在体组织工程新概念

Human hair keratin (HHK) artificial tendon is a biomaterial developed by the First Military Medical University in recent years and has been approved for an independent intellectual property right. Now this material has been industrialized and applied into clinical practice. In the past decade of researches into the mechanism and clinical applications of this material, we gradually developed a new concept in tissue engineering in vivo HHK-engineered tendon, and further more, in vivo tissue engineering.

AN OVERVIEW OF ARTIFICIAL TENDON

Traditional and current methods for repairing limb function defects resulting from tendon defect, shortness, deformation or congenital defect of hand tendons include the following[1].

Tendon autograft or tendon transposition

The most prominent advantages of this method are avoidance of immune rejection, expectable histological healing of the anastomosed sites, and structural recovery of both normal anatomy and histology. This method, however, has to "maintain one place at the expense of others", which not only incurs additional surgical trauma, but also affects the function of the donor limbs, and is therefore poorly received by the candidate patients.

Synthesized materials

Currently available tendon substitutes include silks, metallic alloy, colloxylin, tantalum silks, plastics, nylon, dacron, synthetic fibers, carbonic fibers, silastics, arteries, polyester fibers, hydroxyapatite and untreated human hair, etc. These materials are only used as momen- tary substitutes due to their poor histocompatibility or strong potential for immune rejections, shrinkage, splitting or degradation as time following the implan- tation prolonged, considering also their progressive attenuation of tensile stress or extensive adhesion with the neigh- boring tissues.

Tendon allografts

Untreated fresh tendon allografts cause obvious inflammatory reaction and rejection. Those treated under ultra-low temperature or by lyophilization may have lowered antigenicity and thus are still widely used in clinical practice, but their limited resources, complicated procedure, possibility of disease transmission (especially true for HIV and HBV), potential rejection, adhesion, delayed healing, obvious attenuation of

tensile stress and expensive cost, all restricted their use.

Human hair tendons

Huang et al[2] first reported the use of untreated hair- weaved material to replace normal tendons, which greatly inspired us. But after that, few reports were available to describe its clinical use as human hair can not be degraded in vivo, and is liable to give rise to adhesion with the surrounding tissues, hence its poor effects in digital tendon repair of the hands.

TISSUE ENGINEERING AND TISSUE-ENGIN- EERED TENDONS

Traditional concept of tissue engineering and tissue- engineered tendons

The concept of tissue engineering was proposed in 1980s. The so-called tissue engineering is a multidis- ciplinary/interdisciplinary field that applies the prin- ciples of biology and engineering to develop tissue/ organ substitutes in vitro to restore, maintain, or improve the function of diseased or damaged human tissues/ organs. Scaffold-guided tissue engineering involves acquisition and culturing of seed cells, highly porous biodegradable scaffolds, seeding and culturing the scaffolds with the donor cells to develop an active three- dimensional complex of seed cells and the scaffolds, and in vivo implantation of such complex to induce and direct the growth of the constructed tissue/organ. As the viable cells in the scaffold material can proliferate, more and more researchers have inclined to develop substitutes of tendons and ligaments by way of tissue engineering.

The key components of tissue-engineered tendons include the seed cells and extracellular matrix/scaffold materials. Currently reported seed cells for tissue-engineering of the tendons are mostly derived from autogeneous or allogeneic skin fibroblasts, tenocytes, transformed or modified human embryo tenocytes, mesenchymal stem cells in the bone marrow or connective tissue; the extracellular matrix materials are mainly from human amnion and small intestinal submucosa, etc., and the scaffold materials primarily from degradable and absorbable high polymers, e.g. collagen stents, polyglycolic acid (PGA), polyactic acid (PLA), and PLGA (homoconjugate of both PGA and PLA), polydioxanone (PDS) , and polyglycolic acid fibers, etc.

These researches suggest that the tissue-engineered tendon was possible, more or less, to transform into a permanent and organic tendon. We call this procedure "in vitro tissue engineering" because the above-men- tioned manipulations for constructing tissue-engineered tendons, including the acquisition and culture of seed cells and seeding these cells into the scaffold materials, are all performed in vitro.

