

Tissue Engineering of Skin and Soft Tissue Augmentation, Medical View

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Tissue engineering is one application of the regenerative medicine, which aims to promote replace, repair or regeneration of tissue or organ due to congenital abnormalities, disease, trauma, or aging. This field applies the principles of physical sciences, engineering, medicine and the life sciences. To integrate knowledge of stem cell biology, tissue scaffold biocompatibility and degradation, bioreactor on cell growth and differentiation may overcome some limitation of autologous tissue grafting, allogenic tissue rejection. Tissue engineering is really a new hope for future medicine.

Keywords: Tissue engineering, Skin, Skin graft, Soft tissue augmentation

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Regenerative medicine is a multidisciplinary field involving biology, medicine, and engineering that is likely to revolutionize the ways improving the health and quality of life by restoring, maintaining, or enhancing tissue and organ function. Approaching of regenerative medicine can be stem cells biology, engineering biomaterial science, biochemical growth factors those effect cells growth and differentiation and tissue engineering. Tissue engineering is a subfield of biomaterials of a combination of cells, engineering materials, methods and suitable biochemical factors to remake a new tissue. This article reviews medical aspect about causes of tissue defect, stem cells, bioreactors and scaffold in tissue engineering, limitation in clinical application and future of tissue engineering.

Tissue defects

The causes of soft tissue and epithelial defect could be congenital anomalies, diseases, traumatic events or even normal aging processes. Previously, the treatment option of soft tissue and epithelial lost were autologous tissue transfer, *e.g.* flaps transfer, or allogenic soft tissue transplantation. There were some limitations of treatment in each treatment choices. The autologous tissue transfer has no rejection problem but that can be done in the small recipient area, which

the donor site can cover the entire recipient site. Contrary with the allogenic tissue transfer has some difficulties to find the donor tissue to fit the quality and site of donor to the recipient site.

Moreover allogenic tissue transplantation has to control tissue rejection reaction and some problems with side effect of immunosuppressive medicine⁽¹⁻⁴⁾. Tissue engineering with the autologous cells source, activating with suitable growth factor, to direct desire direction of cell growth and differentiation, on the biocompatible scaffold seems to be the solution of shortest of tissue in autologous tissue transfer and rejection problem with allogenic tissue rejection⁽⁵⁻⁹⁾.

Cells sources

Cell source in tissue engineering or cell therapy can be autologous, allogenic, or xenogenic⁽¹⁰⁻¹⁴⁾. The best cell population to remake a new tissue has to remain their stem cell properties, which are remaining the capability of renewing themselves, unspecialized cell type, and can give rise to specialized cell types or differentiation^(15,16). There are two main types of stem cells, embryonic stem cells (ESCs) and adult or somatic stem cells. ESCs derive from specific site of embryonic tissue, inner cell mass (ICM) of blastocyst. Adult or somatic stem cells are cells those can be found in adult tissue and still remain all three main stem cell properties. Adult tissues those have been report success in stem cell extraction are hematopoietic tissue, adipose tissue, neural tissue and skin tissue⁽¹⁷⁻²⁰⁾. By ethical issue and plenty of source, adult stem cells seem to be the perfect

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source for tissue engineering, though it has to grow in the proper culture system with right specific growth factors to stimulated growth and differentiation those adult stem cells into the desired direction.

Bioreactors

Bioreactor is a term to describe method of extraction, culture system, growth factors those can affect tissue culture into desired growth and differentiate direction^(10,21). There were several reports about growth factors those effect cell growth and differentiation. In certain types of tissue engineering, in vitro culture system is needed to create culture environments as in native conditions⁽²²⁻²⁴⁾. Finally in the large industrial scale, machines or method those are involved in the in tissue engineering formation are needed to be precise to obtain the same quality products from each individual product lot to obtain the same product quality⁽²⁵⁻²⁸⁾.

Material scaffold

Biological scaffold is a remake tissue extracellular matrix for cells to attach and growth on. This can be divided into 2 main groups due to their origin, natural and synthetic scaffold⁽²⁹⁻³³⁾.

