Research & Reviews: Journal of Veterinary Sciences

Natural Biomaterials for Veterinary Regenerative Therapy

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Research Article

Received date: 11/06/2015

Accepted date: 02/09/2015

Published date: 09/09/2015

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Keywords: Stem cells, Biomaterials, Cellular delivery, Tissue engineering, Cell therapy.

ABSTRACT

Natural and synthetic biomaterials play an important role in the treatment of different diseases. Current research is trying to obtain different biomaterials with optimized characteristics. Mesenchymal stem cells with biomaterial scaffolds can provide a promising strategy for tissue engineering and cellular delivery. Because these cells are key elements of cell therapy of various diseases, evaluation and use of specific substrates is highly important. Concomitant use of stem cells and biomaterial scaffolds offer a hopeful strategy for tissue engineering. In this review, we examine the applications of the different types of natural scaffolds (collagen, fibrinogen, gelatin etc.) and evaluate their use in combination with stem cells for tissue engineering applications.

INTRODUCTION

Tissue engineering is a rapidly developing area that might restore, maintain or improve tissue functions [1,2]. The major elements of tissue engineering are: integrate cells, scaffolds and biologically active molecules [3-10]. These components proceed synergistically to regulate stem cell propagation and differentiation consequently ensuring tissue regeneration [11]. Scaffolds provide the environment and space for cells [4,12,13] and the bioactive molecules are required to induce regeneration [14]. The fundamental idea of tissue engineering is to induce tissue regeneration at diseased tissues or organs with cells and their environment [15]. This requires a local environment that enables to augment the proliferation and differentiation of cells [12,15]. The minimum requirements for biomaterials refer to present excellent biocompatibility, controllable biodegradability, appropriate mechanical strength, flexibility and ability to absorb body fluids [16]. The surface morphology is also very important on the attachment of surrounding cells and tissues after implantation. Efficient modification of the scaffold surface may play a significant role in facilitating tissue engineering. Recent findings have reported that surface modification of scaffolds with nano-sized materials or combinations of several biomaterials may stimulate bioactivity, cell proliferation, tissue compatibility and controllable biodegradability [4,17].

SOURCES OF STEM CELLS

The biotechnology of harvesting and use stem cells is the major interest given by their ability to differentiate into mature somatic phenotypes. Recent interest in stem cell biology and its therapeutic potential has led to search an accessible new source of stem cells. Stem cells are definied as cells with clonogenic ability, self-renewing and differentiation capacity in one or more specialized cell lineage [18].

Stem cells can be generally classified according to the origin into embryonic and adult (postnatal) stem cells or according to their plasticity into totipotent, pluripotent, multipotent and unipotent stem cells. While adult stem cells are derived from adult body, embryonic stem cells can be harvested from embryo from the inner cell mass [19,20]. Compared with embryonic stem cells that are often surrounded by controversy, mesenchymal stem cells (MSCs) have received wider attention because they can be easily isolated from different sources [21] including the oral cavity [22].

Mesenchymal stem cells (MSCs) which can be isolated from almost all postnatal organs and tissues [23], are stromal unspecialized cells that have the ability to self-renewal through cell division and also exhibit multilineage differentiation and immunosuppressive functions [21,24,25].

Oral cavity such as dental pulp, dental follicle, dental papilla and periodontal ligament (PDL), coronal pulp, apical papilla, subepithelial layers of oral mucosa, the gingival tissues, exfoliated deciduous teeth have been identified as easily accessible sources of multipotent stem cells that could be cryopreserved and used for autogenic or allogenic cell therapy [20,21].

An important subject for the development of differentiated cells is the practical aspects of producing optimal culture conditions (substrates, cultures medium, growth factors, etc) of these cells [26] for prolonged expansion [27]. One of the major interests of regenerative therapy requires the cultivation of stem cells on different specific substrates namely degradable scaffolds to obtain all kinds of tissues through the control and guidance of their differentiation [28].

