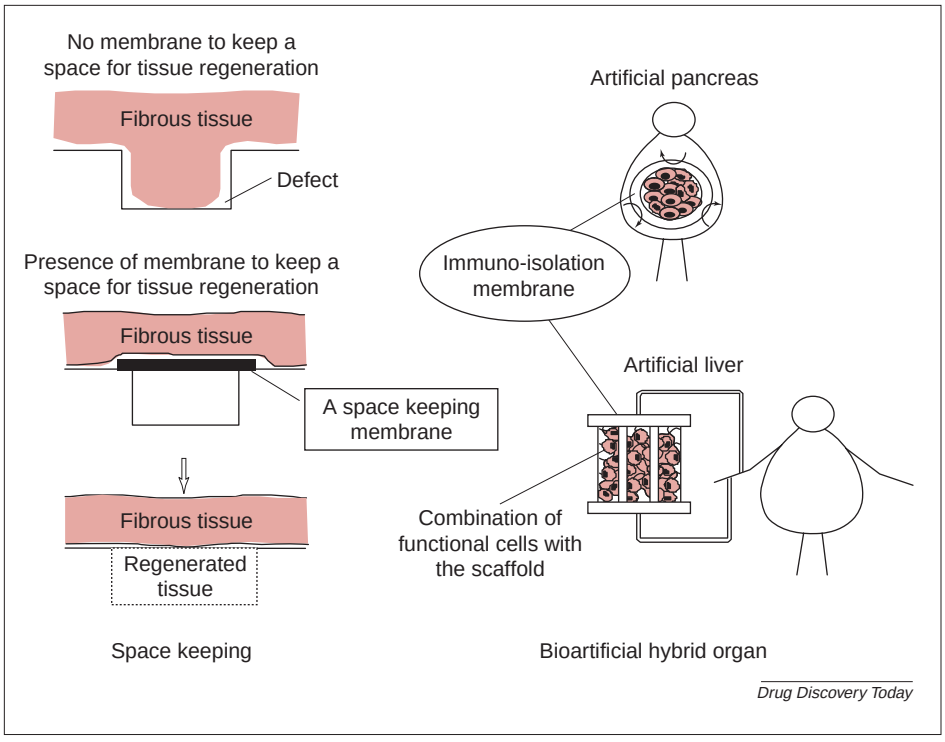

FIGURE 4

The fourth fundamental technology and methodology with biomaterials for tissue engineering. A physical barrier of biomaterial membrane keeps a body space to induce the regeneration of tissues and organs from the ingrowth of cells and tissues. Functional transplanted cells are isolated from immunological attack by host proteins and cells by the barrier membrane to substitute the biological functions of injured organs.

problem would be to genetically engineer stem cells by gene transfection to activate their biological function. So far, such cell activation has been tried by using virus vectors: this has been a great success but cannot be applied to the clinic because it is virus-based. Therefore, it is necessary to develop a system of non-virus gene transfection. Thus, a DDS technology or methodology could bring about the realization of a nonviral system with the same efficiency of gene transfection as a viral system [14].

Successful tissue engineering by release technology

A biodegradable hydrogel has been prepared from gelatin and the induction of tissue and organ regeneration by the controlled release of various biologically active growth factors has been achieved, as shown in Table 2. This controlled release system enabled luciferase plasmid DNA to enhance the level and prolong the time period of gene expression [15,16]. In addition, the hydrogel system can release not one type of growth factor but two or more types at the same time or in a time-order fashion.

Upon applying a hydrogel incorporating low doses of either basic fibroblast growth factor (bFGF) or transforming growth factor β1 (TGF-β1) to a bone defect in rabbit skulls, no bone was regenerated at the defect. However, a synergistic effect on bone regeneration was observed by the simultaneous release of two factors. bFGF was originally characterized *in vitro* as a growth factor for fibroblasts and capillary endothelial cells and *in vivo* as a potent mitogen and chemoattractant for a wide range of cells. In addition, bFGF is reported to have a variety of biological activities [17] and be effective in enhancing wound healing through induction of angiogenesis and regeneration of bone, cartilage and nerve. Recently, human bFGF in solution has been on the Japanese market for the treatment of decubitus, a chronic skin ulcer caused by prolonged pressure (Fibrast® spray, Kaken Pharmaceutical Co., Tokyo; www.kaken.co.jp). When the bFGF was incorporated into a gelatin hydrogel and subcutaneously implanted into the mouse back, significant angiogenic effect was observed around the implanted site, in contrast to controls injected with bFGF solution or higher doses, or the site implanted with bFGF-free, empty gelatin hydrogel [18].