But unsolved problems are still numerous in tissue-engineered tendons constructed with these methods for their general use in clinical practice. These include the histocompatibility of the seed cells, aging and dysfunction of the cells during cell passaging, biocompatibility and bio-affinity of the scaffold materials, synchronization between the rate of the scaffold material degradation and cell growth, the effect of the degraded products on the surrounding physiolo- gical environment, source of the seed cells, and construction of simulated three-dimensional tension environment, etc. After considerable progress has been achieved in researches in the above-mentioned fields, it is

still necessary to study these materials for their intermediate links connecting the laboratory experi- ments and in vivo clinical trials, including the material preservation, maintenance of their activity after preser- vation, cell revival before grafting, manner of transpor- tation, and in vivo response after grafting etc., also known as the researches of industrialization of this technique. For this purpose, we have developed a completely new permanent tendon substitute—HHK artificial tendon.

HHK artificial tendons

The study of HHK artificial tendon can be dated back to 1991, when we were inspired by the study of untreated human hair conducted by Huang et al[2]. Xiao et al[4] subsequently prepared three HHK components that degraded at slow (Z), moderate (B), and fast (F) absorption rate respectively by treating normal human hair with sequential and controlled biochemical procedures of various degrees. The term HHK artificial tendon derived from the cysteine-rich α-keratin, which is the chief component of human hair. Analysis of the chemical components of HHK artificial tendons showed that the biodegradability and absorbability of HHK artificial tendons in vivo was much credited to the destruction of disulfide bonds among α-keratin polypep- tides, which maintain the stabilization of human hair structure.

Later researches confirmed the reliability, excellent biocompatibility and histocompatibility as well as adequate biomechanics of the grafted HHK artificial tendon. But the most exciting research was the body response after it was implanted into the body.

First of all, experimental research was conducted on the implantation of the material as an artificial tendon. Cao et al[5] bridged the Achilles tendons using HHK artificial tendons in New Zealand rabbits. Five weeks later, the implants broke into many small pieces, each of which was wrapped by mass of collagen fibers. Collagen fibers had grown into the residual artificial tendons infiltrated with some macrophages. Seven weeks later, it was difficult to distinguish by appearance the grafts from the normal tendons, and the boundary between them was not clear, most of the implants absorbed and replaced by collagen (collagenization). In the twelfth week, the implants were completely replaced by collagen fibers, most of which had been transformed into approximately normal tendon tissue ("tendonization"). The results showed that the grafted HHK artificial tendon was absorbable and could induce the surrounding tissue to form new tendon in rabbits in about 12 weeks. Similar results were achieved by Li et al[6], Piao et al[7], Lou et al[8][9], Wang et al[10], Jiang et al[11], and Hu et al[12] in their studies using HHK artificial tendons to bridge the defect in Achilles tendons and gastrocnemius tendons.

Second, the study of the mechanism by which HHK artificial tendons induces the formation of auto- logous tendons was conducted, including the mecha- nisms of the degradation and absorption of artificial tendons and the formation of the autologous tendons. The results showed that, firstly, the degradation and absorption of each component of HHK artificial tendon occurred simultaneously with the formation of autologous tendons after in vivo grafting; secondly, the degradation of HHK artificial tendons was the result of precise synergy between ubiquitin-dependent pathway and lysosome-dependent pathway; thirdly, the formation of the autologous tendons was a highly complicated process involving the stimulation of the proliferation and differentiation of tenoblasts in the neighboring tissues, especially at the transected ends, into tenocytes by HHK artificial tendon components and their degradation products, the activation of

tenocytes to synthesize and secrete collagen, the regulation of this process by certain cytokines secreted by other cells, and finally, the formation of autotendons; in addition, it was also found that the tenocytes themselves were collagenized in the later stages of autologous tendon formation, similar to the keratinization of the epidermis.