In vitro studies have shown that cartilage extracellular matrix (ECM) components (collagen, elastin, fibrionectin and growth factors (BMP-2, BMP-4, FGF, IGF, VEGF etc.) regulate the differentiation of stem cells. The three-dimensional (3D) nature of ECM can greatly affect a number of associated cells [29-31] and plays a crucial role in regulating cell behavior [11]. The dynamic composition of ECM acts as a reservoir for soluble signaling molecules and mediates signals from other sources to migrating, proliferating and differentiating cells [32]. ECM of each organ is different in its composition and in its relations with the cells is unique to that organ [31].

Artificial substitutes for ECM are some 3D structures, called tissue scaffolds, which may contain natural or synthetic polymers or a mixture of both [33].

STEM CELLS CULTIVATION ON NATURAL BIOMATERIALS

Biomaterial-based scaffolds are the most important tool in providing a 3D environment for cells, both in culture and inside the body. The main properties of biocompatible scaffolds (synthetic or natural) consist in optimal fluid transport, delivery of bioactive molecules, material degradation, cell-recognizable surface chemistries, mechanical integrity and the ability to induce signal transduction [34,35].

Natural biomaterials used for stem cells cultivation can consist of components found in the ECM such as alginate, cellulose, chitosan, collagen, fibrinogen, hyaluronic acid, silk fibroin, glycosaminoglycans (GAGs), hydroxyapatite (HA) etc., and therefore have the advantage of being bioactive, biocompatible, and with similar mechanical properties as native tissue [36].

Ideally the scaffold must provide certain properties a) controlled degradation; b) with the potential to maintain cell viability, differentiation, and ECM production; c) with probable diffusion of nutrients and waste products; d) adherence and integration capacity e) and mechanical integrity [37].

Collagen

Collagen is the key constituent of the extracellular matrix characterized by exceptional biocompatibility, low antigenicity [38] increased adhesion capacity and high degree of biodegradability [36], is an ideal scaffold or carrier for tissue engineering. Collagen contains specific cell adhesion domains [36] and its derivatives isolated from bovine cartilage are a classic natural material for tissue engineering; this organic constituent provides mechanical strength in tissues [39]. Collagen membranes ensure the attachment, growth and migration of mesenchymal stem cells without influencing the expression of the stemness genes [40].

Fibrinogen and fibrin

Fibrinogen and fibrin glue are another class of tissue-derived natural materials that can be utilized to create three-dimensional scaffold materials, widely utilized as a biomaterial. Fibrinogen is one of the primary components of the coagulation cascade [41]. The haemostatic coagulation processes require a combination between fibrinogen and thrombin under the catalysis of calcium ions [42,43]. It is attractive as a natural scaffold because it can be made from autologous blood.

Studies in nude mice have demonstrated the fibrin glue capacity as a good biomaterial, because the degradation and polymerization time can be controlled [37,44]. Fibrin glue can also combined with other polymers like polyurethane, in order to maintain cell viability, attachment and distribution with increased expression of aggrecan and type II collagen [37,45].

Gelatine

Gelatine, another biocompatible substrate, derived from collagen, can be modified as photopolymerizable gelatine that can crosslink through polymerization induced by irradiation with visible light [46]. Gelatine/alginate gels can promote chondrocyte proliferation and expression of hyaline matrix molecules and type II collagen with increased spatial deposition of proteoglycans [47]. Gelatin-based hydrogels are biodegradable, with high biocompatibility, and offer possibilities to introduce functional groups and/or ligands [48].

Silk fibroin

Silk fibroin is composed of a filament core protein called fibroin with a glue-like coat of sericin proteins. Is a natural biomaterial isolated from silkworm cocoons, spiders, scorpions, mites and flies. Silk it can be converted into porous scaffolds using gas foaming or salt leaching methods [49-52] and is widely used as suture materials for surgical applications. This biomaterial shows good biocompatibility and suitable mechanical properties. The combination with mammalian cell makes silk fibroin an attractive material for tissue engineering [49].

