Corresponding author's email: kamakura@tohoku.ac.jp

Octacalcium phosphate and collagen composite (OCPcol) demonstrated superior bone regeneration with angiogenesis (1, 2), and have been commercialized recently in Japan (3). Teriparatide (TPTD) is a bioactive recombinant form of parathyroid hormone that is approved for osteoporosis treatment. And OCPcol with a local single administration of TPTD enhanced bone repair of a rodent critical-sized bone defect (4, 5). Because mandibular bone reconstruction after segmental resection is a key clinical problem, it was examined whether single-dose local administration of OCPcol with TPTD can affect recovery after this procedure. OCPcol was prepared, and a commercially available hydroxyapatite and collagen composite (HAPcol) was used as a control. A 15 mm length segmental bone defect was made in the mandibular region of male beagle dogs. The experimental animals were divided in four groups. OCPcol treated with TPTD (OCPcol+TPTD), OCPcol, HAPcol treated with TPTD (HAPcol+TPTD), or HAPcol was implanted into the defect. The radiopaque areas of the implanted site were measured and statistically analyzed, and histological examination was performed after 6 months. The value of radiopaque area in total region of OCPcol+TPTD was highest, followed in order by OCPcol, HAPcol+TPTD, and HAPcol, and that of OCPcol+TPTD was significantly higher than that of HAPcol+TPTD or HAPcol. All segmented mandibles of OCPcol+TPTD and a part of those of OCPcol were bridged with newly formed bone, whereas no bone bridges were observed in HAPcol+TPTD or HAPcol. These results suggested that OCPcol treated with TPTD enabled bone reconstruction after segmental mandibular resection more than other three groups.

References

1. Kamakura S, Sasaki K, Honda Y, Anada T, Suzuki O. Octacalcium phosphate (OCP) combined with collagen orthotopically enhances bone regeneration. J Biomed Mater Res B Appl Biomater 79, 210, 2006; 2. Kouketsu A, Matsui K, Kawai T, Ezoe Y, Yanagisawa T, Yasuda A, Takahashi T, Kamakura S. Octacalcium phosphate collagen composite stimulates the expression and activity of osteogenic factors to promote bone regeneration. J Tissue Eng Reger Med 14, 99, 2020; 3. Kawai T, Kamakura S, Matsui K, Fukuda M, Takano H, Iino M, Ishikawa S, Kawana H, Soma T, Imamura E, Kizu H, Michibata A, Asahina I, Miura K, Nakamura N, Kibe T, Suzuki O, Takahashi T. Clinical study of octacalcium phosphate and collagen composite in oral and maxillofacial surgery. J Tissue Eng 11, 2041731419896449, 2020; 4. Kajii F, Iwai A, Tanaka H, Matsui K, Kawai T, Kamakura S. Single-dose local administration of teriparatide with a octacalcium phosphate collagen composite enhances bone regeneration in a rodent critical-sized calvarial defect. J Biomed Mater Res B Appl Biomater 106, 1851, 2018 5. Iwai A, Kajii F, Tanaka H, Sasaki K, Matsui K, Kawai T, Kamakura S. Bone regeneration by freeze-dried composite of octacalcium phosphate collagen and teriparatide. Oral Dis 24, 1514, 2018

Abstract 52

REGENERATIVE MEDICINE APPROACHES TO INTERVERTEBRAL DISC, IMPORTANCE OF PATHOLOGY

Christine Le Maitre[1]

[1]*Sheffield Hallam University*

Corresponding author's email: c.lemaitre@shu.ac.uk

Low back pain is the leading cause of morbidity worldwide and yet most therapies fail to target the cause and are purely symptomatic or end stage surgical options. Intervertebral disc degeneration is associated with approximately 40% of low back pain cases and thus a target for potential regeneration. Intervertebral disc degeneration is a catabolic process caused by altered cell behaviour and tissue biomechanics, leading to a harsh environment for potential cell therapies. A viscous cycle of degeneration, whereby cellular changes impact on matrix composition and biomechanical environment interact, leading to acceleration of degeneration. Degeneration leads to ingrowth of nerves into the normally aneural disc and increased synthesis of pain sensitizers leads to increased pain formation. To generate a successful regeneration strategy for the intervertebral disc this harsh environment must be considered. Here, the pathogenesis of disc degeneration will be discussed to highlight the importance of understanding the disease processes prior to developing regenerative approaches. The potential influence of the pathogenic processes which lead to disc degeneration will be discussed in light of regenerative approaches under development. Cellular, gene and biomaterial approaches for regeneration will be highlighted and their potential to halt the viscous cycle of degeneration enabling regeneration.

