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The Influence Of TGF-B1 Blood Level Regulation on Regenerative Processes in The Human Body

Golib Tolmasovich Kurbanov
Ph.D., Samarkand State Medical University, Uzbekistan

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Abstract: According to Charles Darwin's first rule of regeneration, the higher the level of biological organization in a species, the lower its regenerative capacity. Regeneration is the biological process through which living organisms restore worn-out or damaged structures, often synonymously referred to as reparation. From a biological standpoint, regeneration is considered an adaptive mechanism. Virtually all diseases cause structural damage to tissues and organs, while recovery depends on the organism's ability to regenerate these structures. This article explores the role of transforming growth factor beta 1 (TGF-β1) in tissue regeneration, highlighting its action through both dependent and independent signaling pathways.

Keywords: Regeneration, transforming growth factor beta 1 (TGF-β1), signaling pathways, tissue repair, cytokines, homeostasis.

Introduction: The regulation of tissue repair and regeneration is governed at multiple levels of biological organization. These regulatory mechanisms ensure tissue integrity and functional recovery in response to injury or pathological conditions. The primary regulatory systems include:

- **Intracellular and intercellular mechanisms**
- **Hormonal and cytokine signaling**
- **Neural regulation**
- **Functional (compensatory) responses**
- **Inter-organ coordination**

Each of these systems plays a critical role in orchestrating the complex processes of regeneration and maintaining homeostasis following tissue damage.

Intracellular and Intercellular Regulation. Intracellular regeneration is a universal feature shared by all cells, including neurons. Under normal physiological conditions, cellular proliferation is restrained by chalones—a class of glycoproteins that inhibit cell division. When tissue injury occurs, antichalones are produced to counteract chalones, thereby promoting cell proliferation.

Additionally, degradation products released from damaged cells can exert stimulatory effects on neighboring undamaged cells, prompting them to enter the mitotic cycle and contribute to tissue restoration.

Hormonal and Cytokine Mechanisms. Experimental studies have demonstrated that hormones secreted by the pituitary gland, thyroid, adrenal cortex, gonads, and pancreas influence reparative processes. Notably, TGF-β1 exhibits three principal biological effects:

1. Inhibition of proliferation in most somatic and immune cells
2. Stimulation of growth in certain mesenchymal cells
3. Immunosuppressive action, particularly enhancing the production of extracellular matrix components

As such, TGF-β1 is integral to tissue remodeling and fibrosis, particularly in chronic inflammatory conditions and wound healing.

Neural Mechanisms. The nervous system fulfills a trophic role in regeneration through the release of neurotrophic factors from nerve terminals. These factors stimulate cell survival, differentiation, and

proliferation, thereby contributing significantly to tissue repair.

Functional (Compensatory) Mechanisms. In the context of organ or tissue damage, the remaining viable cells are subjected to increased physiological workload, which results in elevated metabolic activity. This metabolic shift triggers intracellular regenerative processes and may also lead to cell proliferation or hypertrophy, thereby compensating for functional loss.

Inter-Organ Coordination. Inter-organ regulatory mechanisms involve the coordination of multiple organ systems, facilitated through neuroendocrine pathways. These include the hypothalamic-pituitary-adrenal axis and autonomic signaling, which mobilize immune cells and stem/progenitor cells to sites of tissue injury, thereby enhancing regeneration.

Regeneration can be stimulated through a variety of localized interventions, which include:

- Physical stimuli: e.g., mechanical injury that initiates a regenerative response;
- Chemical agents: the application of specific chemical compounds;
- Biological materials: use of biological tissues to promote regeneration;
- Prosthetic methods: implementation of temporary or permanent prostheses to facilitate structural or functional restoration.

Additionally, a number of pharmacological agents and nutritional strategies are employed to support regenerative processes. For example, in experimental settings, fetal serum has been shown to accelerate the union of long bones. Hormones secreted by various endocrine glands also contribute significantly to reparative regeneration. Furthermore, diet has a considerable impact on the dynamics and effectiveness of the regenerative response.