A. Natural scaffold

Natural polymers are categorized in to 3 main categories, due to their natural source; polysaccharides, proteins and hydroxyalkanoates^(34,35). There were several review about scaffold, which are made from polysaccharides; chitosan, hyaluronic acid, glycosaminoglycans^(33,36), protein and protein based polymers; collagen, elastin, fibrin/fibrinogen, fibronectin, silk^(35,37-39) and polyhydroxyalkanoated; polyhydroxybutyrate (PHB)^(40,41). The advantage of these natural scaffold is most of these natural origin scaffold are already existed in extracellular matrix of natural tissue, for example collagen and elastin are the natural dermal matrix, so they react property with cells, which are co-culture with them. The disadvantage is because its origin, this has to be extracted from natural tissue, xenogenic or allogenic source, which may cause some foreign body reaction from the contaminated xenogenic or allogenic proteins.

B. Synthetic scaffold

Synthetic biodegradable scaffold for the tissue engineering purposes are the polymers those are not originated from natural process but they are made of synthetic polymers, which can be apply for

tissue scaffold. Because they are not naturally derived, all synthetic material those are designed for tissue scaffold have to be tested their biocompatible properties^(30,42,43). The advantage of synthetic material is easily reproduction and can be easily processed into desired shape and form^(32,44). There were several reports using of degradable polymers in tissue engineering such as poly (lactic) acid (PLA), poly glycolic acid (PGA) and their copolymers (PLGA)^(45,46). In the industrial scale, this synthetic scaffold may be a more favorable choice for tissue engineering.

Autologous tissue grafting

Reconstructive surgery by tissue transfer is the treatment of choice in tissue lost. There will be no grafting rejection reaction. Although there were some limitations of the donor site in order to cover the entire recipient site^(1,47). In the case of large tissue defect, such as burns patients, lost extremities, or wide spread tissue defect, tissue transfer may not able to cover the entire recipient area due to the limitation of the donor site.

Allogenic tissue grafting

Above-mentioned limitation of autologous tissue transfer to treat the lost tissue, there was a report of allogenic tissue grafting in human facial soft tissue from the brain-dead donor to a victim of dog bite, which had lost her lower facial soft tissue and cannot be treated with her own tissue flap⁽²⁻⁴⁾. This allogenic tissue grafting has good cosmetic outcome with a favorable function of patient lower face portion. Like the other allogenic tissue grafting, immunosuppressive drugs have been used to suppress the tissue rejection reaction^(48,49). The disadvantages of allogenic tissue transfer are shortage of donor site and necessary to suppress tissue rejection reaction by immunosuppressive drugs, which may cause some side effect.

Future application of tissue engineering

Tissues engineering, which are made of (1) proper cell source that is not caused acute and chronic tissue reaction and has self renewal properties that can re-growth and differentiate to a new tissue, (2) proper biodegradable scaffold and (3) proper bioreactors can control the quality of tissue. With all the advantage of reproducible tissue engineering technologies, this can be the future hope for tissue repair, replacement or regeneration in regenerative medicine in the treatment of lost tissue, impair functions those are caused

congenital abnormalities, trauma, diseases or aging processes^(5,7,20,50-54).

