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Growth factor and small molecule influence on urological tissue regeneration utilizing cell seeded scaffolds ☆

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ABSTRACT

Regenerative medicine strategies combine various attributes from multiple disciplines including stem cell biology, chemistry, materials science and medicine. The junction at which these disciplines intersect provides a means to address unmet medical needs in an assortment of pathologies with the goal of creating sustainable, functional replacement tissues. Tissue damage caused by trauma for example, requires rapid responses in order to mitigate further tissue deterioration. Cell/scaffold composites have been utilized to initiate and stabilize regenerative responses in vivo with the hope that functional tissue can be attained. Along with the gross reconfiguration of regenerating tissues, small molecules and growth factors also play a pivotal role in tissue regeneration. Several regenerative studies targeting a variety of urological tissues demonstrate the utility of these small molecules or growth factors in an in vivo setting.

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1. Introduction

Numerous attempts have been made to regenerate functional urological tissue utilizing an assortment of cell types combined with synthetic or biological-based scaffolding material. These studies have targeted dysfunctional bladder tissue, aspects of ureteral and urethral tissue engineering as well as various facets of kidney regeneration. Pivotal to the success of engineered tissue is the selection of scaffolds that serve as the structural foundation in tissue regeneration studies. This is

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essential for the subsequent reconstruction of anatomically correct and physiologically functional tissue. The eventual tissue mimicry required by cell/scaffold composites encompasses multiple characteristics including mechanical compatibility, tissue adaptability, non-toxic biodegradation, and immunological naïveté. Secondary to scaffold selection is cell sourcing. The plasticity of the cells utilized for regeneration should include the potential to differentiate into components of the targeted urological organ while providing bona fide physiological function. These cells should ideally exist as autologous, non-pathological entities in order to avoid undue immunological reactions and the elimination of disease reoccurrence. The physiological prowess of multipotent stem/progenitor cells may provide a suitable alternative to current urological regenerative conundrums. Finally, growth and signaling molecules expressed by cell/scaffold composites in this setting could provide an indispensible tool to delineate molecular mechanisms of urologic tissue regeneration. Within the framework of this review article, we will examine the relationship of cell seeded scaffolds and growth factors/signaling molecules in the context of urological regeneration.

2. Cell sources utilized for urologic tissue engineering

In order to properly recapitulate native urological tissues utilizing ex vivo generated "starter" tissues, it is imperative to identify cell sources that possess the ability to differentiate into urological tissue in form and function. Multiple investigators spanning decades of research have utilized a myriad of differing cell types with assorted states of cellular potency in order to attempt to attain positive results with regard to urological regeneration. Each cell type expresses different cytokines and growth factors that can exert either positive or negative influences on tissue remodeling. These include autologous induced pluripotent stem cells (iPSCs) and allogeneic embryonic stem (ES) cells [1] as well as smooth muscle cells (SMCs) and urothelial cells (UCs) from a variety of different donor types. As SMCs and UCs have been adequately described elsewhere and studies utilizing iPSCs and ES cells are limited in the urological regeneration realm, our focus in this review will concentrate on two multipotent cell types and the factors that they express along with their potential influence on urological tissue regeneration.

2.1. Mesenchymal stem cells

The plastic nature of multipotent mesenchymal stem cells (MSCs) has been described in detail and studied quite extensively for several decades [2–7]. This heterogeneous cell population has been isolated from a variety of tissue sources namely bone marrow, adipose tissue, and umbilical cord blood and resides in virtually all post-natal tissues and organs. MSCs have contributed to multiple regenerative medicine-related studies and continue to serve as a multi-purpose vehicle for drug delivery, gene therapy, and immune-modulation studies as their therapeutic potential is still being discovered [8–11]. The plasticity of MSCs makes them ideal candidates for urological regeneration and they have been utilized in a number of settings including models of sphincter incontinence, urethral and ureteral reconstruction, and urinary bladder regeneration [12–17]. This is crucial since MSCs in this setting express essential factors that facilitate regeneration in a scaffold seeded context. The physical attributes of MSCs in these settings in-part provide for the structural foundation of the aforementioned tissues and organs but the complex nature of the MSC secretome is what is found to be scientifically intriguing as this drives the regenerative process. MSCs are known to express growth factors and cytokines that can be classified into many different categories that can non-exclusively affect cell proliferation, apoptosis, and angiogenesis, important factors in tissue regeneration.