Hyaluronan or hyaluronic acid

Hyaluronan or hyaluronic acid is an acidic glycosaminoglycan, one of the major components of the extracellular matrix and represents an extremely attractive natural biomaterial [53]. It is present in tissues as a gel-like substance but can be chemically modified for efficient processing into fibers, membranes, or microspheres. A modified type of hyaluronic acid is commercially available as Hyaff® [54].

Chitosan

Chitosan is a biosynthetic polysaccharide derivative of chitin harvested from exoskeletons of arthropods. This polymer is biocompatible, degraded *in vivo* by lysozymes, and can interact with growth factors and adhesion proteins. The biodegradable and biocompatible capacity is similar with glycosaminoglycans often used for in vitro studies [55-59].

Matrigel™

Matrigel™, a product currently available commercially, is comprised of a variety of ECM components including laminin, collagen IV, and heparan sulfate proteoglycans [53,54] and has been used extensively in cell culture [54,56]. Is an ECM-mimicking hydrogel produced by mouse Engelbreth-Holm-Swarm tumors. It closely resembles the native ECM with a similar composition and assembling structure [55]. The cell microenvironment plays a significant role in determining progenitor cell fate and function. Therefore the accurate coordination of interpreting spatial and temporal cues from their microenvironment is really essential for stem cells to generate complex, functional tissues [60].

CONCLUSION

New biomaterials are being continuously developed. Their interaction with inserted cells and growth factors has a decisive role for regenerative medicine. Understanding the complex mechanisms involved in stem cells adhesion and division allows us to obtain useful biodegradable biomaterials for cell therapy. Successful combination of these scaffolds lead to mimicking cellular microenvironment and maintaining pluripotent ability of these cells.

ACKNOWLEDGMENTS

This review paper was published under the frame of European Social Found, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/138776.

REFERENCES

1. Leor J, et al. Cells, scaffolds, and molecules for myocardial tissue engineering. Pharmacology & Therapeutics. (2005);105: 151–163.
2. Ungaro F, et al. Bio activated Polymer Scaffolds for Tissue Engineering. Topics in Tissue Engineering. (2005);2: 1-39.
3. Goessler UR, et al. In-vitro analysis of the expression of TGFB-superfamily- members during chondrogenic differentiation of mesenchymal stem cells and chondrocytes during dedifferentiation in cell culture. Cellular & Molecular Biology Letters. (2005);10: 345–362.
4. Kanayama I, et al. Comparative study of bioactivity of collagen scaffolds coated with graphene oxide and reduced graphene oxide. International Journal of Nanomedicine. (2014);9: 3363–3373.
5. Kim RY, et al. Soft tissue engineering in craniomaxillofacial surgery. Ann Maxillofac Surg. (2014);4: 4–8.
6. Payne KF, et al. Tissue engineering technology and its possible applications in oral and maxillofacial surgery. Br J Oral Maxillofac Surg. (2014);52: 7-15.
7. Beiguera S and Ribatti D. Endothelialization approaches for viable engineered tissues. Angiogenesis. (2013);16: 1–14.
8. Brochhausen C, et al. Signalling molecules and growth factors for tissue engineering of cartilage-what can we learn from the growth plate?. J Tissue Eng Regen Med. (2009);3:416-429.

9. Kasaj A, et al. In vitro evaluation of various bioabsorbable and nonresorbable barrier membranes for guided tissue regeneration. Head & Face Medicine. (2008);4: 1-8.

10. Leor J, et al. Cells, scaffolds, and molecules for myocardial tissue engineering. Pharmacology & Therapeutics. (2005);105: 151–163.

11. Dolatshahi-Pirouz A, et al. A combinatorial cell-laden gel microarray for inducing osteogenic differentiation of human mesenchymal stem cells. Scientific Reports. (2014);4: 3896

12. Langer R and Vacanti JP. Tissue engineering. Science. (1993);26: 920–941.

13. Stock UA and Vacanti JP. Tissue engineering: current state and prospects. Annu Rev Med. (2001);52: 443–451.

14. Hughes FJ, et al. Periodontal regeneration: A challenge for the tissue engineer? Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine. (2010);224: 1345-1358.

