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Synergetic roles of TGF-β signaling in tissue engineering

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Abstract

Recent advances in tissue engineering highlight biomaterial designs with context-specific growth factors, cytokines and various small molecules to better mimic the natural extracellular matrix (ECM) microenvironments. These efforts have led to direct improvements in cell-cell and cell-ECM interactions while mitigating undesirable cellular and immunogenic responses. In this short review, we focus on the crucial roles and regulation of transforming growth factor β (TGF-β) signaling in biomaterial applications during tissue repair and regeneration.

Keywords

Biomaterials; Tissue engineering; Regenerative medicine; TGF beta; Inflammation

1. Introduction

Biomaterial scaffolds based on natural and synthetic polymers are now widely employed in regenerative medicine [1–3]. Collagen, fibrins and decellularized extracellular matrices (ECMs) are examples of natural polymers often used for the repair or reconstruction of skin and other soft-tissues because of their superior biocompatibility, functionality and degradation characteristics. In contrast, synthetic polymers tend to be less biocompatible but easier to formulate with greater consistency in mechanochemical properties. Indeed, a variety of macromolecules such as polycaprolactone (PCL) [4], poly-lactic acid (PLA) [5,6] and polymethyl methacrylate (PMMA) have been used in the replacement, repair and regeneration of bone, vessel or other organs [1,7,8].

But despite significant progress, the most prominent technical challenges faced in tissue engineering still relate to long-term cell retention following transplantation or mitigating immunologic responses triggered by the biomimetic ECM scaffolds (Fig. 1). Since physical contact with biomaterial surfaces can alter cell behavior and signaling, biomaterial designs have incorporated growth factors, cytokines and other small molecules to better mimic the

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natural ECM environment for specific cell and tissue types. This review highlights our current understanding of how transforming growth factor β (TGF-β) signaling is influenced by and modulates cell behavior in different bioactive implant materials.

1.1. TGF-β as a mediator of cell adhesion, growth and ECM deposition

The multifunctional TGF-β superfamily ligands comprise over 40 members including TGF-β [1–3], activin and bone morphogenetic proteins (BMP), many of which have diverse roles in embryonic development, tissue homeostasis and various disease states [9–11]. The prototype ligand TGF-β1 signals through the ubiquitous type I (TβRI/ALK5) and type II (TβRII) serine/threonine kinase receptors to transcriptionally regulate numerous genes related to growth, differentiation and wound healing. Besides gene expression, TGF-β signaling is regulated heavily through its bioavailability, which in most cell types is coordinated by a multi-step proteolytic processing and release from the ECM [12,13].

To mimic these physiologic checkpoints, exogenous TGF-β ligands are incorporated into layered synthetic biomaterials to modulate their local delivery and signaling (Fig. 2). These biomimetic cues have proven crucial for adhesion of tissue scaffolds with transplanted cells, but also for their proper migration, survival and differentiation. For instance, silk fibroin and decellularized cartilage extracellular matrix have demonstrated exceptional biochemical and mechanical properties with a well-controlled TGF-β3 release system that support cell adhesion, proliferation and differentiation of adipose-derived stem cells (ADSCs) [14].

Likewise, hyaluronic acid (HyA) derivatives are also highly capable biomimetic systems that enhance retention and survival of transplanted cells. In a recent study, HyA-based hydrogels co-decorated with RGD peptides and TGF-β1 were shown to promote the formation of vascular-like networks by human cardiosphere-derived cells (hCDC) [15]. These hydrogel-encapsulated cells notably demonstrated improved cell survival, proliferation and endothelial differentiation through the canonical TGF-β1/endoglin/TβRII pathway that normally mediates proangiogenic responses [16]. TGF-β can also enhance ECM production itself in many cases, as reported by numerous studies demonstrating the dramatic increase in matrix synthesis and deposition by vascular smooth muscle and endothelial cells when grown on PEG hydrogels with tethered TGF-β [15,17]. Hence, considering its ease of modification, bioactivity and biodegradable characteristics, these and other semi-synthetic HyA hydrogels represent viable therapeutic strategies for many ischemic injuries.