References

1. Wallace CG, Wei FC. The current status, evolution and future of facial reconstruction. *Chang Gung Med J* 2008; 31: 441-9.
2. Devauchelle B, Badet L, Lengele B, Morelon E, Testelin S, Michallet M, et al. First human face allograft: early report. *Lancet* 2006; 368: 203-9.
3. Kanitakis J, Badet L, Petruzzo P, Beziat JL, Morelon E, Lefrancois N, et al. Clinicopathologic monitoring of the skin and oral mucosa of the first human face allograft: Report on the first eight months. *Transplantation* 2006; 82: 1610-5.
4. Dubernard JM, Lengele B, Morelon E, Testelin S, Badet L, Moure C, et al. Outcomes 18 months after the first human partial face transplantation. *N Engl J Med* 2007; 357: 2451-60.
5. Park DH, Borlongan CV, Eve DJ, Sanberg PR. The emerging field of cell and tissue engineering. *Med Sci Monit* 2008; 14: RA206-20.
6. Placzek MR, Chung IM, Macedo HM, Ismail S, Mortera BT, Lim M, et al. Stem cell bioprocessing: fundamentals and principles. *J R Soc Interface* 2009; 6: 209-32.
7. Cubukcuoglu DG, Durdu S, Akar AR, Ozyurda U. Biotechnology and stem cell research: a glance into the future. *Anadolu Kardiyol Derg* 2008; 8: 297-302.
8. Discher DE, Mooney DJ, Zandstra PW. Growth factors, matrices, and forces combine and control stem cells. *Science* 2009; 324: 1673-7.
9. Sands RW, Mooney DJ. Polymers to direct cell fate by controlling the microenvironment. *Curr Opin Biotechnol* 2007; 18: 448-53.
10. Evans ND, Minelli C, Gentleman E, LaPointe V, Patankar SN, Kallivretaki M, et al. Substrate stiffness affects early differentiation events in embryonic stem cells. *Eur Cell Mater* 2009; 18: 1-14.
11. Dalgetty DM, Medine CN, Iredale JP, Hay DC. Progress and future challenges in stem cell-derived liver technologies. *Am J Physiol Gastrointest Liver Physiol* 2009; 297: G241-8.
12. Mizuno H. Adipose-derived stem cells for tissue repair and regeneration: ten years of research and a literature review. *J Nippon Med Sch* 2009; 76: 56-66.
13. Kuci S, Kuci Z, Latifi-Pupovci H, Niethammer D, Handgretinger R, Schumm M, et al. Adult stem cells as an alternative source of multipotential (pluripotential) cells in regenerative medicine. *Curr Stem Cell Res Ther* 2009; 4: 107-17.
14. Snykers S, De Kock J, Rogiers V, Vanhaecke T. In vitro differentiation of embryonic and adult stem cells into hepatocytes: state of the art. *Stem Cells* 2009; 27: 577-605.
15. Filip S, Mokry J, Horacek J, English D. Stem cells and the phenomena of plasticity and diversity: a limiting property of carcinogenesis. *Stem Cells Dev* 2008; 17: 1031-8.
16. Scott CT. Stem cells: new frontiers of ethics, law, and policy. *Neurosurg Focus* 2008; 24: E24.
17. Thirumangalathu S, Barlow LA. In vivo fate tracing studies of mammalian taste cell progenitors. *Ann NY Acad Sci* 2009; 1170: 34-8.
18. Trounson A. New perspectives in human stem cell therapeutic research. *BMC Med* 2009; 7: 29.
19. Chidgey AP, Layton D, Trounson A, Boyd RL. Tolerance strategies for stem-cell-based therapies. *Nature* 2008; 453: 330-7.
20. Trounson A, Elefanta A. Stem cells in biology, tissue engineering and medicine: the leading edge keeps moving. *Curr Opin Biotechnol* 2007; 18: 432-3.
21. Zhu S, Wurdak H, Wang J, Lyssiotis CA, Peters EC, Cho CY, et al. A small molecule primes embryonic stem cells for differentiation. *Cell Stem Cell* 2009; 4: 416-26.
22. Sanmano B, Mizoguchi M, Suga Y, Ikeda S, Ogawa H. Engraftment of umbilical cord epithelial cells in athymic mice: in an attempt to improve reconstructed skin equivalents used as epithelial composite. *J Dermatol Sci* 2005; 37: 29-39.
23. Mizoguchi M, Suga Y, Sanmano B, Ikeda S, Ogawa H. Organotypic culture and surface plantation using umbilical cord epithelial cells: morphogenesis and expression of differentiation markers mimicking cutaneous epidermis. *J Dermatol Sci* 2004; 35: 199-206.
24. Metallo CM, Azarin SM, Moses LE, Ji L, de Pablo JJ, Palecek SP. Human embryonic stem cell-derived keratinocytes exhibit an epidermal transcription program and undergo epithelial morphogenesis in engineered tissue constructs. *Tissue Eng Part A* 2010; 16: 213-23.
25. Lammers G, Tjabringa GS, Schalkwijk J, Daamen WF, van Kuppevelt TH. A molecularly defined array based on native fibrillar collagen for the assessment of skin tissue engineering biomaterials. *Biomaterials* 2009; 30: 6213-20.