2.1.1. Cell migration

In an in vivo regenerative milieu, the ability of cells from grafted tissues to migrate and differentiate is crucial for graft survival. MSCs express a number of different factors that can modulate the expression of cellular migration via paracrine mechanisms [4,18]. Gnecchi et al. describe putative paracrine factors that are secreted by MSCs and their role in the remodeling of cardiac tissue [19]. These factors include stem cell factor (SCF), leukemia inhibitory factor (LIF), fibroblast-growth factor-7 (FGF-7), thrombospondin-1, and tissue inhibitor of metalloproteinase-1 (TIMP-1) and all affect some aspect of cell migration. As these factors influence the muscular aspect of cardiac regeneration, it may be speculated that similar effects including enhanced cellular migration could be seen in urological tissue that has been grafted with MSC seeded scaffolds. The smooth muscle layers that encompass the bladder and ureters, for example, may be directly influenced by this paracrine effect. There is currently a paucity of research data that attempts to delineate the mechanisms that describe the paracrine effects of MSCs and cell migration in scaffold-grafted urological regenerative settings.

2.1.2. Apoptosis

Cell seeded scaffolds that have been grafted into injured organs or tissue structures typically face issues with graft sustainability. At the core of most cell/scaffold composites, nutrient and gas exchange is very poor once placed in vivo especially at the beginning of the regenerative program and typically leads to cell (and eventually tissue) death via apoptosis.

It has been shown that the exposure of MSCs to angiopoietin-1 protects MSCs from apoptosis and ensures their survival [20]. Liu et al. describe the treatment of MSCs with angiopoietin-1 under hypoxic conditions with a dramatic reduction in components of the apoptosis pathway. These included the decreased activation of caspase 3 and 9 with the concomitant phosphorylation of Akt and an increased Bcl-2/Bax (anti-apoptotic/pro-apoptotic) ratio. Interestingly, MSCs also express angiopoietin-1 and can be regulated via autocrine pathways so that apoptosis may be avoided [19,21,22]. Hence it would be advantageous to utilize MSC seeded scaffolds so that early regenerative events including angiogenesis can be initiated and that dense tissue has the opportunity to become vascularized.

2.1.3. Angiogenesis

It is of paramount importance to establish functional vascular conduits to regenerating tissue following cell seeded grafting. MSCs possess a battery of pro-angiogenic growth factors that initiate and facilitate new blood vessel growth. Ghajar et al. demonstrate an approximate 7-fold increase in blood vessel network formation when bone marrow derived MSCs were seeded onto a 3D fibrin matrix compared to control [23]. A number of enzymes known to be involved with the proteolytic preparation of tissue immediately prior to angiogenesis are the family of MMPs (matrix metalloproteinases). A number of MMPs including MMP-2, MMP-9, and MT1-MMP were greatly up-regulated upon MSC addition with MT1-MMP playing a significant role in blood vessel formation and development. Global evaluation of the MSC secretome further corroborated previous studies describing the power of MSCs and their complex role with the angiogenic process. Utilizing liquid chromatography/tandem mass spectrometry methods Estrada et al. profiled the proteome of bone marrow derived MSCs [24]. 258 different proteins were identified from the extracts of MSCs including a variety of angiogenesis-related proteins. Of great interest (and completely understudied within the field of urological regeneration) is cysteine rich angiogenic inducer 61 (Cyr61/CCN1) which was identified and demonstrated to be expressed at high levels in MSCs. Cyr61 is a member of a distinct family of CCN proteins that modulate various facets of vasculogenic and angiogenic events [25,26]. The aforementioned study goes on to demonstrate that depleting Cyr61 within in vitro and in vivo settings abolishes the pro-angiogenic capabilities of MSCs. Cyr61 has proven to be a key player in the establishment of revascularization in other organ systems but there is a dearth of critically evaluated data with regard to urological tissue engineering. The examination of Cyr61 expression in bladder regeneration is an ongoing study that is