自組裝生物反應器於骨組織工程之應用

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組織工程是一個跨領域，結合了細胞、支架、生長環境等等因子，以生物科學以及醫學工程的角度，實現人類組織的重建以及再生的現代學科。其中骨組織再生的研究長久來一直受到極高的重視，尤其在因應老年化的社會到來，年齡相關的骨科疾病和骨缺損已成為一個重要的公共健康問題，骨組織工程再生的研究是刻不容緩的議題。目前細胞療法對於骨組織工程和再生醫學的研究，提供新穎並具有潛力的解決方法，然而培養具有功能性的細胞或適合臨床使用的組織仍是一道艱難的挑戰。

本研究團隊提出一種可培養功能性類骨組織的技術，由人類成骨細胞（human osteoblasts）、鈣交聯褐藻酸生物支架（Ca-Alginate scaffolds，以下簡稱為 Ca-Alginate 支架）和一個封閉式生物反應系統（bioreactor system）所建構的平台，提供硬骨（bone）自體移植的功能性類骨組織。本技術所使用的生物反應器是一個封閉系統，細胞培養液於其中迴流來提供養分，避免了因為更換細胞培養液所造成可能的汙染；而利用鈣離子交聯的褐藻酸生物支架則適合成骨細胞的增生、分化以及維持其功能。其最大的優勢在於此培養技術是相對安全、易於架構並且低成本，對於病人而言，自體移植去除異體移植引發免疫排斥之風險，也避免等待適合捐贈者所耗費的寶貴時間及心理煎熬，更不會造成經濟上巨大的負擔，未來期許能夠提供病人一個兼顧生活品質的選擇。

在這項研究中，我們利用封閉式生物反應系統及三維（3-dimentional；3D）多孔鈣交聯褐藻酸生物支架來模擬體內環境，藉由適當的分化誘導，形成類硬骨組織團塊。對於細胞療法而言，如何維持細胞功能性完整是相當重要的關鍵，透過這項技術所培養之類硬骨組織團塊，此培養技術結合安全性、便利性及低成本等三大優勢，期許未來能夠提供病人安全有效並兼顧生活品質的選擇，因此獲得第十三屆永信李天德醫藥基金會優秀論文獎肯定，並已申請國際專利，並技轉給國璽幹細胞應用技術股份有限公司，國璽幹細胞公司有細胞製劑臨床研究經驗，相信能夠有效將本技術進行臨床轉譯。

The Self-designed Bioreactor System for Bone Regenerative Medicine

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Age-related orthopedic disorders and bone defects have become a critical public health issue, and cell-based therapy is potentially a novel solution for issues surrounding bone tissue engineering and regenerative medicine. Long-term cultures of primary bone cells exhibit phenotypic and functional degeneration; therefore, culturing cells or tissues suitable for clinical use remain a challenge. A platform consisting of human osteoblasts (hOBs), calcium-alginate (Ca-Alginate) scaffolds, and a self-made bioreactor system was established for autologous transplantation of human osteoblast cell clusters.

The Ca-Alginate scaffold facilitated the growth and differentiation of human bone cell clusters, and the functionally-closed process bioreactor system supplied the soluble nutrients and osteogenic signals required to maintain the cell viability. This system preserved the proliferative ability of cells and cell viability and upregulated bone-related gene expression and biological apatite crystals formation. The bone-like tissue generated could be extracted by removal of calcium ions via ethylenediaminetetraacetic acid (EDTA) chelation, and exhibited a size suitable for injection. The described strategy could be used in therapeutic application and opens new avenues for surgical interventions to correct skeletal defects.

In this study, we developed a functionally-closed process bioreactor with a 3D porous Ca-Alginate scaffold cell culture system to mimic the in vivo environment in order to form bone-like tissue. For the purpose of cell therapy, reproduction of the conditions found in the cell niche in vivo is a key factor to maintain cell functionality. In the bioreactor system described in this work, hOBs could ingrowth, differentiate into mineralizing cells and produce bone-like tissues. The described strategy could be used in therapeutic application and opens new avenues for surgical interventions to correct skeletal defects.