Terminal urothelium differentiation of engineered neoureter after in vivo maturation in the "omental bioreactor"

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Eur Urol. 2007; 52: 1492-8

Objective: Long ureteric defects may theoretically be repaired with the use of tissue-engineered neoureter. However, attempts to construct such a neoureter in animal models have failed because of major inflammatory response. Avoidance of such inflammation requires a well-differentiated urothelium. We investigated whether omental maturation of a seeded construct in a pig model could achieve terminal differentiation of the urothelium to allow construction of a stricture-free neoureter.

Material and Method: Bladder biopsies were taken to allow urothelial and smooth muscle cell cultures. These cultured cells were used to seed small intestinal submucosa (SIS) matrix. After 2 wk of cell growth, the in vitro SIS-seeded construct was shaped around a silicone drain and wrapped by the omentum to obtain neoureters. These neoureters were left in the omentum without any contact with urine, and then harvested 3 wk later for histologic and immunohistochemical studies.
Results: Before implantation, the in vitro constructs were composed of a mono- or bilayer of undifferentiated urothelium overlying a monolayer of smooth muscle cells. After 3 wk of omental maturation, these constructs were vascularized and comprised a terminally differentiated multilayered urothelium with umbrella cells over connective tissue and smooth muscle cells, with no evidence of fibrosis or inflammation.
Conclusion: We obtained, for the first time, with this model of in vivo maturation in the omentum, a mature neoureter composed of a well-differentiated multilayered urothelium.

Editorial Comment

The anatomy and structure of the ureter is still not completely understood. Because of its embryonic development the blood supply restricts the reconstructive possibilities. Over a decade researchers look into the option to find a better substitute of a ureter than the common used ilium interpronat (1). With the improvement of Mitrofanoff the diameter of the segment was adjusted but still complications are seen although the needed length of ileum was significantly reduced and the resorption reduced (2).

Baumert et al. (3) present impressively a “sandwich model” with differentiated urothelium and a single layer of smooth muscle cells on SIS® different to others (4).

During the recent years researchers presented remarkable results demonstrating the progress tissue engineering (5). One important lesson, even known in the reconstructive surgery prior, was the need of the optimized nutrition of the in vitro created tissue. Atala et al. reported an optimized outcome of the clinical used in vitro pre-seeded scaffold for bladder reconstruction with an omental flap wrapping (6).

On the one hand the presented indication of a neo-ureter using an omentum flap makes the created ureter even more maneuverable compared to the possible “short” mesenterium of the ileum interpronat. On the other hand, Dahms et al. (7) published 10 years ago the ureter replacement by an acellular matrix, which was regenerated by urothelium and smooth muscle cells and functional, but in the following study in the rodent as well in the large animal model the created ureter shrunk after the stent removal although the prior seen urothelium lining was present (data not published). Some might argue that the presented approach will prevent the shrinking but as the author state it needs to be proven. Because others have made similar experiences - probably only a minority is published - it should be considered to report the outcome of an extended follow-up after the stent removal and as a replacement for a ureter.

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A quantitative method for evaluating the degradation of biologic scaffold materials

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Biomaterials. 2007: 28: 147-50

Scaffolds derived from naturally occurring extracellular matrix (ECM) have found extensive use in the fields of tissue engineering and regenerative medicine. Many of these scaffolds are designed to degrade rapidly as they are replaced by new host tissue. Other scaffolds are chemically crosslinked to slow the rate of degradation or add strength to the scaffold. Commercially available ECM scaffolds have considerable variability with regards to tissue origin and methods of processing, and little is known about their rate of degradation and the fate of their degradation products. A novel method is described herein to integrally label ECM with a radioactive isotope ((14)C). It was found that a number of tissues are efficiently labeled, including heart, liver, trachea, pancreas, small intestine, and urinary bladder tissue. Of the tissues analyzed, only spleen was not found to contain detectable levels of (14)C. The technique is extremely sensitive, accurate, and safe, but requires access to accelerator mass spectrometry, and is expensive and time consuming. This model represents the first described quantitative method to determine the rate of degradation for an ECM scaffold and to track the fate of the degradation products.

Immune response to biologic scaffold materials

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Semin Immunol. 2007; Dec 11; [Epub ahead of print]

Biologic scaffold materials composed of mammalian extracellular matrix are commonly used in regenerative medicine and in surgical procedures for the reconstruction of numerous tissue and organs. These biologic materials are typically allogeneic or xenogeneic in origin and are derived from tissues such as small intestine, urinary bladder, dermis, and pericardium. The innate and acquired host immune response to these biologic materials and the effect of the immune response upon downstream remodeling events has been largely unexplored. Variables that affect the host response include manufacturing processes, the rate of scaffold degradation, and the presence of cross species antigens. This manuscript provides an overview of studies that have evaluated the immune response to biologic scaffold materials and variables that affect this response.

Editorial Comment

Biologic scaffold materials in the currently available form are unsatisfactory for reconstruction of the lower urinary tract. They are to some extend an obstacle to vascularization and re-innervation of the reconstructed

segment, but they also lead to a reaction of intact surrounding tissue due to a normal immune and inflammatory response. In the two papers selected here, the authors have tried to develop a model for a quantitative determination of the degradation process and the tracking of extracellular matrix used as scaffold for urinary bladder reconstruction, for example. Furthermore the host response which is or maybe responsible for scaffold degradation has been worked up. These data are very important and very timely because due to the problems with artificial matrix acellular derived from human or animal sources are currently the most commonly used materials in tissue engineering for clinical purposes.

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