Reparative Regeneration: Typology and Mechanisms. Reparative regeneration refers to the restoration of a body part following its damage or loss. It is classified into two primary types:

- Typical reparative regeneration: the lost part is replaced with an identical structure. This may result from external injury (e.g., amputation) or through autotomy—a deliberate shedding of a body part for survival, such as a lizard detaching its tail.
- Atypical reparative regeneration: the regenerated structure differs quantitatively or qualitatively from the original tissue.

Regeneration Forms Based on Morphological Outcomes

1. Homomorphosis: the exact same organ or part is restored at the site of the loss.

Example: A new limb develops in a newt following amputation.

2. Heteromorphosis: a different organ or structure forms in place of the lost one.

Example: In crustaceans, an antenna may regenerate at the site of an excised eye.

3. Hypermorphosis: more than one structure regenerates in place of a single lost organ.

Example: Two forelimbs may grow in a newt in place of one removed.

4. Regenerative hypertrophy: only the mass of an organ is restored, not its form.

Example: After partial hepatectomy, the remaining liver tissue increases in volume rather than regenerating the exact removed segment.

5. Compensatory hypertrophy: the remaining organ of a paired system enlarges and assumes the function of the lost one.

Example: Enlargement of one kidney after the removal of the other.

6. Somatic embryogenesis: a complete organism develops from a fragment of the body.

Example: A hydra can regenerate entirely from one of its ~200 body segments.

Types of Regeneration Based on Mechanism

1. Epimorphosis: the missing part is reconstructed via outgrowth from the wound site.

Example: Limb regeneration in salamanders.

2. Morphallaxis: structural reorganization of the remaining tissue forms a smaller but functionally complete organ.

Example: Limb regeneration in cockroaches.

3. Endomorphosis: enhanced cell proliferation within the remaining part of an organ restores its function.

Example: Regrowth of liver tissue in vertebrates.

Stem Cells in Regenerative Medicine. Some experts in regenerative medicine posit that regenerative function can be reactivated through the use of stem cells. In adults, stem cells are rare and are typically located in the lower spine, near the dorsal root ganglia. These are pluripotent cells that played a fundamental role in embryogenesis. The first eight cells formed after fertilization are classified as primordial stem cells, which initiate embryonic development.

Researchers have proposed that stimulating these cells may require activation of a specific vortex field (often referred to in esoteric contexts as Merkaba), which

could potentially induce stem cell proliferation and systemic regeneration—an ideal yet speculative vision in regenerative medicine.

Role of TGF-β1 in Regeneration. Transforming Growth Factor Beta 1 (TGF-β1) is a multifunctional cytokine that regulates:

1. Inhibition of proliferation in most somatic cells;
2. Stimulation of mesenchymal cell growth;
3. Immunosuppressive activity, including enhancement of extracellular matrix (ECM) synthesis.

Since the early 2000s, especially after 2005, TGF-β1 has been recognized as a key mediator in the immune pathogenesis of hereditary connective tissue diseases and other immune-related conditions.

The TGF-β family was first described in 1978, with TGF-β1 being the first identified isoform, initially isolated from platelets in the 1990s. The TGF-β1 gene is located on chromosome 19. The name reflects the protein's ability to induce phenotypic transformation in cultured normal cells.

Cellular Sources and Activation of TGF-β1

TGF-β1 is produced by:

- Monocytes and macrophages (primary sources);
- Fibroblasts, endothelial cells, neutrophils, eosinophils, mast cells, smooth muscle cells, and various tumor cells.

It is synthesized as an inactive precursor (prepropeptide). Following processing, a signal peptide and prodomain are cleaved off, resulting in the mature protein. However, the latency-associated peptide (LAP) remains non-covalently bound to the mature TGF-β1, rendering it biologically inactive and stored in the extracellular matrix.