Other TGF-β family ligands such as BMPs are also widely used in biomaterial applications for tissue regeneration [18,19]. In one study, implanted collagen sponges containing both TGF-β1 and BMP2 were shown to strongly induce osteoinductive activity and markedly accelerate bone regeneration than by BMP2 alone [20]. Indeed, there exist many variations of BMP-based matrices demonstrating similarly promising results toward improving bone and joint repairs-including a study in which surface delivery of BMP2 at tunable doses from polymeric scaffolds allowed enhanced bone regeneration, while in another study BMP-2 and TGF-β3 were covalently linked on polycaprolactone (PCL) scaffold surfaces to help stimulate the neighboring human mesenchymal stromal cells (hMSCs), thereby resulting in osteogenic and chondrogenic differentiation [21–25].

1.2. Role of TGF-β signaling in modulating the inflammatory response

Despite numerous advances in applied biomaterials, complications still arise in tissue engineering particularly from host inflammatory responses [26]. Indeed, immunologic responses remain one of the primary factors affecting tissue regeneration, and accordingly, considerable efforts have aimed at identifying new immunomodulatory materials to improve clinical outcomes.

In particular, how the physicochemical properties of a biomaterial surface affect host immune cell behavior is a key consideration in maintaining tissue homeostasis and long-term implant functions [19]. TGF-β is a potent regulator of both innate and adaptive immunity, as it inhibits chemotactic migration and proliferation of neutrophils, macrophages as well as suppression of T cell maturation [27,28]. The molecular bases for these immunosuppressive effects primarily involve the transcriptional inactivation of a number of proinflammatory cytokine genes such as interleukin 2 (IL-2) that are necessary for T cell growth and differentiation. In addition, TGF-β can either regulate cell growth by increasing the expression of cell cycle inhibitors such as p21 and p27, or conversely, repress key mitogenic factors including c-Myc, Cyclin D2, CDK2, Cyclin E[29]. To further inactivate gene targets related to inflammation, Smad6 combined with Pellinos E3 ubiquitin ligase can regulate the Toll-like receptor/interleukin receptor (TIR) while its homolog, Smad7, blocks IL-6 expression and impair NF-κB signaling [30–32].

Recent efforts have exploited these immunosuppressive properties of TGF-β and similar immune modulators to resolve inflammation within hybrid biomaterials (Fig. 3) [29,33,34]. One such study by Liu et al. effectively demonstrated the role of TGF-β in regulating inflammation surrounding the transplanted microporous polylactide-coglycolide (PLG) scaffold [35]. Here these TGF-β1-embedded immune-modulator scaffolds reduced inflammation by curtailing the local production of proinflammatory cytokines and leukocyte infiltration. In another study, McHugh et al., investigated a nanocarrier-based approach using polylacticglycolic acid (PLGA) loaded with TGF-β and IL-2 as a means of directly targeting the CD4+ cell surface for immunosuppression [36]. Similar studies involving nanoparticles and even TGF-β1 affinity peptides (HSNGLPL) have now been reported to improve the biocompatibility of various biomaterials in several contexts including orthotopic cartilage regeneration[37] and skeletal muscle repair [38].

2. Conclusion

TGF-β family ligands have now been used in a variety of tissue engineering applications with the purpose of modulating important functions related to growth, adhesion and survival of implanted cells as well as their local environments. But like most tissue engineering studies to date, our understanding largely derives from animal models that have yet to be fully characterized and validated in clinical settings. One of the more challenging aspects deal with the highly diverse and often context-specific actions of TGF-β ligands which, at least for the time being, can only translate to their variable success in humans. Indeed, the dichotomous role of TGF-β in the immune system is well recognized in that, while predominantly immunosuppressive, in certain contexts these cytokines can exert precisely the opposite effects. As the next generation of biomaterial platforms begins to take shape,

these risk factors must be into account while aiming to better recapitulate the release kinetics and the overall efficiency of TGF-β ligands in physiologically-relevant manner.

