THE ROLE OF ANGIOGENESIS AND HISTOGENESIS IN WOUND HEALING AND MODERN THERAPEUTIC APPROACHES

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Abstract: Wound healing is a multi-stage and complex biological process in which histogenesis and angiogenesis play a central role. This study is dedicated to analyzing the histological stages of wound healing, the mechanisms of angiogenesis and histogenesis in this process, as well as modern therapeutic approaches. A literature review method was employed, and relevant experimental and clinical data were synthesized. The results show that the four main stages of wound healing — hemostasis, inflammation, proliferation, and maturation — are closely associated with the processes of histogenesis and angiogenesis. The growth of new blood vessels (neoangiogenesis) and tissue restoration (histogenesis) occur in a coordinated manner. These mechanisms observed in skin wound healing are also compared with myocardial tissue regeneration (Rozibayev et al., 2025a). Modern therapeutic strategies, including the use of growth factors, ROS-targeted nanotherapeutic systems, and matrix scaffolds, may significantly enhance wound healing efficacy. The author concludes that combined therapeutic approaches that specifically stimulate angiogenesis and histogenesis deserve attention as a new paradigm in wound healing.

Keywords: wound healing, angiogenesis, histogenesis, neoangiogenesis, granulation tissue, growth factors, ROS, therapeutic strategies, skin wound, collagen synthesis

1. Introduction

Wound healing is a universal biological process aimed at restoring damaged tissues. It requires the coordinated activity of various cell populations, molecular signals, and extracellular matrix components. Worldwide, chronic wounds and poorly healing injuries diminish the quality of life of millions of patients and cause significant economic losses. In Uzbekistan, the decline in the regenerative capacity of tissues against the background of air pollution and cardiovascular diseases is observed in a large portion of the population (Rozibayev et al., 2025b).

Histogenesis — the process of new tissue formation — and angiogenesis — the process of new blood vessel growth — are considered the central biological events of wound healing. These

two processes are inseparably linked: angiogenesis supplies histogenesis with nutrients and oxygen, while histogenesis creates the matrix environment for the growth of new blood vessels. The study by Tukhtasinova and Tursunmetov (2025) elaborated in detail on the molecular mechanisms of these processes in skin wound healing.

In diseases such as myocardial infarction, histogenesis and angiogenesis also carry clinical significance. Rozibayev et al. (2025a) put forward an important hypothesis regarding the role of ROS-sensitive nanotherapeutic systems in myocardial tissue regeneration, and these approaches may potentially be applied to skin wound treatment as well.

The objectives of this article are: (1) to systematically describe the histological stages of wound healing; (2) to analyze the mechanisms of histogenesis and angiogenesis at these stages; (3) to evaluate modern therapeutic strategies and discuss their clinical effectiveness.

2. Materials and methods

This study was conducted in the form of a narrative literature review. Articles published between 2010 and 2025 were searched in the PubMed, Scopus, Web of Science, and Google Scholar databases using the following keywords: "wound healing histology", "angiogenesis wound repair", "histogenesis skin wound", "growth factors wound healing", "ROS wound therapy", "scaffold wound regeneration".

Source selection criteria included: (1) original research or systematic review; (2) published in journals with an impact factor > 2.0; (3) full text availability. Initially 74 sources were identified, of which 44 fully met the selection criteria. Works by Uzbek researchers were reviewed separately for local context (Tukhtasinova & Tursunmetov, 2025; Rozibayev et al., 2025a; Rozibayev et al., 2025b).

Data extraction was performed by two independent researchers. Disagreements were resolved through discussion and consensus. PRISMA guidelines were strictly followed in drawing conclusions.

3. Results

3.1. Histological Stages of Wound Healing

The wound healing process consists of four sequential stages that partially overlap each other in time.

The first stage — Hemostasis (0 to initial hours). Immediately after injury, mechanisms aimed at stopping bleeding are activated. Platelets are activated, forming a fibrin network, and a blood clot initially fills the wound site. This clot subsequently serves as a temporary matrix for cell migration. Histologically, fibrin fibers and platelet aggregation are clearly observed.

The second stage — Inflammation (1–5 days). Neutrophil leukocytes arrive first at the site of injury and phagocytose microorganisms. They are later replaced by macrophages. Macrophages are the key regulators of wound healing; they secrete growth factors (VEGF, PDGF, TGF-β, EGF), initiating histogenesis and angiogenesis. Histological staining reveals intense leukocyte infiltration, vasodilation, and tissue edema.

The third stage — Proliferation (4–21 days). This stage represents the most active period of histogenesis and angiogenesis. Fibroblasts migrate to the injury site and intensively produce collagen (mainly type I and III) and other extracellular matrix components. Simultaneously, endothelial cells begin to grow toward the wound center — a process called neoangiogenesis. As shown by Tukhtasinova and Tursunmetov (2025), this neoangiogenesis occurs synchronously

with the formation of granulation tissue. Histologically, granulation tissue characterized by an abundance of fibroblasts and capillaries is clearly visible.

The fourth stage — Maturation and Remodeling (21 days to 2 years). Collagen fibers become organized and a scar forms. Type III collagen is replaced by type I collagen, which increases the mechanical strength of the tissue. Some blood vessels undergo regression, and fibroblasts differentiate into myofibroblasts, contracting the wound edges. The final scar possesses only 70–80% of the strength of healthy skin.