Activation of TGF-β1 occurs in response to tissue injury and involves several mechanisms, including:

- Proteolytic cleavage,
- Integrin interactions,
- pH shifts, and
- Reactive oxygen species (ROS).

Once activated, TGF-β1 initiates downstream signaling cascades crucial to tissue remodeling, fibrosis, and wound healing.

Three main types of TGF-β receptors are distinguished: Type I, II, and III receptors. Type I and II receptors are transmembrane glycoproteins with molecular weights of approximately 55 and 70 kDa, respectively. Due to its dimeric structure, TGF-β1 can simultaneously bind to both type I and type II specific receptors, while type III receptor facilitates this interaction by steric support.

The type I receptor possesses serine/threonine kinase activity, which enables it to phosphorylate a group of intracellular proteins known as Smads (Smad and mad-related proteins). Upon TGF-β1 binding, the type I and type II receptor complex undergoes trans-

phosphorylation, activating the signaling cascade.

Once activated, type I receptors phosphorylate receptor-regulated Smads (R-Smads), which then form a complex with Smad4. This complex translocates into the nucleus, where it regulates transcription of target genes. Divergent inhibitory Smads (Smad6 and Smad7) act as negative regulators of the TGF-β1 signaling pathway.

TGF-β1 exhibits inhibitory effects on the proliferation of T and B lymphocytes, as well as on the maturation and activation of macrophages, thus playing a critical role in immune homeostasis, particularly in downregulating inflammatory responses. Additionally, TGF-β1 suppresses NK cell activity, inhibits cytotoxicity of CD8+ T lymphocytes, as well as lymphokine-activated killer cells, and reduces cytokine production and secretion of certain immunoglobulins.

In lymphoid, epithelial, and endothelial cells, TGF-β1 functions as a growth inhibitor. It is also involved in nephron development, especially in the formation of the glomerular capillary network.

Clinical Implications and Diagnostic Utility. Measurement of TGF-β1 levels in peripheral blood is recommended in the diagnosis and monitoring of various conditions associated with chronic inflammation, including:

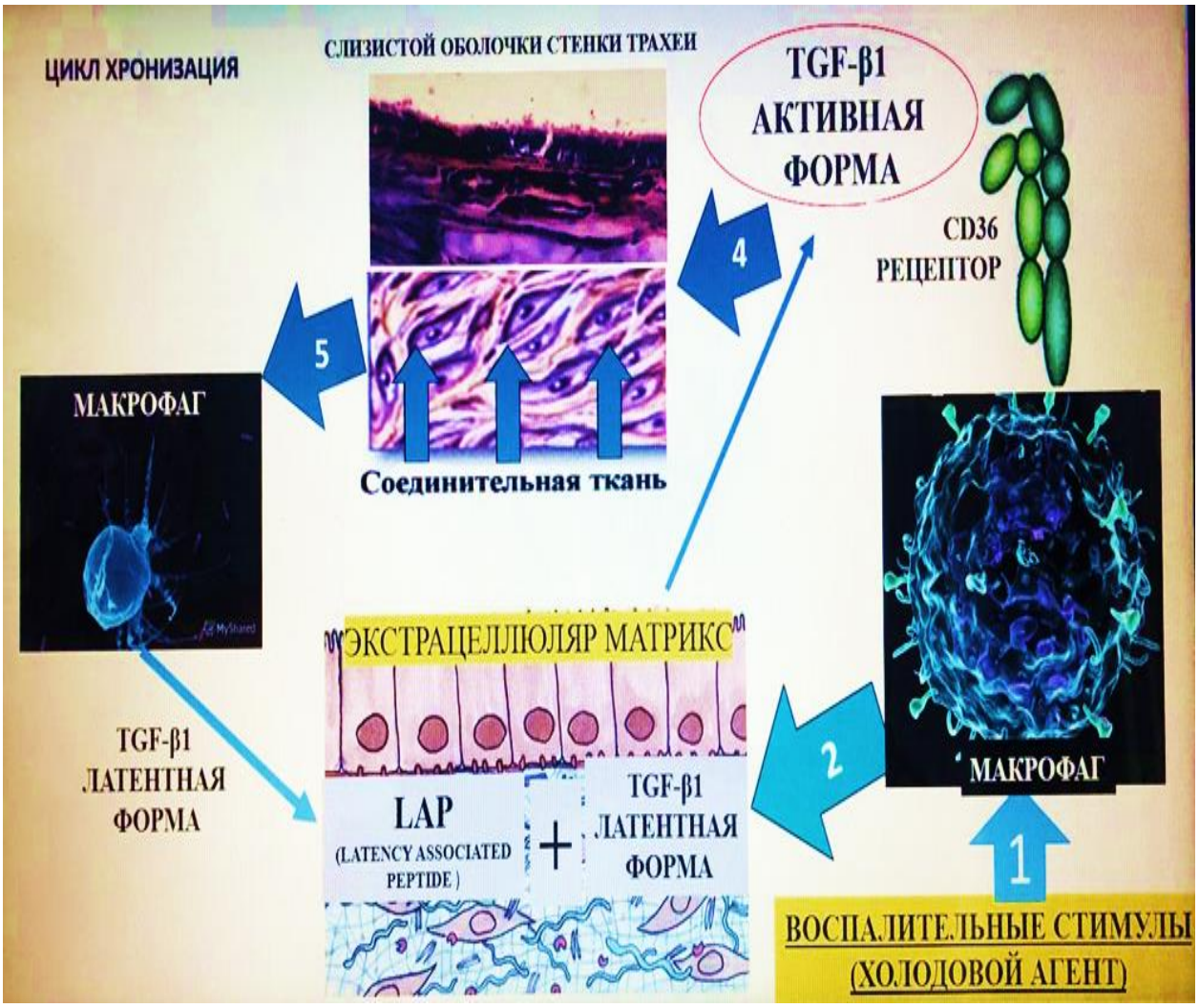
- Alzheimer's disease
- Down syndrome
- Acquired immunodeficiency syndrome (AIDS)
- Parkinson's disease
- Bone marrow and skeletal disorders
- Glomerulonephritis
- Nephropathy
- Diabetes mellitus
- Glomerulosclerosis
- Systemic lupus erythematosus
- Autoimmune hepatitis
- Chronic fatigue syndrome
- Sepsis
- Stroke
- Various cancers (e.g., prostate, bladder, liver)

Elevated levels of TGF-β1 have been detected in chronic fatigue syndrome and in patients with Guillain–Barré–Strohl syndrome. In Kawasaki disease, an inverse correlation between TGF-β1 levels and disease activity has been observed, particularly in patients with IgA deficiency.

Increased serum TGF-β1 levels in patients with thrombocytopenic purpura suggest its involvement in hematopoiesis. The cytokine also plays an essential role in bone marrow metabolism, and its regulatory function in osteoblast-osteoclast interactions is currently under investigation.

Elevated TGF-β1 expression has been reported in prostate cancer, bladder cancer, and hepatocellular carcinoma. In contrast, reduced serum levels of TGF-β1 observed in sepsis and stroke may reflect alterations in the patient's immunoinflammatory status.

Furthermore, it is hypothesized that inhibition of TGF-β1 signaling pathways may contribute to atherosclerotic changes in the vascular wall, by enhancing inflammation and reducing collagen synthesis, thereby weakening atheromatous plaques.



It has been established that elevated levels of TGF-β1 in patients represent one of the key prognostic markers of pathological fibrosis. The activation of stromal elements is considered a central mechanism in the airway wall remodeling process. The number of stromal mesenchymal cells increases proportionally with the thickening and densification of the reticular collagen layer.

In patients with ischemic heart disease, serum TGF-β1 levels are significantly higher compared to healthy individuals. Several authors suggest that a dysbalance between pro-inflammatory and anti-inflammatory cytokines, with a predominance of the latter, underlies the development and maintenance of chronic inflammation, which ultimately culminates in fibrosis.

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