Abstract 53

INJECTABLE HYDROGEL FOR DISC REGENERATION STUDY OF INJECTABLITIY AND MECHANICAL PROPERTIES IN WHOLE HUMAN INTERVERTEBRAL DISCS

Christine Le Maitre[1], Joseph Snuggs[1], L Beckman[2], Hosni Cherif[2], Simon Partridge[1], Lee Breakwell[3], Ashley Cole[3], Neil Chiverton[3], Chris Sammon[1], Lisbet Haglund[2]

[1]*Sheffield Hallam University*
[2]*Montreal General Hospital*
[3]*Sheffield Hospitals NHS Trust*

Corresponding author's email: c.lemaitre@shu.ac.uk

INTRODUCTION: We have previously reported the development of an injectable hydrogel (NPgel), which has the potential to deliver patients own stem cells, via small bore needles, decreasing damage to the annulus fibrosus. NPgel drives stem cell differentiation to NP cells, and can inhibit the degenerate niche. However, clinical success of NPgel is dependent on the capacity to inject NPgel into naturally degenerate human discs, restore mechanical function to the IVD, and prevent extrusion during loading. Here, we investigated the injection of NPgel containing IOHEXOL to enable visualization during injection into human cadaveric discs and performed extrusion testing to determine whether NPgel was retained in the disc. METHODS: Cadaveric discs were prepared with intact vertebral bone, X-ray images were captured from transverse and sagittal planes together to determine disc height. Discs were pre-warmed to 37°C prior to mechanical analysis, discs were loaded under simulated walking conditions to calculate Moduli. Following initial testing discs were injected with NPgel containing IOHEXOL using fluoroscopy to visualize injection and disc height measured. Moduli measurements were determined post injection prior to ultimate strength testing to determine whether any NPgel extruded.

RESULTS: NPgel (600-1000µl) was easily injected into cadaveric discs where it filled cracks and fissures. NPgel injection resulted in significant increase in disc height and youngs moduli, furthermore NPgel was not extruded during failure testing. CONCLUSIONS: These results support the use of NPgel as an injectable therapy for regeneration of disc degeneration.

References

1. A. Thorpe, et al., Acta biomaterialia. 2016, 36, 99-111.

Abstract 54

A FIBER-ORIENTED MUSCLE MODEL FOR PREDICTING THE SOFT TISSUE DEFORMATION DURING MUSCLE CONTRACTION

Lei Tang[1], Cunqing Shan[1], Ling Wang[1], Dichen Li[1], Senay Mihcin[2]

[1]*State Key Laboratory for Manufacturing System Engineering, School of Mechanical Engineering, Xi'an Jiaotong University, 710054, Xi'an, ShaanXi, China*
[2]*Mechanical Engineering Department, Izmir Institute of High Technology, Urla, Izmir, Turkey*

Corresponding author's email: tanglei@stu.xjtu.edu.cn

Effective designing of rehabilitation apparatus with high comfort and functionality depends upon the accurate characterization of the shape of the residual limb as well as its volume and shape fluctuations. The active behavior of skeletal muscles, which plays an important role in the interfacial biomechanics of human-machine interaction, is not considered in the current design processes of the rehabilitation apparatus. In this study, a three-dimensional finite element (FE) model of the human thigh was proposed to simulate the soft tissue deformation caused by muscle contraction. In this model, the muscle model was composed of personalized muscle geometries and parametric muscle fibers. For obtaining the nearest computational deformation response to the real muscles, the model parameters of the muscle fibers were adjusted iteratively according to the differences between the deformation distributions obtained from the numerical calculation and the experimental measurements. The FE model with optimized parameters proved to be effective in accurately predicting the dynamic deformation responses of the soft tissue. The results demonstrated that the average errors for soft tissue deformation in the expanding and shrinking regions of the thigh were 1.34mm and 2.27mm, respectively. For different gaits, the average difference in the equivalent volume and cross-sectional area changes were less than 0.83% and 1.86%, respectively. The soft tissue deformation data can be used in data-driven computational algorithms for the design of prosthetic sockets or orthoses as well as other wearable technologies mechanically interfacing with the skin.

Abstract 55

EFFECTS OF EXTRACORPOREAL SHOCKWAVE THERAPY ON PERIPHERAL NERVE REGENERATION AFTER AUTOGRAFT REPAIR OF THE RAT MEDIAN NERVE

Johannes Heinzel[1,2,3], Claudia Keibl[2,3], Viola Oberhauser[2,3], Nicole Swiadek[2,3], Barbara Schädl[2,3], Michaela Sima[2,3], Helen Frick[2,3], Gregor Längle[2,3], Cosima Prahm[1], Jonas Kolbenschlag[1], David Hercher[2,3]

[1]*BG Clinic Tübingen, Department for Hand-, Plastic-, Reconstructive and Burn Surgery, Schnarrenbergstraße 95, 72076 Tübingen, Germany*
[2]*Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstraße 13, 1200, Vienna, Austria*
[3]*Austrian Cluster for Tissue Regeneration*

Corresponding author's email: hannes.heinzel@gmx.de

Introduction: Recent studies investigating the effects of extracorporeal shockwave therapy (ESWT) on peripheral nerve regeneration in the rat have shown proregenerative effects of this noninvasive treatment approach. However, results of ESWT treatment after conduit repair of peripheral nerve defects have remained unstudied yet. It was the aim of this study to investigate the effects of ESWT treatment on nerve regeneration following conduit repair of the rat median nerve.

