ISMRM 2009 Morning categorical: MRI Applications to Tissue Engineering

Urinary Bladder: Imaging the Regeneration of a Dynamic Organ

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Urinary Bladder Disorders and Current Therapies

Bladder disorders are not well recognized, but a range of conditions can damage or compromise bladder function, necessitating eventual organ replacement or repair. In children, the most common congenital abnormalities involve the genitourinary system, including bladder exstrophy, urinary tract defects (1 in 500 children) that damage the bladder and kidneys (e.g. obstructive uropathy), and neurogenic bladders due to myelomeningocele (1 in 800 children). These disorders can result in a high-pressure, low-compliant bladder that requires substitution.

The traditional treatment strategy uses gastrointestinal segments for replacing bladder tissue. This approach can be problematic because gastrointestinal tissue absorbs solutes that urinary tissue excretes. Due to this difference in tissue function, several complications can arise, such as infection, metabolic disturbances, urolithiasis, perforation, and malignant disease [1]. Alternative methods and materials have been investigated, most notably tissue expansion [2] and free grafts made from natural (e.g. small intestinal submucosa, bladder submucosa) or synthetic (e.g. gelatin sponge, polyvinyl sponge) materials [3,4]. However, these attempts have met with limited success due to biocompatibility, mechanical, structural, and functional problems. Thus, the use of gastrointestinal segments has remained the gold standard despite its limitations.

Tissue Engineering for Bladder Replacement

Tissue engineering a functional new bladder substitute can potentially address issues of organ rejection or availability and overcome the limitations associated with traditional reconstruction techniques. Cell-seeded allogeneic acellular bladder matrices have been used successfully to engineer bladders in dogs [5]. The matrix provides a scaffold for 3D tissue formation and also the necessary environment to promote cell migration, growth, and differentiation. Matrices based on bladder tissue maintain the proper biochemical and mechanical properties (e.g. compliance) difficult to achieve with synthetic materials [5]. Acellularization, or removal of all cellular components, ensures that the matrix does not elicit an immunogenic response [6]. Finally, seeding the matrix with cells reduces fibrosis and graft contracture and improves the overall cellular organization [5].

Although these results are promising, much remains to be accomplished toward engineering a fully functional bladder. Inadequate angiogenesis and cellular repopulation remain the two common causes of failure. As for any tissue-engineered organ, angiogenesis must be established promptly for cell expansion and to avoid scarring, but this has been very difficult to achieve [7]. Inadequate cell expansion may also arise from failure to achieve the optimal combination of scaffold, cells, and biomolecules. For example, the optimal scaffold properties are unique for the bladder. Whereas a porous scaffold is generally desirable to enhance cell attachment and penetration, the bladder scaffold must also be impermeable to urine penetration and its toxic effect on tissue regeneration [8]. The scaffold must also be able to stretch and

relax, accommodate a blood supply, and be cell-friendly (i.e. not elicit an immune reaction). The source of cells to expedite regeneration and appropriate growth factors are also important, and there is great interest in using stem cells for its immense regenerative capacity [1]. In addition to these criteria on the “cellular” level, there are “mechanical” requirements common to the bladder and all *dynamic* organs (e.g. heart). The organ must contract at certain intervals, and low pressure needs to be maintained. In essence, there remains much to be determined in creating a suitable bladder substitute with the proper 3D structure and biological function. Research into appropriate materials and methods is currently hampered by standard assessment methods, which rely on histology and, therefore, preclude evaluation in humans (likely to be different from animals) and longitudinal monitoring.

The Role of MRI in Bladder Tissue Engineering

Magnetic resonance imaging (MRI) is an ideal non-invasive candidate to study tissue function and structure in 3D, and can substantially accelerate the development and evaluation of effective regeneration strategies. The ability to assess serially is important in all stages of development: in-vitro and in-vivo animal testing of new materials and methods, assessment of graft status pre-implantation, and post-implantation in-vivo monitoring of host-implant interaction and long-term success. Conceivably, a spectrum of information can be garnered: cell growth and distribution within the construct, the presence and functioning of a new blood supply to provide nutrients and remove waste products, continuity of pores (to ensure all cells are in close proximity to a blood supply), metabolic activity, and viability of the construct both pre- and post-implantation. What is required is the ability to evaluate structure and function on a microscopic level, whether directly (through very high-field imaging) or indirectly inferred from macroscopic MR properties (using large-bore scanners at lower field strengths).

To date, application of MRI in tissue engineering has demonstrated its potential to monitor cell growth in static tissues, mainly cartilage [9,10] and bone [11]. The study of *dynamic* organs such as the bladder will present further challenges, requiring rapid acquisition sequences for quantifying structure and function. MRI studies of the tissue-engineered bladder have been few, but it has been shown recently that MRI can quantify the degree of angiogenesis in-vivo in the regenerating rabbit bladder [12,13]. On-going efforts also suggest that monitoring the regenerating graft may require an understanding of its constituents and how they evolve differently with time under in-vitro versus in-vivo conditions. The required MRI technical developments and the biological questions they seek to answer must be addressed hand-in-hand. The greatest challenge for MRI is to achieve absolute quantification to serve as a histological surrogate. In doing so, it must be able to identify cellular repopulation, distribution, and differentiation; assess the functionality of newly created blood vessels; assess graft viability; measure physical and mechanical properties. Quantification accuracy is important, as is speed of MRI acquisition. Furthermore, if these MRI techniques can be applied at lower clinical field strengths, in-vivo studies of larger animals and humans would be possible, which is valuable for optimizing imaging and regeneration strategies relevant for the human system.

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