Third, clinical trials were attempted on the basis of the experimental results. The first successful clinical use of HHK artificial tendon was carried out in Nanfang Hospital, an affiliated hospital of the First Military Medical University, in 1994. After that, clinical trials were performed in Kunming General Hospital of Chengdu Military Command[13][14] and the affiliated hospital of the Medical Collage of Qingdao University [15][16]. In the past decade, HHK artificial tendons were further improved, and used in clinical practice in more than 2 000 cases in several hundreds of hospitals located in Guangdong, Yunnan, Shandong, Hunan, Henan, Hebei, Guangxi, Tianjin, Jiangxi, Guizhou, Anhui, and Beijing. The primary indications are, primarily, repair and reconstruction of the injuries of the flexor/extensor digital tendon, flexor/extensor pollicis longus tendon, abduct pollicis longus tendon, flexor/extensor digiti tendon of the foot, Achilles tendon, malleolus flexor/extensor tendon, flexor/ extensor carpi tendon of the forearm, flexor/extensor tendon of the upper arm; secondly, tendon transfer in orthopedic procedure for equinovarus and equinovalgus, functional reconstruction for brachial plexus injury, and the reconstruction of shoulder sleeves; and thirdly, the reconstruction of tracheal ligaments and inner/outer collateral ligaments in the knee joint, the replacement of anterior/posterior cruciate ligament and patellar liga- ment. There were no apparent adverse effects (fever for example) after operation. Most of the wounds healed by first intention with an excellent recovery rate as high as 95%.

Finally, we also found during the experimental research and clinical application that HHK artificial tendons disappeared and were replaced by newly formed muscle tissue when grafted in the injured muscle tissue[17][18]; the tube-like HHK artificial tendons were finally replaced by nerve tissues when grafted between the two transected nerve ends[19][20], and HHK artificial tendon components crossing the bone tissue for clinically repairing and rebuilding injured collateral ligaments were replaced by normal bone tissue.

These results suggest that there is a common pathway of the interaction between HHK artificial tendon and the body, which we call "in vivo tissue engineering".

IN VIVO TISSUE ENGINEERING AND IN VIVO HHK TISSUE-ENGINEERED TENDON

In vivo tissue engineering is defined as in vivo construction of a nearly normal tissue/organ substitute. The grafted absorbable scaffold biomaterial itself and its degradation products can activate the mitosis, prolifera- tion, and differentiation of the seed cells (or adult stem cells) in the surrounding tissues. These cells organically interact with the material to form an organic complex under in vivo physiological conditions. Finally the matrix material is completely replaced by the complex, a structure consistent with normal tissue in anatomy and histology, which constructs a so-called tissue-engineered tissue/organ.

It is reasonable that we put forward the concept of in vivo tissue engineering. The primary consideration is that, adult stem cells exist in almost all tissues. For instance,

the mesenchymal cells in the connective tissues with low capacity of differentiation can differentiate into various connective tissue cells, smooth muscle cells and endothelial cells, while muscle satellite cells in skeletal muscle tissue into skeletal muscle cells. It is also confirmed by many researches that, in certain conditions, stem cells have the potential of reverse differentiation, an ability of differentiation into their progenitor stem cells, or in a sense, adult stem cells have wider and more powerful differentiation ability than we generally expect. In addition, the body usually produces a stress response to injuries, during which various cells participate by secreting corresponding factors to regulate the activities of adult stem cells. The most important evidence is that we have made many successful achievements in HHK artificial tendons. We regard HHK artificial tendon as an "in vivo tissue- engineered tendon" on the basis of how it induces the formation of the autologous tendon.

