Outlines on nanotechnologies applied to bladder tissue engineering

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Tissue engineering technologies are more and more expanding as consequence of recent developments in the field of biomaterial science and nanotechnology research. An important issue in designing scaffold materials is that of recreating the ECM (extra-cellular matrix) functional features – particularly ECM-derived complex molecular signalling – to mimic its capability of directing cell growth and maintaining morphogenesis. In this way the nanotechnology may offer intriguing chances, biomaterial nanotube-based scaffold geometry behaving as nanomechanical transducer complex interacting with different cell nanosize proteins, especially with those of cell surface mechanoreceptors. To fabricate 3D-scaffold complex architectures, endowed with controlled geometry and functional properties, bottom-up approaches, based on molecular self-assembling of small building polymer units, are used, sometimes functionalizing them by incorporation of bioactive peptide sequences such as RDG (arginine – glycine – aspartic acid), a cell-integrate binding domain of fibronectin, whereas the top-down approach are useful to fabricate micro/nanotextured structures, such as microvasculature within an existing complex bioarchitecture. Synthetic polymer-based nanofibers, produced by electrospinning process, may be used to create fibrous scaffold that can facilitate, given their nanotextured geometry and surface roughness, cell adhesion and growth. Also bladder tissue engineering may benefit by nanotechnology advances to achieve a better reliability of the bladder engineered tissue. Particularly, bladder smooth muscle cell adhesion to nanotextured polymeric surface is significantly enhanced in comparison with that to conventional biomaterials. Moreover nanotextured surfaces of bladder engineered tissue show a decreased calcium stone production. In a bladder tumor animal model, the dispersion of carbon nanofibers in a polymeric scaffold-based tissue engineered replacement neobladder, appears to inhibit a carcinogenic relapse in bladder genitourinary material. Facing the future, a full success of bladder tissue engineering will mainly depend on the progress of both biomaterial nanotechnologies and stem cell biology research.

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Essentials on bio-nanotechnologies

The nanobiotechnology represents a broad interdisciplinary field concerning the manipulation of various materials at micro/nanometer level (from 100 nm to 10 nm), to obtain structures which might mimic the micro/nanoscale-based architecture of native tissues (4, 5).

The nanoparticle-modified scaffold surface – nanoparticles behaving as mechanotransducers interacting, at precise size geometry level, with different cell proteins, especially with those peculiar of cell surface mechano-receptors – can make easier not only cell adhesion, -growth and differentiation but also cell functions including cell/molecule signalling, gene expression, hence protein synthesis. From that, it’s possible to deduce that biomaterial nanostructure geometry (nanodots, nanopits, nanorods, nanopillars) and roughness. So, to mimic the native structural features of extra-cellular matrix (ECM), the electrosprinning process has been used to produce polymeric nanofiber-based biomaterial (e.g., poly-3-hydroxybutyrate-co-3-hydroxyvalerate, PHBV) fibrous scaffolds able to enhance the growth of bone marrow-derived mesenchymal stem cells, moreover the different nanofiber arrangement/orientation influencing distinct effects on stem cell differentiation by variously driving cytoskeletal structure and dynamics (13, 14).

Since the specific lineage-differentiation of stem cells requires a well modulated spatial-temporal presence of different growth factors and cell signalling molecules, the biomaterials may be provided with nano- -micro particles able to control the release rates of such molecules (15-17). In this regard, supply of scaffold with bioactive factors prior to implantation can promote, just it has been placed into the host, an appropriate in situ host stem cell/progenitor cell recruitment and differentiation (18, 19).

Synthetic enzymatically biodegradable nanohydrogels, composed of PEG, poly-ethylene glycol, and MMP, matrix metalloproteinase, have been tuned-up for culture of bladder smooth muscle cells (SMC), and human mesenchymal stem cells to achieve a significant...
increase in SMCs, the supply with appropriate signalling molecules allowing a specific stem cell differentiation (20).

**Applications of the nanotechnology to bladder tissue engineering**

Different approaches of nanotechnology, such as either nanomaterials self-assembling to coat surfaces of existing conventional scaffolds or the resort to electrospinning to obtain de novo fibrous scaffolds, may be properly applied to bladder tissue engineering (21). Particularly bladder smooth muscle cell adhesion to nanostructured polymeric surfaces is significantly enhanced in comparison with that to conventional polymeric materials (Table 1) (1).

Different either bottom-up or top-down tissue engineering approaches by using nanoscale-based polymeric materials allow to achieve a significant improvement in the functional bladder tissue generation, respectively to create a multilayer bladder wall or, on the other hand, to obtain a microvascular structure within an existing scaffold construct (3, 9-11, 22). Moreover, nanostructured polymeric surfaces of bladder engineered tissue show a decreased calcium stone formation (2).
As far as bladder tumor surgery is concerned – bladder replacement after radical cystectomy – nanostructured polymeric scaffolds may allow the fabrication of a bladder engineered tissue more properly than tissue engineering conventional techniques, as enhancing, besides the urothelial and smooth muscle cell/scaffold adhesion, the production of ECM proteins (23). Intriguingly, the dispersion of carbon nanofibers within a polyurethane elastomer-based scaffold seems to inhibit the carcinogenic relapse into the prosthetic material, as it has been shown in bladder tumor animal models, where, after cystectomy, the bladder replacement has been performed by resorting to such tissue engineered organ (24).

In the field of neurogenic bladder, the therapeutic management, a part from both traditional-palliative (clean intermittent catheterization, drug therapy) and electronic device-mediated measures (transurethral bladder stimulation, sacral neuromodulation), the nanotechnology applied to stem cell-mediated bladder tissue engineering, could offer novel chances for bladder augmentation surgery, where conventional tissue engineering techniques have already been clinically validated (25-28).

Conclusive remarks

Nanotechnology, by providing scaffold materials with the property of «directly speaking the language of cells» at nanometer level, has opened new ways – via top-down or bottom-up approaches – for intriguing applications in the field of tissue engineering technologies (3).

Particularly, nanostructured polymeric scaffolds allow the creation of bladder neotissue more properly than conventional ones – considering both cell-adhesion and growth – moreover showing a decreased calcium stone formation (2, 23). Even more interesting, in a bladder tumor animal model, the dispersion of carbon nanofibers in polymeric scaffold-based tissue engineered replacement neobladder, appears to inhibit a carcinogenic relapse into the bladder prosthetic material (24).

Nanotechnologies applied to bladder tissue engineering with resort to stem cells, can allow new chances for bladder augmentation surgery (augmentation cystoplasty) in order to lower, in patients with neurogenic bladder, the intravesical pressure together with avoiding or mitigating the development of upper urinary tract changes such as vesicoureteral reflux and hydronephrosis, a critical situation where conventional tissue engineering techniques have already a clinical validation (25-28).

Facing the future, a full success in the realization of bladder tissue engineering will depend on the progress of the science of nanoscale-based materials and the knowledge of stem cell biology (1, 6, 16, 17, 21, 27). In this regard, also about the tissue engineering of other organs (e.g., considering the trachea replacement), a new approach is gaining ground – instead of the use of decellularized human scaffold seeded with autologous cells, sometimes tending to collapse – properly resorting to tailored nanocomposite scaffold seeded with autologous stem cells (29).

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