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REVIEW ARTICLE

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Cytokines TGF-β1, TGF-β2, TGF-β3 -Review of Literature

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ABSTRACT

The transforming growth factor-beta (TGF-β) family consists of three isoforms: TGF-β1, TGF-β2, and TGF-β3, which play pivotal roles in cellular communication and regulation of biological processes, including immune response, inflammation, tissue repair, and development. Despite structural and functional similarities, each isoform exhibits unique expression profiles and cell-specific actions. TGF-β1 (Transforming Growth Factor Beta 1) is well-known for its immunosuppressive effects, particularly in promoting regulatory T-cell differentiation and controlling extracellular matrix (ECM) production. Its dysregulation is linked to fibrosis and autoimmune disorders. TGF-β2 (Transforming Growth Factor Beta 2) plays a critical role in embryonic development, neural tissue differentiation, and regeneration, with alterations contributing to conditions like Marfan syndrome and tumor metastasis. TGF-β3 (Transforming Growth Factor Beta 3) is essential for scar-free wound healing and tissue morphogenesis by minimizing excessive ECM deposition. TGF-β signaling occurs via Smad-dependent and alternative pathways, with crosstalk involving Wnt and NF-κB (Nuclear Factor Kappa B) pathways. Therapeutically, TGF-β inhibitors are under investigation for fibrosis and cancer, while TGF-β3 shows promise in scar reduction. Understanding the distinct roles and signaling mechanisms of TGF-β isoforms enhances prospects for targeted interventions in fibrosis, cancer, and regenerative medicine.

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Introduction

Cytokines are key mediators of intercellular communication, playing a crucial role in regulating immune responses, inflammatory processes, tissue regeneration, and organismal development [1,2]. Transforming growth factor-beta (TGF-β) is a family of cytokines consisting of three main isoforms: TGF-β1, TGF-β2, and TGF-β3. Although these isoforms share structural and functional similarities, they exhibit distinct expression profiles and specific effects on various cell types [3]. The ability to modulate their function has led to increased interest in their potential therapeutic applications, particularly in oncology, fibrosis treatment, and regenerative medicine [4].

Aim

The aim of this review is to analyze the role of TGF-β isoforms in immune regulation, fibrosis, cancer progression, and tissue regeneration. We also aim to explore potential therapeutic strategies targeting these cytokines, including inhibitors and stimulators of their signaling pathways.

Material and Methods

A comprehensive literature review was conducted using databases such as PubMed, Scopus, and Web of Science. We included studies from the last decade focusing on the biological functions of TGF-β cytokines, their role in disease pathogenesis, and clinical trials investigating their therapeutic applications.

Review and Discussion

Characteristics of the TGF-β Family

TGF-β belongs to a superfamily of proteins that also includes bone morphogenetic proteins (BMPs) and activins [5,6]. TGF-β exists in the body in an inactive form, bound to latency-associated proteins (LAPs) that, upon activation, enable TGF-β to bind to cell surface receptors [7,8]. The primary TGF-β isoforms – TGF-β1, TGF-β2, and TGF-β3 – signal through type I and type II receptors (TβRI and TβRII), leading to the phosphorylation of Smad proteins, which transmit signals to the nucleus, activating the expression of target genes [9].

TGF-β in Cancer, Fibrosis, and Wound Healing

Several clinical trials and experimental studies have investigated the potential therapeutic applications of TGF-β modulation:

- **Cancer:** TGF-β inhibitors, such as galunisertib (LY2157299), are currently being tested in clinical trials for hepatocellular carcinoma and glioblastoma [10].
- **Fibrosis:** Antagonists of TGF-β1, including pirfenidone and nintedanib, have been approved for treating idiopathic pulmonary fibrosis [9,10].
- **Wound Healing:** TGF-β3-based formulations (e.g., avotermin) have shown promise in reducing scar formation post-surgery [9,10]].

These studies highlight the growing interest in TGF-β modulation as a therapeutic strategy.

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Mechanisms of TGF-β Modulation

TGF-β activity can be modulated through:

- **Receptor blockade:** Using monoclonal antibodies or small-molecule inhibitors targeting TβRI and TβRII [9].
- **Gene silencing:** RNA interference techniques to reduce TGF-β gene expression [10].
- **Ligand traps:** Soluble receptor constructs that bind and neutralize TGF-β before it interacts with cell surface receptors [9].

These strategies offer potential therapeutic avenues for conditions involving dysregulated TGF-β signaling [9,10].

Conclusions

Cytokines of the TGF-β family play versatile roles in regulating cellular processes, both physiological and pathological [9,10]. TGF-β1, TGF-β2, and TGF-β3 share structural similarities but differ in their specific actions and expression across tissues [11,12]. Each isoform has essential functions in organismal development, immune responses, and tissue regeneration [13,14]. Understanding the signaling mechanisms of TGF-β and its interactions with other pathways opens new avenues for therapeutic interventions targeting various diseases, from fibrotic disorders to cancer [15,16]. Future research should focus on refining TGF-β-targeted therapies to maximize their clinical utility while minimizing adverse effects.

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