Animal experiments showed that a pseudosynovial sheath or a membrane-like coating appeared around the graft 3 weeks post-operation. There was no obvious adhesion of HHK artificial tendon to the surrounding tissues during autologous tendon formation when the graft was implanted into the sheath of the flexor digital tendon in numerous clinical cases, where the functional restoration of the injured digits was excellent. This phenomenon arises from the stimulation by HHK artificial tendon of the adult stem cells including the tenoblasts, synovial precursor cells and mesenchymal cells in the autogenous subaponeurotic tissue, vincula tendinum as well as injured tendon stumps. Induced by HHK artificial tendon and its degradation products, these cells divide, proliferate and differentiate into tenocytes and synovium cells, and then migrate into the degradation areas, synthesize and secrete collagen there, and finally form new autologous tendon and synovium.

As "in vivo tissue-engineered tendon", HHK artificial tendon is characterized by the following features: HHK artificial tendon is a scaffold biomaterial with satisfactory biocompatibility and bioaffinity; it is absorbable, whose intermediate degradation products include various polypeptides, some directly stimulating the division, proliferation and even differentiation of adult stem cells (including tenoblasts, synovial precur- sor cells and mesenchymal cells) in the surrounding tissues to eventually form tenocytes, while others regulating the above-mentioned process by inducing other cells to secrete cytokines; furthermore, almost all the final degradation products of HHK artificial tendon are amino acids (proline holds nearly 9% and glycin nearly 4%) and materials for the synthesis of collagen proteins (proline holds nearly 20% and glycin nearly 30%) of new autologous tendon.

The real significance of in vivo tissue engineering lies in its powerful potential in clinical application and the construction of tissue-engineered tissue/organ rather than its theoretical value, which is confirmed by our primary studies.

HHK artificial tendon components were woven to ducts by Hu et al[19][20] to bridge the defected tibial nerve in rabbits. After 92 d, the muscle-nerve conducting velocity (MNCV) of the experimental nerves was notably different from that in the normal control. A great deal of Schwann cells proliferated around HHK artificial tendon and myelin sheath formation was observed under electron microscope. The organells such as the mitochondria were seen in the neurofibrils. One year later, the defected nerve was well repaired with complete absorption of the graft, suggesting that in the process of degradation in vivo,

HHK artificial tendon and its degradation products induced nerve stem cells in the surrounding tissues to divide, proliferate and differentiate into glial cells (Schwann cells) to repair the defected nerve.

HHK artificial tendon materials were used to repair gluteus maximus muscle defect 5 cm ×3 cm×2 cm in size in rabbits by Qiao et al[21]. Five weeks later, parts of HHK artificial tendon components were degraded into small granules and absorbed by macrophages, and the residual granules scattered in the matrix. Meanwhile, newly formed muscle fibers with nuclei in the center were seen. Skeletal muscle tissue consists of highly ordered muscle fibers aligned in the same direction, and it is difficult for full spontaneous repair to occur in a short term in case of massive injury. The experiment showed that the degradation products of HHK artificial tendon materials activated the existing skeletal muscle stem cells and muscle satellite cells (usually in quies- cent phase under physiological condition) to divide, proliferate and differentiate into muscle cells.

PROSPECTS

The most prominent advantage of in vivo tissue engineering is "in vivo construction" of tissue/organ substitutes in anatomy, histology and function by way of seed cell culture under in vivo microenvironment and precise regulatory mechanisms. It greatly overcomes the intrinsic defects of the in vitro tissue- engineered tissues/organs, enormously saves the costs, and bridges the gap between the theoretical supposition and clinical applications. In vivo tissue-engineering, in contrast to traditional in vitro tissue-engineering, can be applied in the construction of almost any tissue/organ. It can best meet the need for clinical use, solving such problems as immune rejection against seed cells, variation and functional deterioration of the seed cells, complicated preservation procedure, transportation difficulty and high cost. HHK artificial tendon has won recognition by several distinguished academicians inclding Gu Yu-dong, Wang Zheng-guo, Wang Shu-huan and Professor Wei Jia-ning. We plan to develop one or two HHK-based products under the direction of in vivo tissue engineering theory, and carry out massive animal experiments and subsequent clinical trials. Meanwhile, we believe that HHK analogues or new materials better than HHK will be developed in the near future.

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回结果列表