There are two important objectives of angiogenesis in tissue engineering; the therapy of ischemic disease and 'in advance angiogenesis' for cell transplantation. As the first example, when injected into the ischemic site of myocardial infarction [19] or leg ischemia [20], gelatin microspheres incorporating bFGF induced angiogenesis to a significantly greater extent than the bFGF solution. This angiogenic therapy for leg ischemia has been permitted by the ethics committee of Japanese university hospitals and a clinical trial has begun.

The sufficient supply of nutrients and oxygen to transplanted cells is indispensable for cell survival and the maintenance of biological functions. For successful cell transplantation, it is beneficial to induce angiogenesis throughout the site where cells are transplanted in advance, by using the bFGF release system. This technology of 'in advance angiogenesis' efficiently improved the biological functions of pancreatic islets [21], cardiomyocytes [22] and kidney cells [23], as well as the engrafting of a bioartificial dermis–epidermis skin-tissue construct. We succeeded in improving the cardiac functions of ischemic rat hearts by combining cardiomyoblasts implantation with 'in advance angiogenesis' induced by gelatin microspheres incorporating bFGF. These findings indicate that the 'in advance induction of angiogenesis' at the transplanted site was effective in successfully engrafting transplanted cells and grafted tissue constructs. The release system enabled the enhanced activity of bFGF, TGF-β1 and bone morphogenetic protein-2 (BMP-2) to induce bone regeneration and bone healing, as well as to synergistically promote bone regeneration induced by mesenchymal stem cells of bone marrow [24]. For surgical heart grafts, the bilateral sternum artery is normally used because of its high potency. However, despite successful graft surgery, sternum repair is often delayed and, much worse, infection at the

TABLE 2

Regeneration induction of body tissues and organs based on the controlled release of bioactive growth factors from biodegradable hydrogels

Materials	Growth factor	Animal	Effect	Objective	References
Acidic gelatin (pI = 5.0)	bFGF	Mouse, rat, and dog	Angiogenesis	Transplantation of Islets of Langerhans for diabetes therapy	[31,32]
		Rat	Angiogenesis	Tansplantation of hepatocytes for therapy of enzyme deficiency disease	[33]
		Rat	Angiogenesis	Transplantation of renal epithelial cells	[23]
		Rat and dog	Angiogenesis	Transplantation of cardiomyocytes	[22]
		Rat and guinea pig	Angiogenesis	Promoted repair of skin dermal layer	[34]
		Rat and pig	Angiogenesis	Treatment of cardiac infarction	[19,35]
		Rabbit	Angiogenesis	Treatment of lower limb ischemia	[20]
		Rat, dog and monkey	Osteogenesis and angiogenesis	Repair of sternum and connective tissue	[25,36,37]
		Rat, rabbit and monkey	Osteogenesis	Repair of skull and long bone	[38,39]
		Mouse	Adipogenesis	Repair of breast and soft tissue reconstruction	[26]
		Mouse	Angiogenesis and activation of hair-follicle tissue	Promotion of hair growth	[40,41]
		Dog	Periodontium repair	Repair of periodontium	[42]
		Dog	Peripheral nerve repair	Nerve repair	[43]
		Dog	Osteogenesis	Repair of mandibular bone	[44]
	TGF-β1	Rabbit and monkey	Osteogenesis	Repair of skull bone	[45–48]
		Sheep	Chondrogenesis	Repair of tracheal cartilages	[49]
	HGF	Mouse	Angiogenesis and activation of hair-follicle tissue	Promotion of hair growth	[41]
		Rat and pig	Angiogenesis and inhibition of apoptosis	Treatment of dilated cardiomyopathy	
	bFGF or TGF-β1	Rabbit	Osteogenesis	Repair of skull bone	
	CTGF	Rabbit	Chondrogenesis	Repair of articular cartilage	[50]
Basic gelatin (pI = 9.0)	BMP-2	Rat, dog and monkey	Osteogenesis	Repair of skull and mandibular bone	[51]
		Dog	Chondrogenesis	Repair of tracheal cartilages	[52]
Collagen	TGF-β1	Rabbit	Osteogenesis	Repair of skull bone	[53]
		Rabbit	Osteogenesis	Promotion of engraftment of soft tissue grafts	[54]
		Mouse	Angiogenesis and activation of hair-follicle tissue	Promotion of hair growth	[41,55]

