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Development of Small Intestinal Submucosa as Biomaterial in Tissue Engineering

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Abstract. Small intestinal submucosa as a kind of natural ECM was widely studied as biological material from now on. Attachment on SIS, the proliferation, migration and differentiation of numerous cells were found be influence. Due to its excellent biocompatibility, biomechanical properties and biological activity, SIS had been extensive used as biomaterial in regenerative medicine. This article reviews the recent progress in the characterization and medical application of SIS respectively.

1. Introduction
Small intestinal submucosa (SIS) is a kind of biomaterial common used in clinical. The construction, biological activity and immune response of SIS were suit for implanting in body. Nowadays, it often used as scaffolds in tissue engineering and regenerative medicine to organs such as the artery [1], bladder [2], intestinal tract [3], valve [4], esophagus [5], and tendon [6]. The SIS has approved by FDA which could used in humans for urogenital procedures. cystoplasties, ureteral reconstructions and so on [7]. The scholars discussed to process SIS to numerous types such as injection, patch, scaffold and so on, in order to enlarge its utility.

2. The Characteristics of the SIS

2.1. Biochemical Properties of SIS
Lei shi and Vincent Ronfard concluded the structural properties and biochemical composition of SIS as documented in Table 1[8]. The basic component of SIS is collagen. And the collagen in SIS, were mainly collagen type I and a few of other types [9]. Small amount of elastin, fibronectin, laminin glycosaminoglycans and proteoglycans also were found in SIS [10-13]. The collagen contracted wound and promoted healing. The multidomain glycoproteins regulated cell attachment on ECM. And the proteoglycans supplied cell adherence binding site, inhibited substrate degrading enzyme [14-16]. Additionally, the growth factors such as fibroblast growth factor-2 were released by SIS too [17, 18]. The compositions of SIS above-mentioned were influence tissue healing that is why SIS becomes popular biomaterial on tissue engineering.

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Table 1. Characteristic and Component of Small Intestinal Submucosa [8]

characteristic	Description
Thickness	50 to 220 μm
Ultrastructure	0.020 to 0.030 mm
Mechanical properties	1 layer: 20.6 MPa (dry) and 7.2 MPa (wet) 4 layer: 36.7 MPa (dry) and 22.4 MPa (wet)
component	Collagen, Elastin ,Fibronectin ,Laminin Glycosaminoglycans and proteoglycans Fibroblast growth factor-2 (FGF-2), Transforming growth factor-beta1 (TGF-ß1), Vascular endothelial growth factor (VEGF)

2.2. SIS Effects on Cell Proliferation and Differentiation

Cells and ECM related and interacted with each other, with reaching a kinetic balance [19].These interactions happened while cellular microenvironment transformed, during tissue repair, embryogenesis, malignant transformation and angiogenesis [20].

The interaction between cells and ECM was thought to be mediated through integrin. And the mechanism, how SIS influences cells, is related to integrin binding. The peptide sequences of fibronectin were researched. And researchers thought fibronectin played a significance role in adherence of cells to Small intestinal submucosa [21]. The study displayed that RCG and REDV were important for adherence on SIS. Furthermore, the integrin which influence RCG and REDV may mediate cell adherence. Some researchers suggested that the adherence of endothelial cells to Small intestinal submucosa hinged on its structure and formation [22]. Additionally, the β1, β4, and α6 integrins changed the attachment of cancer cells on SIS [23]. This study suggested neutralization of integrin entire effect on adherence of cells.

The growth factors, from Small intestinal submucosa, may mediate cell differentiation and angiogenesis which were carried on [21]. Hodde found that the differentiation of pc12 affected on small intestinal submucosa was controlled by neutralizing antibody against FGF-2. This study showed a new regulatory approach that FGF-2 perhaps adjust the biological response of Small intestinal submucosa [24].

2.3. Mechanical Properties between Different Matrix Layers of Sis

The structure of 1-4 layer small intestinal submucosa were researched. The scholars contrast the mechanical properties with different layers of SIS [25]. The thickness of one layer is about 50μm. In wet condition, the ultimate tensile strength and elastic modulus were measured. The same detection indexes also were measured in dry condition. Determined in dry conditions, peak strength enhanced while the number of SIS layer rise. But the material elongated when the number of layers increased. The elastic modulus of different layers of SIS was similar which shown they had resemblance mechanical property as biomaterial.

