Basic Ideas and Concepts about Tissue engineering: A Review

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Abstract— Injuries or diseases of the human body are usually treated by therapeutics or surgery. Even in the past century, the treatment of disorders by the process of transplantation was concidered futuristic. With advancement in bio sciences, we have been able to discover new concepts and have performed procedures like never before. Yet our ultimate goal is to completely repair or regenerate human tissue. This is where the concept of tissue engineering plays a vital role. Tissue engineering is the amalgamation of engineering and life sciences. This field is rapidly developing and has the potential to impact significantly on the system of bio medicine. To be successful in the field of tissue engineering, we need to have clear ideas about the basic principles and concepts of tissue regeneration. This article reviews the background information and provides a basic description about the components necessary for tissue engineering.

Index Terms— Tissue engineering, Regeneration, Stem Cells, Scaffold, Signalling Molecule, Growth Factors, Bioreactors

INTRODUCTION:

Injuries to different parts of the human body heals and regenerates to some extent but beyond that , healing occurs by scar formation which usually causes loss of function , structure and aesthetics. Extensive surgery, resection, burns, wounds or trauma are a few examples where healing occurs by secondary intention. Aggressive tumors in the maxillofacial region require extensive surgical intervention. In severe cases, mandibular hemisection is also performed. In such situations the individual is unable to perform vital functions like swallowing, talking etc. Aesthetics is also hampered causing immense psychological trauma.

For rehabilitative purposes, grafts are used for reconstruction of bone, vessels, skin, cartilage etc. This procedure again requires extensive surgery not only in the recipient site but also at the donor site causing much more inconvenience to the patients [1]. Allogenic grafts might be rejected by the host or xenogenic grafts might not have proper biocompatibility. These drawbacks have directed scientists and clinicians to research and implement the science of tissue engineering in surgical reconstruction.

Tissue engineering is the process where a biological substitute is developed for preserving tissue structure and function. It is an interdisciplinary field that incorporates engineering and life sciences [2].

Initial use of the process of tissue engineering can be found at around 1980 where researchers reported that skin regeneration was performed by the use of "cells in collagen gels or the use of collagen glcosaminoglycan compounds" [3, 4]. Gradually tissue engineering developed and advanced with the help of research. In 2004, Warnke et. al. studied the use of tissue engineering for the regeneration of mandible. The research showed good three dimensional outcomes [5].

For the regeneration of a living tissue, a proper cell source is required and a backbone for the cells in the form of a scaffold or a template is needed. These components are then cultured in a proper culture environment and the final tissue is then introduced into effected site. The major components for tissue engineering are:

1. Cells
2. Scaffold
3. Signalling molecules
4. Culture environment

This review article mainly emphasize on the basic idea of tissue engineering with a short description about the components that are mainly required for the process.

CELLS:

The cellular component is the most important part of the engineered tissue. Different types of cells that are used for the purpose are [6]:

- Autologous cells (cells obtained from the patient)
- Allogenic (cells obtained from other human being)
- Xenogenic (colls obtained from other species)

The cells may be directly extracted from the donor site or it may also be extracted and increased in number by growing outside the body, it may also be cloned or genetically modified. Autologous cells are usually preferred as the chance of graft rejection can be completely eliminated. However there are certain drawbacks, for example the donor cells might be unhealthy or there might not be enough number of cells or there is always a doubt that the cells might not be able to survive for the optimal time required for regeneration. Allogenic and xenogenic grafts always have a possibility of graft rejection. These prob-

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lems were addressed by the discovery and advancement in stem cell research.

Initially it was thought that stem cells belonged only in the embryonic stages and after completion of development these cells were lost. Later it was established that even in adulthood, stem cells do persist in our body, at specific sites for example skin, bone etc. [7,8] .Mesenchymal stem cells are remnants of mesenchymas cells which during development arises from neural crest cells, migrate and undergo differentiation to give rise to almost all craniofacial structures for example, bone cartilage muscles ligaments tendons periodontium teeth etc.[9] . Different types of stem cells that are found in the craniofacial region are: Periodontal Ligament Stem Cells, Stem Cells from Human Exfoliated Deciduous Teeth, Dental Pulp Stem Cells etc.