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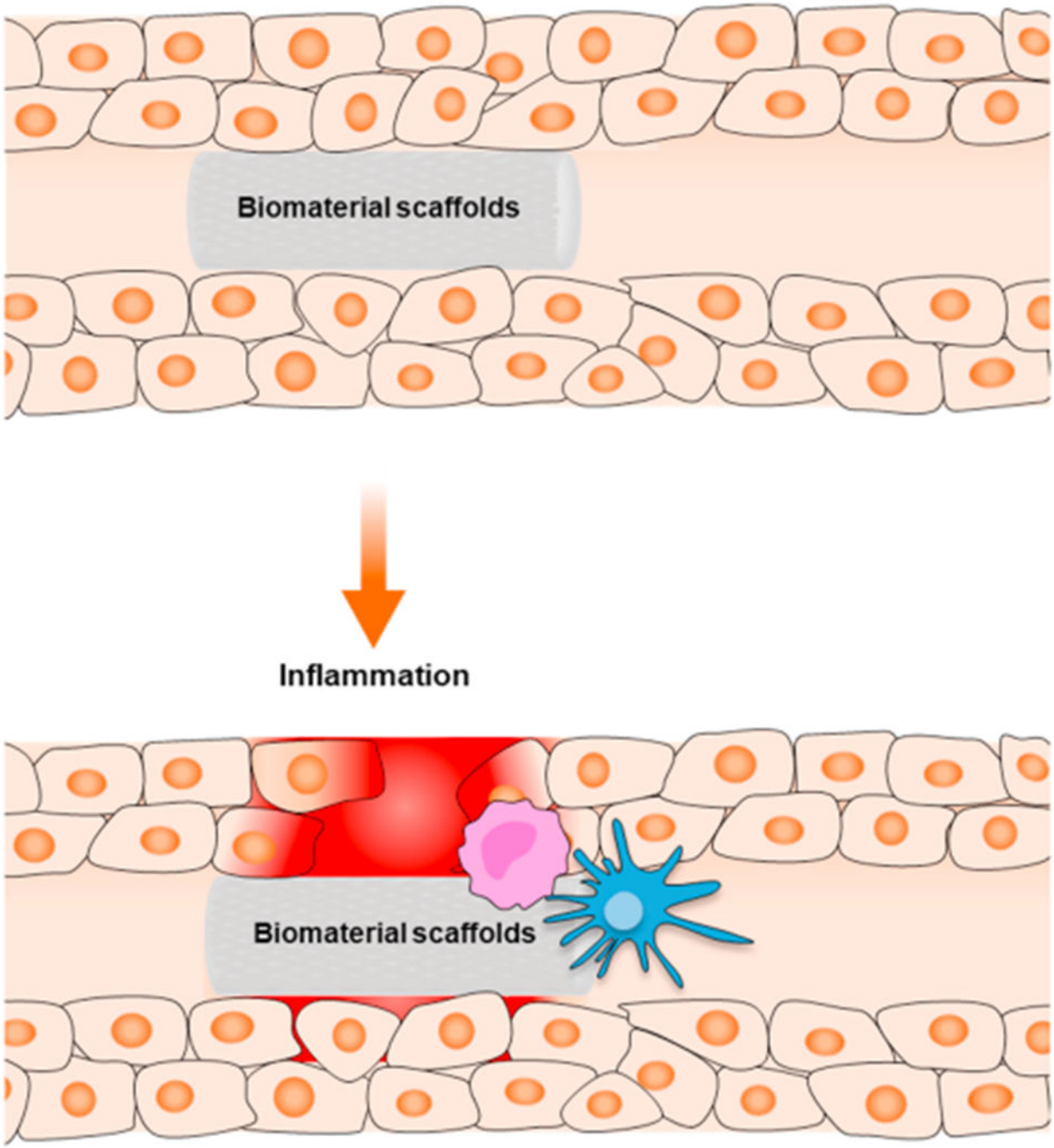

Fig. 1.

Overview of inflammatory responses commonly faced by biomaterials and transplanted tissues. Both acute innate (e.g., resident macrophages) and adaptive immune responses (e.g., T-cells) can be triggered by tissue injury and the presence of foreign materials.