Testing in wet conditions, the results of peak strength were lower than dry conditions [25]. And the peak strengths of the multi-layer small intestinal submucosa specimens, in wet conditions, were obviously higher than the 1 layer small intestinal submucosa specimens. But compared with multi-layers each other, there were not obviously difference of peak strength. In wet conditions, when the number of layers and peak strength increased, the elongation was declined. The one layer small intestinal submucosa elongated the most, about 130%. However, all of multi-layers small intestinal submucosa elongated 30%-40% [25].

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3. Medical Application of SIS

Abdominal wall defects were common clinical symptoms which usually caused serious complication by unfit repair method. The previous studies for the material used in abdominal wall defects were limitation. Recently, the researchers used SIS patches for restoring abdominal wall defects in dogs. And contrast the biological and mechanical properties between SIS and SIS + polypropylene mesh. The dogs were undergone surgery for constructing a model of abdominal wall defects and use the two kinds of material to repair defects. To evaluate the mechanical property, biocompatibility, toxicology of SIS and SIS + polypropylene mesh, the main purpose was shown the effectiveness and safety of two kinds of biomaterials. The research results display that SIS had better biocompatibility and histocompatibility than SIS + polypropylene mesh [26].

SIS also used in bone tissue engineering generally, in order to improve bone healing of animal experiment. Small intestinal submucosa scaffold had excellent biocompatibility which usually applied in tissue engineering. Bone cell could be repaired by SIS, because of its biological characteristics which could influence migration, proliferation, differentiation and adherence of cells. In animal models, mice were subjected to surgical resection to bring about calvarial defect. The growth of defective bone was significantly improved with the mice implanted in small intestinal submucosa scaffold. The researcher found SIS could upregulate the expression of BMP-2 and CD31; simultaneously increase the downstream target gene ID-1. The results of this research point out that, because of the biological and mechanical property, regulating in regeneration of cells which participate in bone regeneration, SIS maybe a kind of excellent biomaterial used in bone tissue [27].

Preliminary researchers found that small intestinal submucosa scaffold can be used as superior biomaterial in vascular transplantation. The artificial vessel that manufactured by small intestinal submucosa transplanted into the canine carotid artery of dogs [28]. Then, the artificial vessel performance vascular mechanical properties and gradually evolve into carotid artery. Other studies found SIS also can be excellence material used as a basement membrane because of its biological properties to promote epidermal cells attaché fibroblasts [11]. The research shown small intestinal submucosa encourages proliferation of endothelial progenitor, rather than prevent. The endothelial progenitor growth on SIS which has excellent cell morphology and the rate of proliferation was increased. Furthermore, seeded on SIS surface, the endothelial progenitor could grow, migrate and differentiate. All the results shown that SIS was excellence biomaterial without any cytotoxicity, even promote proliferation of epidermal cells.

The restore of full thickness corneal wound in animals, which used SIS as corneal replacement material, were suggested for many years. Nowadays, the preliminary evaluation about biocompatibility of SIS as rabbit corneal replacement biomaterial was completed. The results display that corneal base transparent while used SIS with producing only a small amount of scar tissue [29,30]. The small intestinal submucosa was an excellent material could be recommend used in veterinary ophthalmology.

It is a complex process of repairing tracheal defects by surgery when the gold standard treatment with primary end-toend anastomosis is not possible. SIS has been used as graft material for bioengineering applications and to promote tissue regeneration. There are sixteen rabbits used as animal models that randomly divided into two groups. To cut the trachea by surgery, one group of rabbit use SIS material as transplanting alternatives cover the incision and another group use noting as control. The area of perimeter of tracheal gap narrower by 22% and 15%, respectively, in the SIS group than in the control group. Histological analysis revealed immature cartilage, pseudostratified ciliated epithelium, and connective tissue about 55% of the SIS group, while no cartilaginous regeneration was observed in the control group.Although tracheal SIS engraftment could not prevent stenosis in a rabbit model of tracheal injury; it produced some remarkable changes, efficiently facilitating neovascularization, reepithelialization, and neoformation of immature cartilage [31].

4. Conclusion

Small intestinal submucosa as a kind of natural ECM was widely studied as biological material from now on. With the biological property, outstanding improving the cure effect, SIS common suggested which applied in tissue repair. Attachment on SIS, the proliferation, migration and differentiation of numerous cells were found be influence. Simultaneously, growth factor, encouraged secreting by SIS, could induce angiogenesis to affect new blood vessel. And the biodegradability of SIS also showed illustrious histocompatibility without cytotoxicity in vivo. At present, SIS products have been applied in different forms, including tablet, granular, spongy and gel, but it is still difficult to meet different clinical needs. In order to satisfy the needs of various tissue repairs, the combination of SIS with other materials, cells and drug factors to improve the properties of SIS, is an important direction for future development.

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