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

resection area often occurs while healing of the surrounding soft tissue is also delayed due to surgical elimination of their nutrient artery. In one trial, the bFGF release system was applied to this surgical therapy because bFGF has an inherent potential to induce bone regeneration, as well as angiogenesis. A hydrogel sheet incorporating bFGF was applied to the soft tissue around the sternum of diabetic rats of which the sternum was cut and the bilateral arteries were ligated. As expected, bone regeneration at the cut line of sternum was achieved together with enhanced angiogenesis and the recovery of blood flow at the surrounding soft tissue [25]. *De novo* adipogenesis was succeeded by the preadipocytes isolated from human fat tissues, gelatin microspheres incorporating bFGF and a collagen sponge of cell scaffold [26]. Appropriate combination of all the three materials was required to induce adipogenesis.

It has been found that a plasmid DNA released from a biodegradable hydrogel of cationized gelatin derivative enhanced the level of gene expression, as well as prolonging the time period of expression [15,16]. When intramuscularly injected into the ischemic leg of rats, the cationized gelatin microspheres incorporating FGF-4 plasmid DNA induced angiogenesis to a significantly higher degree than plasmid DNA solution alone, even at doses of 100- or 1000-times lower than that of solution [27]. The microspheres incorporating plasmid DNA were effective in genetically activating cells and consequently enhancing the efficacy of cell therapy. Cationized microspheres incorporating the plasmid DNA of adrenomedulin were prepared to enable their internalization into endothelial progenitor cells. Intracellular controlled release of plasmid DNA enhanced the efficiency of gene transfection to a higher level than that of adenovirus transfection. The genetically engineered