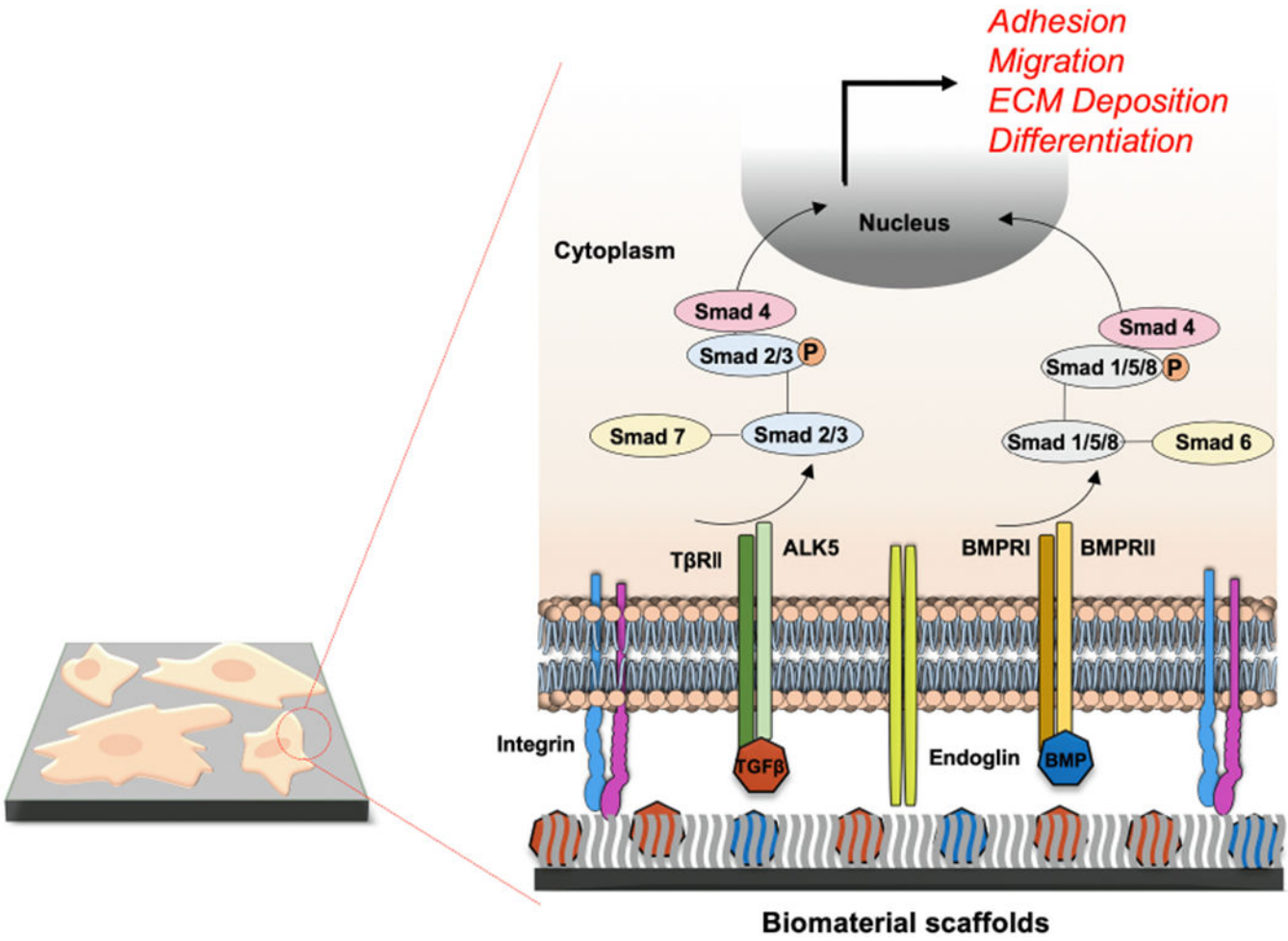

Fig. 2. Enhanced TGF-β signaling mediated by various biomaterial platforms.

