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Bioengineered Bladder Tissue—Close but Yet So Far!

CURRENT clinical strategies to augment or reconstruct dysfunctional bladders rely on the use of intestine as a tissue substitute. Although this has been the standard protocol for decades, bladder augmentation with gastrointestinal tissue is fraught with short-term and long-term complications. In response to the need for a better bladder tissue substitute urological researchers have turned to tissue engineering strategies. While certain aspects of bladder tissue engineering have elevated the promise of this technology, the lack of success in a recent pediatric clinical trial of bladder augmentation using engineered bladder grafts highlights the gaps between theory and practice that still exist.

The complex functions of the bladder create unique challenges for bioengineering tissue. As bladder function relies on proper organization of and a concerted effort among muscle, urothelium, nerves and blood supply, the choices of scaffold, cell type and cell source for bioengineering bladder tissue are critical. Tissue engineered bladder models have to date encompassed natural or synthetic scaffolds seeded with or without various bladder cell types. While natural scaffolds such as bladder acellular matrices (BAMs) are optimal choices due to the presence of native architectural and mechanical properties, the reproducibility of acellular matrices is not guaranteed. Synthetic scaffolds can be easily reproduced but are limited in their ability to fulfill the architectural and mechanical properties required for bladder function. Nonetheless, iterations of natural and synthetic scaffolds have been of significant interest in the field to support bladder tissue regeneration.

Cell seeded scaffolds have fared better upon bladder transplantation, particularly in larger animal models and humans.[1] Most bioengineered bladder models have focused on seeding scaffolds with smooth muscle and urothelium. While autologous cell sources are favorable to prevent rejection of the graft, their use is precluded in certain patients with bladder disease, particularly bladder cancer. As such the cells derived from pluripotent sources such as human embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) are attractive candidates for bladder tissue engineering. While urothelium has been efficiently derived from ESCs and iPSCs in vitro, the safety and efficacy of using these pluripotent cell sources clinically has yet to be validated.[2]

The organization of the individual tissue layers is critically important to regenerate a bladder tissue that is physiologically functional in its ability to fill and void. The urothelial architecture facilitates contraction and expansion, and provides an impermeable barrier. Most bioengineered bladder grafts have been seeded with urothelial cells without significant attention to the differentiation and stratification of the urothelium. In this issue of The Journal Bouhout et al (page 834) describe a culture system that uses urine and submersion to induce a fully differentiated, pseudostratified urothelium in a 3-dimensional engineered bladder.[3] The significance of using a bladder graft prepared with a fully differentiated and functional urothelium is the immediate urine impermeability provided upon transplantation, thereby protecting the scaffold and patient during the vital regenerative period. However, the long-term survival of the cells or their progeny after transplantation is questionable.[4]

A recent bladder augmentation clinical trial demonstrated that a synthetic scaffold of polyglycolic acid seeded with autologous smooth muscle and urothelial cells was not sufficient to provide significant increases in capacity or compliance in pediatric patients.[5] The high rate of graft contraction and perforation points to an inefficient blood supply as a primary factor in the inadequacy of the grafts. Vascularization is a pressing issue in the bioengineering of most tissues but until recently it was largely tabled in urological tissue engineering. Thick tissues such as human bladder grafts require vascularization for nourishment. Clinicians often use omentum, a highly vascularized peritoneal tissue, to wrap the bladder after reconstruction. While this surgical technique is helpful in traditional augmentation procedures, omentum appeared to be essential for engineered grafts.[6] However, based on the results of the most recent clinical trial omentum was not able to provide an expedient and/or sufficient blood supply to

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a completely avascular bioengineered tissue.[5] Complete regeneration of a vascular network in a large avascular graft in vivo does not occur in a manner timely enough to prevent graft contraction, ischemia and/or other downstream consequences. If the full potential of bioengineered bladder tissue is to be realized, significant strides must be taken to ensure quick and efficient delivery of blood to the graft.

Intact bladder tissue grafts are nourished through a mechanism of inosculation that develops within the first week after transplantation.[7] This mechanism by which host vessels grow and connect to graft vessels in the anastomotic region suggests that if blood vessels were present in bioengineered bladder grafts, the blood supply would be promptly initiated in the graft. Indeed, engineering blood vessels in grafts is no easy task. Growth factor and cell based methods to induce neovascularization and/or rapid angiogenesis of the host blood vessel into the graft have been applied with limited success. Urine derived stem cells engineered to express vascular endothelial growth factor and co-cultured with endothelial cells in grafts induced neovascularization upon implantation in mice while bladder grafts seeded in vitro with populations of bone marrow derived adult stem cells showed increased vascularization upon transplantation in a rat model.[8,9] However, it is unlikely that this phenomenon or any method that requires significant neovascularization would induce the timely, organized and sufficient vascularization required by larger human grafts. Ideally grafts containing functional bioengineered blood vessels would provide a bladder graft with the greatest opportunity for prompt inosculation and initiation of blood supply after transplantation. As such whole organ acellular scaffolds such as kidney and liver have been shown to support the regeneration of functional blood vessels by direct implantation of endothelial and tissue specific cells into the existing vascular architecture.[10,11] Endothelial progenitor cells from adipose tissue, which were recently shown to effectively form capillaries in BAMs in vitro, may provide an advantageous source of autologous cells to revascularize bladder tissue.[12]

Significant advancement in bladder tissue engineering hinges on this critical issue of the blood supply. As the feasibility of engineering blood vessels in bladder grafts becomes reality, inosculation and prompt nourishment of grafts upon transplantation will further potentiate the clinical use of bioengineered bladder tissue.

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