INTERNATIONAL MULTI DISCIPLINARY JOURNAL FOR RESEARCH & DEVELOPMENT
eISSN 2394-6334 Impact factor: 7,854 Volume 12, issue 12 (2025)

FEATURES OF CHANGES IN BLOOD CYTOKINES AND PROTEASE INHIBITORS IN PATIENTS WITH LONG-TERM NON-HEALING PURULENT WOUNDS: A COMPREHENSIVE REVIEW

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Abstract: The management of long-term non-healing purulent wounds (LNHW) remains a critical challenge in clinical surgery due to the complex interplay of immunological and biochemical dysregulations. This review synthesizes current scientific evidence regarding the systemic alterations of cytokine profiles and the protease-inhibitor balance in the blood of affected patients. Analysis reveals that chronicity is driven by a "vicious cycle" where persistent pro-inflammatory signaling (high TNF- α, IL- β) and a deficiency in protease inhibitors (such as α_1-antitrypsin) lead to uncontrolled tissue degradation. Understanding these systemic markers is essential for developing predictive diagnostic tools and targeted therapeutic interventions.

Keywords: Long-term non-healing wounds, purulent infection, cytokines, interleukins, tumor necrosis factor-alpha (α), protease inhibitors, matrix metalloproteinases (MMPs), α_1-antitrypsin, inflammation markers, proteolysis, pathogenesis, chronic wounds.

Introduction

The healing of purulent wounds is a sophisticated biological process involving highly coordinated cellular and molecular events. However, in a significant percentage of patients, this process stalls, leading to long-term non-healing purulent wounds (LNHW) [1]. Chronicity is not merely a local failure but a reflection of systemic homeostatic disruption [9].

Recent advances in molecular medicine have identified two key systems responsible for this failure: the cytokine network, which orchestrates the inflammatory response, and the system of proteases and their inhibitors, which regulates tissue remodeling. While acute inflammation is necessary for wound cleansing, its persistence leads to systemic exhaustion of the body's defensive mechanisms [4, 10]. This article reviews the specific changes in these blood parameters and their role in the pathogenesis of delayed wound healing.

Dynamics of the Cytokine Profile

Cytokines are low-molecular-weight proteins that mediate communication between immune cells. In healthy healing, a transient spike in pro-inflammatory cytokines is followed by a rise in anti-inflammatory factors [12].

In patients with LNHW, this transition is absent. Studies show a stable and prolonged elevation of pro-inflammatory mediators such as IL-β, IL-6, and TNF-α in the peripheral blood [2, 3]. TNF-α, in particular, acts as a major disruptor; its systemic persistence inhibits the migration of keratinocytes and fibroblasts to the wound site [8, 13]. Conversely, the levels of anti-inflammatory cytokines, specifically IL-10 and IL-4, are found to be significantly depressed in these patients [10]. This deficiency prevents the "switching off" of the inflammatory phase, resulting in a state of chronic systemic inflammation that consumes the host’s regenerative resources [7].

The Protease-Inhibitor Balance

The structural integrity of the extracellular matrix (ECM) is maintained by a delicate balance between proteolytic enzymes (mainly Matrix Metalloproteinases - MMPs) and their natural inhibitors [14].

In the blood of patients with long-term purulent processes, there is a documented shift towards excessive proteolysis. Normally, enzymes like elastase and collagenase are regulated by inhibitors such as α_1 -antitrypsin and α_2-macroglobulin [11]. Research indicates that in chronic cases, the consumption of these inhibitors exceeds their synthesis, leading to "inhibitor exhaustion" [6, 15]. When the inhibitory capacity of the blood falls below a critical threshold, proteases begin to non-selectively degrade essential proteins, including immunoglobulins, complement factors, and, crucially, endogenous growth factors (EGF, TGF- β) required for healing [5, 14].

Pathogenetic Interaction: The Vicious Cycle

The most critical finding in recent literature is the bidirectional relationship between cytokines and proteases. High levels of IL-1 β and TNF- α act as potent inducers of MMP expression in neutrophils and macrophages [15].

As these proteases degrade the ECM and cellular receptors, the resulting breakdown products act as DAMPs (Damage-Associated Molecular Patterns), which further stimulate the production of pro-inflammatory cytokines through NF-ϰB pathways [2, 7]. This creates a self-sustaining "vicious cycle" where inflammation fuels proteolysis, and proteolysis sustains inflammation. In patients with LNHW, the systemic blood markers reflect this local catastrophe, showing a high "proteolytic-cytokine index" which correlates with the duration of the wound's existence [3, 6].

Diagnostic and Therapeutic Implications

Monitoring the blood levels of TNF-α and the activity of α_1-antitrypsin offers significant prognostic value. A failure of these markers to normalize within the first 7-10 days of treatment is a reliable predictor of wound chronicity [3, 11].

From a therapeutic perspective, the literature suggests that local treatment alone is often insufficient. Systemic interventions aimed at modulating the cytokine response or supplementing the inhibitory potential of the blood (using protease inhibitor concentrates) are emerging as promising strategies to break the cycle of chronicity [4, 15].

Conclusion

The transition of an acute purulent wound into a persistent chronic state is not merely a localized clinical event but is characterized by a profound and multifaceted systemic imbalance. This review underscores that the failure of the regenerative process is rooted in the dysregulation of the cross-talk between the immune response and the biochemical remodeling machinery. Specifically, the prolonged elevation of pro-inflammatory cytokines, most notably TNF- α and IL-1β, serves as a systemic indicator of a "stalled" inflammatory phase. These mediators do not simply reflect the presence of infection; they actively drive the pathology by suppressing fibroblast activity and inducing the overproduction of degradative enzymes.

Furthermore, the simultaneous depletion of the protective inhibitor system—specifically the exhaustion of α_1-antitrypsin and α_2-macroglobulin—represents a critical tipping point in the pathogenesis of long-term non-healing wounds. When the blood's inhibitory potential is compromised, a state of uncontrolled proteolysis ensues. This "proteolytic storm" leads to the premature degradation of essential growth factors and structural proteins of the extracellular matrix, effectively stripping the wound of its capacity to re-epithelialize.

Consequently, the systemic levels of these cytokines and protease inhibitors should be viewed as potent diagnostic and prognostic biomarkers. Their monitoring allows for a shift from a reactive treatment model to a proactive, personalized approach. Future research must delve deeper into the genetic predispositions and metabolic factors—such as glycemic control and vascular integrity—that may exacerbate this molecular imbalance in certain patient populations. Establishing standardized "cytokine-protease profiles" will be vital for the development of targeted biotherapies, such as exogenous protease inhibitors or cytokine antagonists, ultimately allowing for earlier, more effective clinical interventions and significantly reducing the morbidity associated with chronic purulent infection.

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