Exogenous TGF-β family ligands including BMPs are integrated into layers of synthetic polymers to promote TGF-β signaling through ALK5 and TβRII and BMPRI/II receptors for Smad2/3 and Smad1/5/8 pathways, respectively. Smads control the adhesion, migration and differentiation of various cell/tissue implants while further augmenting ECM deposition surrounding the biomaterial scaffolds.

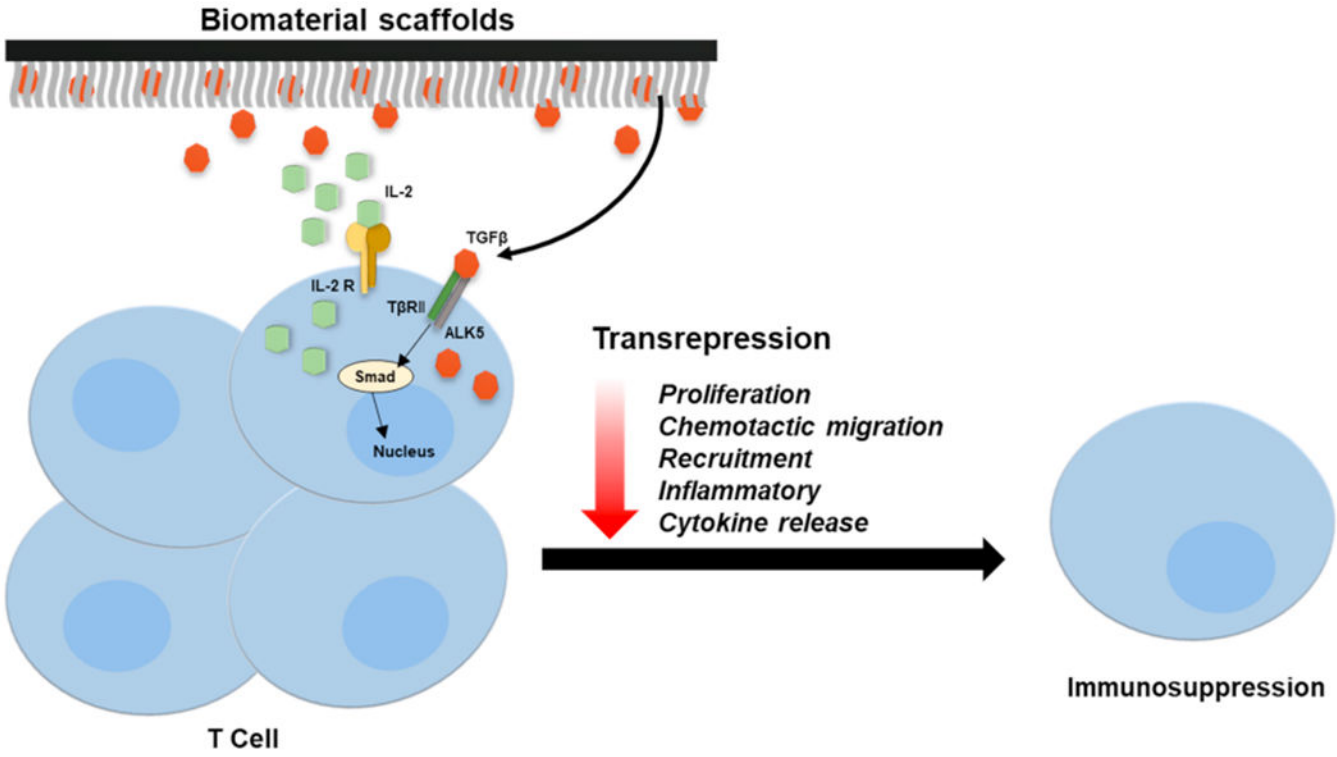

Fig. 3. TGF-β-based immunosuppression in the implant microenvironment.

Biomaterial-based delivery of exogenous TGF-β initiates the transcriptional inhibition of inflammatory cytokines, recruitment and proliferation of various resident macrophages and T-cells to attenuate host immune responses and inflammation.