26. Gelain F. Novel opportunities and challenges offered by nanobiomaterials in tissue engineering. *Int J Nanomedicine* 2008; 3: 415-24.
27. Engelmayer GC Jr, Papworth GD, Watkins SC, Mayer JE Jr, Sacks MS. Guidance of engineered tissue collagen orientation by large-scale scaffold microstructures. *J Biomech* 2006; 39: 1819-31.
28. Kremer M, Lang E, Berger A. Organotypical engineering of differentiated composite-skin equivalents of human keratinocytes in a collagen-GAG matrix (INTEGRA Artificial Skin) in a perfusion culture system. *Langenbecks Arch Surg* 2001; 386: 357-63.
29. Place ES, Evans ND, Stevens MM. Complexity in biomaterials for tissue engineering. *Nat Mater* 2009; 8: 457-70.
30. Place ES, George JH, Williams CK, Stevens MM. Synthetic polymer scaffolds for tissue engineering. *Chem Soc Rev* 2009; 38: 1139-51.
31. Nisbet DR, Forsythe JS, Shen W, Finkelstein DI, Horne MK. Review paper: a review of the cellular response on electrospun nanofibers for tissue engineering. *J Biomater Appl* 2009; 24: 7-29.
32. Bonfield W. Designing porous scaffolds for tissue engineering. *Philos Transact A Math Phys Eng Sci* 2006; 364: 227-32.
33. Tabata Y. Biomaterial technology for tissue engineering applications. *J R Soc Interface* 2009; 6(Suppl 3): S311-24.
34. van Beilen JB, Poirier Y. Production of renewable polymers from crop plants. *Plant J* 2008; 54: 684-701.
35. Shaikh FM, Callanan A, Kavanagh EG, Burke PE, Grace PA, McGloughlin TM. Fibrin: a natural biodegradable scaffold in vascular tissue engineering. *Cells Tissues Organs* 2008; 188: 333-46.
36. Barnes CP, Sell SA, Boland ED, Simpson DG, Bowlin GL. Nanofiber technology: designing the next generation of tissue engineering scaffolds. *Adv Drug Deliv Rev* 2007; 59: 1413-33.
37. Kanungo BP, Gibson LJ. Density-property relationships in collagen-glycosaminoglycan scaffolds. *Acta Biomater* 2010; 6: 344-53.
38. Waite JH, Lichtenegger HC, Stucky GD, Hansma P. Exploring molecular and mechanical gradients in structural bioscaffolds. *Biochemistry* 2004; 43: 7653-62.
39. Li CQ, Huang B, Luo G, Zhang CZ, Zhuang Y, Zhou Y. Construction of collagen II/hyaluronate/chondroitin-6-sulfate tri-copolymer scaffold for nucleus pulposus tissue engineering and preliminary analysis of its physico-chemical properties and biocompatibility. *J Mater Sci Mater Med* 2010; 21: 741-51.
40. Ye C, Hu P, Ma MX, Xiang Y, Liu RG, Shang XW. PHB/PHBHHx scaffolds and human adipose-derived stem cells for cartilage tissue engineering. *Biomaterials* 2009; 30: 4401-6.
41. Deng Y, Zhao K, Zhang XF, Hu P, Chen GQ. Study on the three-dimensional proliferation of rabbit articular cartilage-derived chondrocytes on polyhydroxyalkanoate scaffolds. *Biomaterials* 2002; 23: 4049-56.
42. Liuyun J, Yubao L, Chengdong X. Preparation and biological properties of a novel composite scaffold of nano-hydroxyapatite/chitosan/carboxymethyl cellulose for bone tissue engineering. *J Biomed Sci* 2009; 16: 65.
43. Roeker S, Bohm S, Diederichs S, Bode F, Quade A, Korzhikov V, et al. A study on the influence of biocompatible composites with bioactive ligands toward their effect on cell adhesion and growth for the application in bone tissue engineering. *J Biomed Mater Res B Appl Biomater* 2009; 91: 153-62.
44. Dado D, Levenberg S. Cell-scaffold mechanical interplay within engineered tissue. *Semin Cell Dev Biol* 2009; 20: 656-64.
45. Kim EJ, Yoon SJ, Yeo GD, Pai CM, Kang IK. Preparation of biodegradable PLA/PLGA membranes with PGA mesh and their application for periodontal guided tissue regeneration. *Biomed Mater* 2009; 4: 055001.
46. Tschon M, Fini M, Giavaresi G, Torricelli P, Rimondini L, Ambrosio L, et al. In vitro and in vivo behaviour of biodegradable and injectable PLA/PGA copolymers related to different matrices. *Int J Artif Organs* 2007; 30: 352-62.
47. Lam SM, Glasgold RA, Glasgold MJ. Limitations, complications, and long-term sequelae of fat transfer. *Facial Plast Surg Clin North Am* 2008; 16: 391-9.
48. Reding R, Gras J, Truong DQ, Wieers G, Latinne D. The immunological monitoring of alloreactive responses in liver transplant recipients: a review. *Liver Transpl* 2006; 12: 373-83.
49. Pillai AA, Levitsky J. Overview of immunosuppression in liver transplantation. *World J Gastroenterol* 2009; 15: 4225-33.
50. Sanz-Herrera JA, Moreo P, Garcia-Aznar JM, Doblare M. On the effect of substrate curvature