Methods: In 123 male Lewis-rats a 7-mm segment of the right median nerve was removed and immediately reconstructed using either 1) an autologous nerve graft 2) a muscle-in-vein-conduit 3) a chitosan-conduit or 4) a silk fibroin-conduit. Half of the animals of each group ($n = 10$ - 16) were treated once with ESWT postoperatively. Functional recovery was evaluated until 12 weeks postoperative by means of the grasping test, computerized gait analysis and electrophysiological evaluations.

Results: Despite some positive trends, there were no significant effects of ESWT on grasping strength. Electrophysiological investigations revealed superior results of the autologous graft + ESWT group in comparison to both muscle-in-vein groups ($p < 0.05$) and both silk fibroin groups ($p < 0.05$). There were no significant effects of ESWT detectable via computerized gait analysis.

Conclusion: Despite partial positive effects of ESWT on electrophysiological properties we were unable to detect significant effects on functional recovery. This study's ambivalent results could on the one hand be related to the animal model used, on the other hand the mechanisms, optimal application form as well as application frequency of ESWT remain to be elucidated.

References

1. Hausner T, Nogradi A. The use of shock waves in peripheral nerve regeneration: new perspectives? Int Rev Neurobiol. 2013;109:85-98. 2. Schuh CM, Hausner T, Redl HR. A therapeutic shock propels Schwann cells to proliferate in peripheral nerve injury. Brain Circ. 2016;2(3):138-40. 3. Lee JH, Cho SH. Effect of extracorporeal shock wave therapy on denervation atrophy and function caused by sciatic nerve injury. J Phys Ther Sci. 2013;25(9):1067-9. 4. Hausner T, Pajer K, Halat G, Hopf R, Schmidhammer R, Redl H, et al. Improved rate of peripheral nerve regeneration induced by extracorporeal shock wave treatment in the rat. Exp Neurol. 2012;236(2):363-70. 5. Wu YH, Liang HW, Chen WS, Lai JS, Luh JJ, Chong FC. Electrophysiological and functional effects of shock waves on the sciatic nerve of rats. Ultrasound Med Biol. 2008;34(10):1688-96. (2-5)

Abstract 56

3D HYDROGEL MICROENVIROMENTS OF GELATIN AND HYALURONIC ACID FOR LIVER TISSUE ENGINEERING

Gloria Gallego-Ferrer[1,2], Julio Rodríguez-Fernández[1], Emma García-Legler[1], Sandra Clara-Trujillo[1,2], M. Teresa Donato[3,4], Manuel Salmeron-Sanchez[5,1,2], Laia Tolosa[3,2]

[1]*Centre for Biomaterials and Tissue Engineering (CBIT), Universitat Politècnica de València, Valencia, Spain*
[2]*Biomedical Research Networking Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Valencia, Spain*
[3]*Experimental Hepatology Unit, Health Research Institute La Fe (IIS La Fe), Valencia, Spain*
[4]*Department of Biochemistry and Molecular Biology, School of Medicine, University of Valencia, Valencia, Spain*
[5]*Centre for the Cellular Microenvironment, University of Glasgow, Glasgow, United Kingdom*

Corresponding author's email: ggallego@ter.upv.es

Regenerative therapies aim to enhance liver tissue repair and regeneration in different liver diseases. Hydrogels have been proposed to improve cell engraftment and survival. This study aims to evaluate the ability of biomimetic injectable hydrogels to promote liver functionality of encapsulated human hepatocytes and enhance in vivo outcomes in an animal model of acute liver failure.

Hydrogels of gelatin (GEL), hyaluronic acid (HA) and a GEL/HA mixture 20/80 were prepared by enzymatic crosslinking. GEL gelation is faster (6 min) than in HA (23 min) or in the mixture (13 min). The stiffer hydrogel was HA with a shear storage modulus of 509 ± 136 Pa, whereas GEL was very soft, 35 ± 7 Pa. GEL/HA had similar mechanical properties as HA, 459 ± 103 Pa. Ureogenesis, cytocrome P450 activity and albumin secretion of human hepatocytes encapsulated within GEL/HA hydrogel were enhanced, compared to monolayer cultures. Lyophilized sponges of GEL/HA seeded with human hepatocytes were implanted in mice with acute liver failure. The survival of animals implanted with sponges containing human hepatocytes was 100%, while in the non-transplanted animals it was 65%. Transaminases levels decreased significantly in transplanted animals compared to non-transplanted animals, indicating a positive effect of transplanted cells on recovery from injury.

GEL/HA hydrogel is a good candidate for liver regeneration.

Acknowledgements: This work has been supported by PI18/00993 and CP16/00097 grants form Institute of Health Carlos III and PID2019-106000RB-C21 and -C22 / AEI / 10.13039/501100011033 projects from the Spanish State Research Agency (including Feder funds).

Keywords: gelatin; hyaluronic acid; human hepatocytes

Abstract 57

HUMAN 3D ORGANOTYPIC CULTURE SYSTEMS TO MODEL TISSUE DEVELOPMENT, PHYSIOLOGICAL FUNCTION, PATHOLOGICAL CHANGES AND RESPONSE TO DRUGS

Ivan Martin[1]

[1]*Dept. of Biomedicine, University Hospital Basel*