15. Yamamoto M and Tabata Y. Tissue Engineering of Internal Medicine for Regeneration Therapy. Topics in Tissue Engineering. (2008);4: 1-24.

16. Khan R and Khan MH. Use of collagen as a biomaterial: An update. J Indian Soc Periodontol. (2013);17: 539–542.

17. Ibara A, et al. Osteoconductivity and biodegradability of collagen scaffold coated with nano-ß-TCP and fibroblast growth factor 2. J Nanomater. (2013);46: 1–11.

18. Rodriguez-Lozano FJ, et al. Mesenchymal stem cells derived from dental tissues. International Endodontic Journal. (2011);44: 800-806.

19. Gade NE, et al. Therapeutic potential of stem cells in veterinary practice. Vet World. (2012);5: 499-507.

20. Bojic S, et al. Dental stem cells - characteristics and potential. Histol Histopathol. (2014);29: 699-706.

21. Patel DM, et al. Therapeutic Potential of Mesenchymal Stem Cells in Regenerative Medicine. Stem Cells Int. (2013);1-15.

22. Jones BK and Klein OD. Oral epithelial stem cells in tissue maintenance and disease: the first steps in a long journey. International Journal of Oral Science. (2013);5: 121–129.

23. Porada CD, et al. Adult mesenchymal stem cells: a pluripotent population with multiple applications. Current stem cell research & therapy. (2006);1: 365–369.

24. Kim RH, et al. Therapeutic Potential of Mesenchymal Stem Cells for Oral and Systemic Diseases. Dent Clin North Am. (2012);56: 651–675.

25. Zhang QZ, et al. Human Oral Mucosa and Gingiva A Unique Reservoir for Mesenchymal Stem Cells. J Dent Res. (2012);91:1011–1018.

26. Baharvand H, et al. The effect of extracellular matrix on embryonic stem cell-derived cardiomyocytes. Journal of Molecular and Cellular Cardiology. (2005);38:495–503.

27. Ng CP, et al. Enhanced ex vivo expansion of adult mesenchymal stem cells by fetal mesenchymal stem cell ECM. Biomaterials. (2014);35: 4046-4057.

28. Battista S, et al. The effect of matrix composition of 3D constructs on embryonic stem cell differentiation. Biomaterials. (2005);26: 6194–6207.

29. Venstro KA and Reichardt LF. Extracellular matrix. 2: Role of extracellular matrix molecules and their receptors in the nervous system. FASEB J. (1993);7: 996–1003.

30. Wobus AM, et al. Embryonic stem cells as a model to study cardiac, skeletal muscle, and vascular smooth muscle cell differentiation. Methods Mol Biol. (2002);185: 127–156.

31. Thyber J and Hultgardh-Nilsson A. Fibronectin and the basement membrane components laminin and collagen type IV influence the phenotypic properties of subcultured rat aortic smooth muscle cells differently. Cell Tissue Res. (1994);276: 263–271.

32. Rosso F, et al. Smart materials as scaffolds for tissue engineering. J Cell Physiol. (2005);203: 465–470.

33. Bottaro DP, et al. Molecular signaling in bioengineered tissue microenvironments. Ann N Y Acad Sci. (2002);961,143-153.

34. Shin H, et al. Biomimetic materials for tissue engineering. Biomaterials. (2003);24: 4353–4364.

35. Drury JL, Mooney DJ. Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials. (2003);24: 4337–4351.

36. Chung C and Burdick JA. Engineering Cartilage Tissue. Adv.Drug.Deliv.Rev. (2008);14: 243-262.

37. Pati F, et al. Collagen scaffolds derived from fresh water fish origin and their biocompatibility. Journal of Biomedical Materials Research Part A. (2012);100: 1068–1079.

38. Yamada S, et al. Potency of Fish Collagen as a Scaffold for Regenerative Medicine. BioMed Research International. (2014);1-8.