A stem cell will have 2 important properties, the property of self renewal and the property of differentiation into atleast 2 different types of cells. These properties of a stem cell make it an ideal cell source for tissue engineering [10].

These cells are incorporated with a scaffold or a template which provides a basic structure to the engineered tissue.

SCAFFOLD:

All living tissue consists of extracellular matrix which provides proper structure to the tissue. This ECM also provides the cells with nutrients and oxygen, the most important necessities for survival of the cell. It also aids in eliminating waste products from the cells. Likewise, in an engineered tissue, the scaffold forms the backbone for the cellular structure; it provides the tissue with stiffness and tensile strength. Moreover, the scaffold organizes the cells in a three dimensional structure and produces stimuli which help in the growth and formation of the regenerated tissue [11].

To be able to perform its function, a scaffold should have a few important properties:

Bio-compatibility should provide stability and strength to the engineered tissue, porous [12] and semipermeable, biodegradable etc.

The scaffold material can be synthetic or natural.

Synthetic scaffold: Advantage of a synthetic scaffold is that it can be controlled; regulated and reproduced according the need of the tissue that is to be regenerated. Some synthetic polymers are: polyethylene oxide (PEO), polyvinyl alcohol (PVA), polyacrylic acid (PAA), polypropylene furmarate-co-ethylene glycol (P(PF-co-EG)) , silicone, metals like titanium etc[13].

Natural scaffold: Natural scaffolds are also used in tissue engineering as they are easily incorporated and accepted by the body. This is because these molecules are components of the human body. A commonly used natural scaffold is collagen, its success lies in the fact that it is the main component of the tissue extracellular fluid [14, 15]. Moreover collagen can be easily degraded by the cells present in the engineered tissue. Other commonly used natural scaffolds are hyaluronic acid, alginate, chitosan, hydroxyapatite etc.

Both organic and synthetic scaffolds are used in the form of mesh, foam or sheets [6]. Apart from giving mechanical support, the scaffold also perform important functions like it aids healing by production of incorporated protective gels or helps in localized hormone delivery [17]. The scaffold along with the cells are then introduced to signaling molecules which would help in growth, differentiation of the cells and thus help the formation of the engineered tissue.

SIGNALLING MOLECULES

Signalling molecules are an important component of the engineered tissue. It directs the cells present in the scaffold to differentiate, develop and replicate [16]. Commonly used signalling molecules can be broadly classified as mitogens, growth factors and morphogens. Among the three, growth factors are mostly preferred by tissue engineers [18]. In natural tissue regeneration, growth factors are released into the injured tissue and these molecules play an important role by inducing cell growth and proliferation, angiogenesis etc [17]. These special molecules are produced by different cells and exert a variety of effects. The action of the growthfactors depend highly on the concentration, they have high turnover and thus have a very short half life, a few minutes only.

Growth factors that are commonly used in tissue engineering are:

Angiopoietin 1 and 2 ; Fibroblast growth factor[19] ; Platelet derived growth factor[20,21] , Nerve growth factor [22] ; Insulin like growth factor ; Epidermal growth factor[23,24] ; Haematopoetic growth factor; Transforming growth factor[25] ;Vascular endothelial growth factor [26] ; Bone morphogenetic protein 2 and 7[27].

The growth factors are delivered from special devices or specials cells that are present along with the stem cells in the engineered tissue [28]. The growth factors then act by binding to specific sites on the cell surfaces and the cellular responses that are produced by the signalling molecules determines the cell survival, migration, differentiation or proliferation.