- on cell mechanics. *Biomaterials* 2009; 30: 6674-86.
51. Pozzobon M, Ghionzoli M, De Coppi P. ES, iPS, MSC, and AFS cells. Stem cells exploitation for Pediatric Surgery: current research and perspective. *Pediatr Surg Int* 2010; 26: 3-10.
 52. Burns JW. Biology takes centre stage. *Nat Mater* 2009; 8: 441-3.
 53. Nirmalanandhan VS, Sittampalam GS. Stem cells in drug discovery, tissue engineering, and regenerative medicine: emerging opportunities and challenges. *J Biomol Screen* 2009; 14: 755-68.
 54. Ikeda E, Morita R, Nakao K, Ishida K, Nakamura T, Takano-Yamamoto T, et al. Fully functional bioengineered tooth replacement as an organ replacement therapy. *Proc Natl Acad Sci U S A* 2009; 106: 13475-80.

มุมมองทางการแพทย์เกี่ยวกับวิศวกรรมเนื้อเยื่อเพื่อทดแทนผิวหนังและการเสริมมวลเนื้อเยื่อ

บริสุทธิ์ แสนมโน หาญพานิช

วิศวกรรมเนื้อเยื่อเป็นการประยุกต์ใช้อย่างหนึ่งของการแพทย์เพื่อการฟื้นฟูซึ่งการแพทย์สาขานี้ เน้นไปที่การประยุกต์ใช้เทคโนโลยีต่าง ๆ เพื่อ ทดแทน, ซ่อมแซม, หรือเสริมสร้างเนื้อเยื่อขึ้นมาใหม่ไม่ว่าสาเหตุของการเสื่อมนั้นจะมาจากสาเหตุใดก็ตาม เช่น การผิปกติแต่กำเนิด, การเป็นโรค, อุบัติเหตุหรือแม้แต่ความแก่ชราเองก็ตาม ศาสตร์สาขานี้เป็นการประยุกต์รวมหลากหลายสาขาวิชาเข้ามาประกอบกัน เช่น วิทยาศาสตร์กายภาพ, วิศวกรรมศาสตร์, แพทยศาสตร์, ความรู้ทางด้านเซลล์ต้นกำเนิด, ความรู้เกี่ยวกับโครงสร้างเนื้อเยื่อและระบบที่ใช้ควบคุมการเจริญและพัฒนาของเซลล์เพื่อนำมาพัฒนาเพื่อลดข้อจำกัดจากการใช้เนื้อเยื่อทดแทนจากตนเอง, การปฏิเสธเนื้อเยื่อจากผู้อื่น เป็นต้น องค์ความรู้ที่ได้นั้นหากสามารถนำไปประยุกต์ใช้ได้จะเป็นประโยชน์ อย่างมหาศาล