39. Berne RM and Levy MN. Physiology. Mosby. New York, NY, USA 1998, 1160.

40. Ding L, et al. Transplantation of bone marrow mesenchymal stem cells on collagen scaffolds for the functional regeneration of injured rat uterus. Biomaterials. (2014);35: 4888–4900.

41. Brown AC and Barker TH. Fibrin-based biomaterials: Modulation of macroscopic properties through rational design at the molecular level. Acta Biomaterialia. (2014);10: 1502–1514.

42. Mosesson MW. Fibrinogen and fibrin structure and functions. Journal of Thrombosis and Haemostasis. (2005);3: 1894–1904.

43. Shaikh FM, et al. Fibrin: A natural biodegradable scaffold in vascular tissue engineering. Cells Tissues Organs. (2008);188: 333-346.

44. Silverman RP, et al. Injectable tissue-engineered cartilage using a fibrin glue polymer. Plast Reconstr Surg. (1999);103: 1809–1818.

45. Lee CR, et al. Fibrin-polyurethane composites for articular cartilage tissue engineering: A preliminary analysis. Tissue Engineering. (2005);11:1562–1573.

46. Hoshikawa A, et al. Encapsulation of chondrocytes in photopolymerizable styrenated gelatin for cartilage tissue engineering. Tissue Engineering. (2006);12: 2333-2341.

47. Schagemann JC, et al. Morphology and function of ovine articular cartilage chondrocytes in 3-D hydrogel culture. Cells Tissues Organs. (2006);182: 89–97.

48. Salamon A, et al. Gelatin-Based Hydrogels Promote Chondrogenic Differentiation of Human Adipose Tissue-Derived Mesenchymal Stem Cells In Vitro. Materials. (2014);7: 1342-1359.

49. Kundu B, et al. Silk fibroin biomaterials for tissue regenerations. Advanced Drug Delivery Reviews. (2013);65: 457–470.

50. Gravel M, et al. Responses of mesenchymal stem cell to chitosan-coralline composites microstructured using coralline as gas forming agent. Biomaterials. (2006);27: 1899–1906.

51. Hofmann HH, et al. Control of in vitro tissue-engineered bone-like structures using human mesenchymal stem cells and porous silk scaffolds. Biomaterials. (2007);28: 1152–1162.

52. Wang Y, et al. In vitro cartilage tissue engineering with 3D porous aqueous-derived silk scaffolds and mesenchymal stem cells. Biomaterials. (2005);26: 7082–7094.

53. Bissell SDM, et al. Support of cultured hepatocytes by a laminin-rich gel. Evidence for a functionally significant subendothelial matrix in normal rat liver. J Clin Invest. (1987);79: 801–812.

54. Kleinman HK, et al. Isolation and characterization of type IV procollagen, laminin, and heparan sulfate proteoglycan from the EHS sarcoma. Biochemistry. (1982);21: 6188–6193.

55. Arnaoutova I, et al. The endothelial cell tube formation assay on basement membrane turns 20: State of the science and the art. Angiogenesis. (2009);12: 267-274.

56. Xu C, et al. Feeder-free growth of undifferentiated human embryonic stem cells. Nat. Biotechnol. (2001);19: 971–974.

57. Gerecht S, et al. Hyaluronic acid hydrogel for controlled self-renewal and differentiation of human embryonic stem cells. Proceedings of the National Academy of Sciences of the United States of America. (2007);104: 11298–11303.

58. Brun P, et al. Chondrocyte aggregation and reorganization into three-dimensional scaffolds. J Biomed Mater Res. (1999);46: 337–346.

59. Subramanian A and Lin HY. Crosslinked chitosan: Its physical properties and the effects of matrix stiffness on chondrocyte cell morphology and proliferation. Journal of Biomedical Materials Research Part A. (2005);75: 742–753.

60. Dawson E, et al. Biomaterials for stem cell differentiation. Advanced Drug Delivery Reviews. (2007);60: 215–228.