CULTURE ENVIRONMENT:

The cells along with the scaffold and the signalling molecules would need a culture medium for the development of the engineered tissue. This culture medium will provide optimal environment for cell growth and differentiation. Early researches in tissue engineering utilized basic culture environments, static conditions for example a pertidish [29].But with such simple equipments, maintaining optimal environment needed for the development of the tissue was a difficult task. However with more improvements, complex culture environment were introduced which have shown to improve the conditions of developing tissue in turn helping in the success of tissue engineering.

Thus began the use of bioreactors. Bioreactors are devices that provide optimal culture environment to the developing tissue [30]. Commonly used bioreactors are –

- Spinner Flask Bioreactor[31]
- Rotating Wall Bioreactor[32]
- Hollow Fiber Bioreactor[33]

- Direct Perfusion Bioreactor[34]

Modern varieties of bioreactors do not need human intervention. The ingredients that are needed for tissue engineering are pre loaded, the tissue or cells, in the form of biopsies from the donor are just introduced into the device and on completion of the process, a living engineered tissue is all prepared to be introduced to the human body. Thus the bioreactor provide proper environment for the success of engineered tissue.

CONCLUSION:

Tissue engineering is one of the most pioneering concepts in modern medicine. Yet the process is complex and achieving complete perfection is difficult. We would be able to achieve complete success only if we are able to mimic natural conditions inside the human body. Advances in tissue engineering will help develop a complete organ or organ system in the future and that would change the way we see medicine and therapeutics today. There is immense scope in the field of tissue engineering and extensive research is necessary.

