Journal of Controlled Release 183 (2014) 178

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Biological effect of BMP-2 monitored by PET/CT

The field of tissue engineering has advanced over the last several decades, and many products are available for clinical applications. Current biomaterials and tissue engineered scaffolds have become more and more biomimetic in appearance and function, and this makes detection of such materials by conventional methods difficult. This, in turn, makes it challenging to evaluate the performance of biomaterials for intended applications. For example, the current generation of porous ceramics, such as calcium phosphate cements (CPCs), is widely used in bone augmentation procedures in dental, orthopedic, and plastic reconstructive surgeries. Such materials are injectable and able to harden *in situ*, making them especially suitable for application in non-invasive surgical techniques. The CPC materials are often enriched with polymeric porogen beads to improve bone tissue ingrowth [1], resulting in a composite that can simultaneously act as a drug carrier. In the case of bone repair, bone morphogenic protein 2 (BMP-2), a protein from the transforming growth factor β (TGFβ) super family, is commonly used. BMP-2 can be incorporated into the CPC through the porogen beads, or even by simple mixing into the ceramic starting powders. Since CPC hardens at ambient conditions, the risk of thermal denaturation or loss of protein activity during preparation is minimal.

Although the resulting biomaterial–growth factor delivery system has been proven successful at healing large critical-sized bone defects, the actual assessment of growth factor activity and subsequent tissue regeneration has been difficult. The ceramic is virtually indiscernible from the surrounding host bone due to their similar porosity, appearance, and radiopacity. Previous investigations have established protein release profiles from CPCs with scintigraphic imaging of radiolabeled proteins [2]. This spatial information, however, cannot be extrapolated to the biological effect of BMP-2 (*i.e.*, bone formation). Thus, histological evaluation at various time points is always required. It is necessary to develop non-destructive detection methods that can be used in parallel with the drug release kinetics. Such methods are expected to provide real-time information on the efficacy of the release system, reduce the variability among experimental animals, and present the most attractive means for clinical applications.

The study by the Nijmegen Netherlands Biomaterials research team, headed by John Jansen, sought to explore the feasibility of positron emission tomography (PET) as non-invasive method to monitor the osteogenic potential of a BMP-2 releasing CPC bone substitute [3]. In an animal calvarial defect model, ^{18}F-fluoride PET was used to quantify uptake around a porous CPC/BMP-2 composite bone biomaterial. PET was performed biweekly for a period of 8 weeks post-implantation, while parallel computed tomography (CT) scans were made only for the anatomical reference. As expected, the highest ^{18}F-fluoride signal intensity was measured in the BMP-2 loaded group, with levels up to 5 times higher than the baseline value. This indicates that the released BMP-2 can actively promote bone tissue formation in the defective area. The non-loaded porous cement showed lower uptake, indicating only moderate ingrowth from the circumference, while dense.Autograft had the lowest uptake. Correlation between the PET signal, and the histomorphometrical measurements of new bone formation was evident for the duration of the experiment. Such results support that the measurement of metabolic activity, as measured by PET, can indeed be very indicative for the longitudinal monitoring of the efficacy of growth factor release systems *in vivo*.

For tissue engineering/regenerative medicine to meet their ultimate potential of restoring, maintaining, or enhancing functions of various tissues and organs, the field needs proper tools to evaluate the effectiveness, *i.e.*, bioactivity, of the biomaterials for intended applications. The CPC/BMP-2 composite bone biomaterial, for example, is a drug–device combination product, and its ultimate application in humans requires clear demonstration of the safety and efficacy. The method demonstrated by John Jansen and his colleagues can be readily used in clinical applications, providing a much needed tool for obtaining clinical efficacy data.

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http://dx.doi.org/10.1016/j.jconrel.2014.04.036
0888-7543/