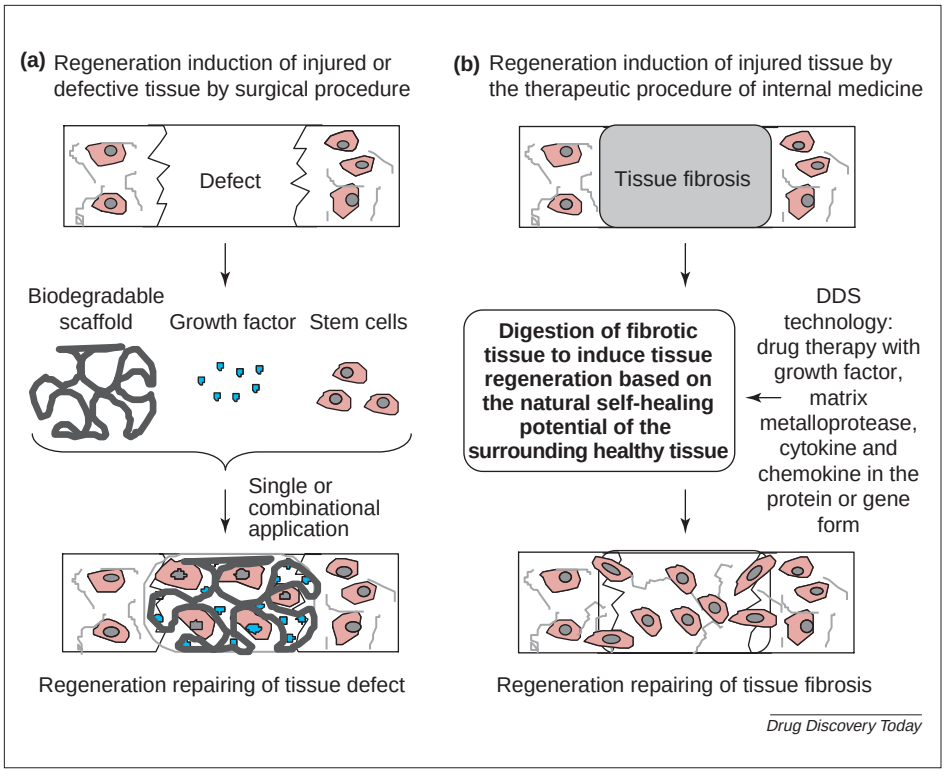

FIGURE 5

The concept of surgical tissue engineering and physical tissue engineering of internal medicine. When the tissue fibrosis of chronic fibrotic disease is physically digested to loosen and eliminate it by DDS technology, it is repaired by regeneration based on the natural self-healing potential of the surrounding healthy tissue. **(a)** Surgical tissue engineering is illustrated on the left hand side and **(b)** physical tissue engineering is shown on the right hand side. This physical tissue engineering by drug therapy is conceptually similar to surgical operation from the viewpoint of induction of regeneration repair.

cells also functioned well to achieve higher therapeutic efficacy [14]. With the recent advent of genomics, the DNA sequence of the human genome has been elucidated and disease therapy on the genetic level will develop in the future. Like proteins, genes are also instable *in vivo*; therefore, DDS technology will have an important role in gene therapy.

A future direction for tissue engineering based on DDS technology

At present, there is no effective therapy for chronic fibrosis diseases, such as lung fibrosis, cirrhosis, dilated cardiomyopathy and chronic nephritis. For these diseases, the injured site is normally occupied with fibrous tissue of excessive collagen fibers and fibroblasts. It is possible that this tissue occupation causes impairment of the natural healing process at the disease site. Therefore, if the fibrosis can be digested to loosen or eliminate it, it is expected that the disease site will be repaired based on the natural regeneration potential of the surrounding healthy tissue. It has been demonstrated that the injection of virus encoding a matrix metalloprotease (MMP) protein suppresses the tissue fibrosis to improve disease symptoms [28]. This finding suggests that when collagen in the fibrous tissue is enzymatically digested, fibrosis is naturally improved or repaired due to the potential of the body to induce tissue regeneration in the surrounding healthy tissue. This therapeutic methodology for chronic fibrosis diseases is a new direction for tissue engineering and is defined as 'tissue engineering of internal medicine' (Figure 5). We have demonstrated that the controlled release of a MMP-1 plasmid DNA at the medulla of chronic renal sclerosis induced the histological regeneration of kidney structure, in contrast to the plasmid DNA solution [29]. When gelatin microspheres incorporating hepatocyte growth factor (HGF) were intraperitoneally injected into rats with liver cirrhosis, the liver fibrosis was histologically cured [30]. However, the injection of HGF solution was ineffective and the tissue appearance was similar to that of the untreated controlled group.

Closing remarks

Regenerative medicine – a new therapy based on the induction of tissue regeneration through cells and tissue engineering – is the third therapy after reconstructive surgery and organ transplantation. To achieve regenerative medicine by use of tissue engineering technologies, substantial collaborative research between material, pharmaceutical, biological and clinical scientists is needed. Although superior stem cells can be obtained, it is impossible to apply these cells and the related scientific results to medical therapies for patients directly (regeneration medicine), unless an environment suitable for cell proliferation and differentiation is produced. However, one of the main problems at present is the shortage of biomaterial researchers of tissue engineering, who focus at combining DDS and biomaterials to tissue engineering, aiming at tissue regeneration and the biological substitution of organ functions. Such researchers must have knowledge in medicine, dentistry, biology and pharmacology, in addition to material sciences. It is indispensable to educate the researchers of an interdisciplinary field who have an engineering background and can also understand basic biology, medicine and clinical medicine. One of the representative interdisciplinary research fields is DDS technology, which is also applicable for producing nonviral vectors in the preparation of genetically engineered cells for regenerative medicine. The development of nonviral vectors with a high efficiency of gene transfection for stem cells is of a high priority. Tissue engineering technology is not only used surgically at the tissue defect but is also applied to develop a therapeutic method for chronic fibrosis diseases by making use of internal medicine.

Tissue engineering is still in its infancy, although some research projects have already come close to clinical application. The increasing significance of drug delivery in the future will help progress tissue engineering.

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