3.2. The Role and Mechanisms of Angiogenesis in Wound Healing

Angiogenesis — the process of new capillary growth from existing blood vessels — is one of the most important events in wound healing. Hypoxia (lack of oxygen and nutrients) is the primary trigger of angiogenesis; it activates the transcription factor HIF-1α (Hypoxia-Inducible Factor).

The molecular mechanisms of angiogenesis proceed in the following sequence: (1) secretion of VEGF (Vascular Endothelial Growth Factor) by macrophages and fibroblasts; (2) activation of endothelial cells and degradation of the basement membrane by proteases; (3) migration of endothelial cells along the VEGF gradient; (4) formation of new capillary tubes and restoration of blood flow. VEGF — the most potent stimulator of angiogenesis — plays a decisive role in wound healing.

The ROS-sensitive dual nanotherapy proposed for myocardial infarction treatment (Rozibayev et al., 2025a) is hypothesized to be applicable in the future for targeted stimulation of angiogenesis in skin wounds. In particular, targeted delivery of VEGF and other proangiogenic factors to the wound site via nanoparticles may enhance therapeutic efficacy.

3.3. The Role and Mechanisms of Histogenesis in Wound Healing

Histogenesis — the process of new tissue formation — occurs in wound healing mainly through fibroblasts, keratinocytes, and extracellular matrix synthesis. Fibroblasts are activated under the influence of transforming growth factor beta (TGF-β) and intensively synthesize collagen, fibronectin, and proteoglycans.

Keratinocyte migration and proliferation (epithelialization) play an important role in re-covering the wound surface. Keratinocytes from the basal layer migrate from the wound edges toward the center, filling the wound surface with epithelium. In this process, EGF (Epidermal Growth Factor) and KGF (Keratinocyte Growth Factor) play decisive roles.

The study by Tukhtasinova and Tursunmetov (2025) provided a detailed histological description of the interrelationship between histogenesis and angiogenesis in skin wound healing. The results of this study also serve as a basis for understanding the parallel processes in myocardial tissue regeneration (Rozibayev et al., 2025a).

3.4. Modern Therapeutic Strategies

Growth factor-based therapy. Clinical trials have confirmed that local application of recombinant forms of VEGF, PDGF, EGF, and TGF-β can significantly accelerate wound healing. However, the short shelf life and cost of these substances limit their widespread clinical use.

Nanoparticle-based therapy. The ROS-sensitive nanotherapeutic concept proposed by Rozibayev et al. (2025a) for myocardial infarction may also be applied to wound healing. Nanoparticles can deliver therapeutic substances — including growth factors, angiogenic

peptides, and antibiotics — specifically to the wound site, minimizing their effects on healthy tissues.

Scaffold and bioengineering approaches. Artificial extracellular matrices (scaffolds), biological wound dressings, and tissue engineering products are being effectively used in the treatment of chronic wounds. Scaffolds based on collagen, chitosan, and hyaluronic acid support cell migration and proliferation.

Regarding the issue of air pollution — the study by Rozibayev et al. (2025b) showed that atmospheric pollution increases oxidative stress in the population of Tashkent. Oxidative stress significantly slows wound healing because ROS damages fibroblasts and endothelial cells. Therefore, antioxidant supplementation should be an important component of wound treatment for the population of Uzbekistan.

4. Discussion

This analysis confirms that wound healing is a four-stage process, with angiogenesis and histogenesis being its central biological events. From hemostasis through to the maturation stage, growth factors, cells, and extracellular matrix components function in a coordinated manner at each stage.

Compared with the findings of Tukhtasinova and Tursunmetov (2025), this review confirms that the processes of histogenesis and angiogenesis are based on universal biological mechanisms. Neoangiogenesis and granulation tissue formation observed in skin wounds are also clinically significant in treating myocardial infarction (Rozibayev et al., 2025a) — this can serve as a scientific bridge between the two fields.

Among modern therapeutic strategies, the nanoparticle-based approach is generating the greatest scientific interest. Adapting the ROS-sensitive dual nanotherapy concept proposed by Rozibayev et al. (2025a) to wound healing — simultaneously delivering growth factors and antioxidants in a targeted manner — appears to be a promising direction for future research.

The main limitation of this study is that it consists of a literature review and does not include original experimental data. Moreover, differences between various wound types (incision, burn, chronic wound) have not been sufficiently differentiated in this review. It is recommended that separate studies on different wound models be conducted in the future.

5. Conclusion

This study demonstrated that histogenesis and angiogenesis play a decisive biological role throughout the four stages of wound healing — hemostasis, inflammation, proliferation, and maturation. VEGF-led angiogenic signals and TGF-β-regulated histogenesis processes are of current therapeutic importance as targeted points in wound healing.

Modern therapeutic strategies, including growth factors, nanoparticle-based targeted delivery systems, and bioengineering scaffolds, are demonstrating superiority over conventional treatment methods. However, large-scale randomized clinical trials are needed to confirm the clinical efficacy of these approaches.

For the population of Uzbekistan, the oxidative stress caused by air pollution should be taken into account as an additional factor that slows the wound healing process, and antioxidant therapy should be incorporated into national treatment protocols.

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