REFERENCES

1. Hernandez F,Ruiz-Magnaz V,Guijarro-Martinez R. Mandible reconstruction with tissue engineering in Multiple Recurrent Ameloblastoma Int J Periodontics and Restorative Dent 2012;32:e82-e86
2. Langer R, Vacanti JP. Tissue engineering. Science 1993; 260:920 26.
3. Bell E, Ehflich P, Buttle DJ, Nakatsuji T. Living tissue formed in vitro and accepted as skin-equivalent of full thickness. Science 1981; 221:1052-54.
4. Burke JF, Yannas IV, Quimby WC, Bondoc CC, Jung WK. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. Ann Surg 1981; 194: 413-48.
5. Waranke PH ,Springer IN, Wiltfang J et. Al. Growth and transplantation of a custom vascularized bone graft in man The Lancet,2004;364:766-770
6. Curtis A, Riehle M, Tissue engineering: the biophysical background. Phys. Med. Biol. 46, R47-R65
7. Caplan AI. Mesenchymal stem cells. J Orthoped Res 1991;9:641–50.
8. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–7
9. Mao JJ, Giannobile WV , Helms JA, Hollister SJ, Krebsbach PH, Longaker MT ,Craniofacial Tissue Engineering by Stem Cells J Dent Res. 2006 November ; 85(11): 966–979.
10. Parker GC, Anastassova-Kristeva M, Broxmeyer HE, Dodge WH, Eisenberg LM, Gehling UM, et al. Stem cells: shibboleths of development. Stem Cells Dev 2004;13:579–584.
11. Yang S, Leong K-F, Du Z, Chua C-K. The design of scaffolds for use in tissue engineering. Part I. Traditional factors. Tissue Eng 2001;7:679–89
12. Hu Y, Grainger DW, Winn SR, Hollinger JO. Fabrication of poly(a-hydroxy acid) foam scaffolds using multiple solvent systems. J Biomed Mater Res 2001;59:563–72.
13. Drury L, Mooney D. Hydrogels for tissue engineering: scaffold design variables and applications Biomaterials (2003);24: 4337–4351
14. Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. Molecular biology of the cell, 3rd ed. New York: Garland Publishing, Inc.; 1994.
15. Lee CH, Singla A, Lee Y. Biomedical applications of collagen. Int J Pharm 2001;221:1–22.
16. Cross, M. & Dexter, T. M. Growth factors in development, transformation, and tumorigenesis. Cell 1991;64:271–280.
17. Whitaker M, Quirk R,Howdle S, Shakesheff K. Growth factor release from tissue engineering scaffoldsJPP 2001;53: 1427–1437
18. Babensee, J. E., McIntire, L. V., Mikos, A. G. Growth factor delivery for tissue engineering. Pharm. Res. 2000;17: 497-504
19. Wissink, M. J. B., Beernink, R., Scharenborg, N. M., Poot, A. A., Engbers, G. H. M., Beugeling, T., van Aken, W. G., Feijen, J. Endothelial cell seeding of (heparinized) collagen matrices: effects of bFGF pre-loading on proliferation (after low density seeding) and pro-coagulant factors. J. Control. Rel. 2000;67: 141-155
20. Lohmann, C. H., Schwartz, Z., Niederauer, G. G., Carnes, D. L., Dean, D. D., Boyan, B. B. Pretreatment with platelet derived growth factor-BB modulates the ability of costochondral resting zone chondrocytes incorporated into PLA}PGA scaffolds to form new cartilage in vivo. Biomaterials 2000;21: 49-61
21. Walsh, W. R., Kim, H. D., Jong, Y. S., Valentini, R. F. Controlled- release of platelet-derived growth-factor using ethylenevinyl acetate copolymer (evac) coated on stainless-steel wires. Biomaterials1995; 16: 1319-1325
22. Krewson, C. E., Saltzman, W. M. Transport and elimination of recombinant human NGF during long-term delivery to the brain. Brain Res. 1996;727: 169-181
23. Chen, G. P., Ito, Y., Imanishi, Y. Photo-immobilization of epidermal growth factor enhances its mitogenic effect by arti®cial juxtacrine signaling. Biochim. Biophys. Acta Mol. Cell Res. 1997;1358: 200-208
24. von Recum, H., Kikuchi, A., Yamato, M., Sakurai, Y., Okano, T., Kim, S. W. (1999) Growth factor and matrix molecules preserve cell function on thermally responsive culture surfaces. Tissue Eng. 1999;5: 251-265
25. Kim, H. D., Valentini, R. F. (1997) Human osteoblast response in vitro to platelet-derived growth factor and transforming growth factor-beta delivered from controlled-release polymer rods. Biomaterials 1997;18: 1175-1184
26. Weatherford, D. A., Sackman, J. E., Reddick, T. T., Freeman, M. B., Stevens, S. L., Goldman, M. H. Vascular endothelial growth factor and heparin in a biologic glue promotes human aortic endothelial cell proliferation with aortic smooth muscle cell inhibition. Surgery 1996;120: 433-439

27. Hollinger, J. O., Leong, K. Poly(alpha-hydroxy acids) : carriers for bone morphogenetic proteins. Biomaterials 1996;17: 187-194

28. Babensee, J.E., McIntire, L.V. & Mikos, A.G. Pharm Res 2000;17: 497.

29. Vunjak-Novakovic G, Freed L, Biron RJ, Langer R. Effects of mixing on the composition and morphology of tissue-engineered cartilage. Am Inst Chem Eng J 1996; 42: 850-60

30. Ivan Martin, David Wendt and Michael Heberer The role of bioreactors in tissue engineering TRENDS in Biotechnology 2004;22(2):81-86

31. Vunjak-Novakovic, G. et al.Effects of mixing on the composition and morphology of tissue-engineered cartilage. AIChE J. 1996;42:850–860

32. Unsworth, B.R. and Lelkes, P.I. Growing tissues in microgravity. Nat. Med.1998; 4:901–907

33. Jasmund, I. and Bader, A. Bioreactor developments for tissue engineering applications by the example of the bioartificial liver. Adv. Biochem. Eng. Biotechnol.2002; 74: 99–109

34. Wendt, D. et al. Oscillating perfusion of cell suspensions through three-dimensional scaffolds enhances cell seeding efficiency and uniformity. Biotechnol. Bioeng. 2003;84: 205–214.