

Neopithelial Signatures in Chronic Wound Pathophysiology

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DESCRIPTION

Chronic wounds remain one of the most complex and persistent challenges in clinical medicine. Unlike acute wounds that progress through well-orchestrated stages of healing, chronic wounds exhibit stalled repair processes, prolonged inflammation, and impaired epithelial regeneration. Among the cellular and molecular factors involved, the emergence and behavior of neopithelium-newly formed epithelial tissue attempting to resurface the wound bed-represent a critical determinant of healing outcomes. The study of neopithelial signatures in chronic wound pathophysiology offers important insights into how tissue regeneration fails or succeeds under pathological conditions.

Neopithelium forms as keratinocytes migrate from the wound edges and attempt to restore the epidermal barrier. In acute wounds, this process is rapid and efficient, supported by an optimal balance of cytokines, growth factors, and extracellular matrix components. In chronic wounds, however, the neopithelium often displays structural abnormalities, irregular cellular organization, and incomplete differentiation. These features reflect a distorted communication between the epidermis and the underlying dermal and vascular compartments. Instead of forming a continuous, functional barrier, the neopithelium in chronic wounds frequently develops as a fragile, thin, and poorly attached layer prone to recurrent breakdown.

One of the defining features of these signatures is the presence of sustained proliferation without orderly stratification. In healthy healing, keratinocytes proliferate at the wound margin and then migrate over the granulation tissue while progressively differentiating into suprabasal and cornified layers. In chronic wounds, the proliferative phase persists abnormally, while differentiation markers such as involucrin and filaggrin are expressed inconsistently or prematurely. This results in a thin neopithelium lacking the mechanical strength and barrier integrity of normal skin. The imbalance between proliferation and maturation also predisposes the tissue to cellular stress and apoptosis, further hindering closure.

The inflammatory microenvironment plays a dominant role in shaping neopithelial behavior. Chronic wounds harbor elevated levels of proinflammatory cytokines and proteases that degrade matrix proteins essential for keratinocyte migration. Excessive proteolysis leads to the loss of basement membrane components like laminin and collagen, depriving neopithelial cells of stable anchorage and directional cues. Moreover, persistent inflammation sustains an influx of immune cells that release reactive oxygen species, amplifying oxidative damage. Under such conditions, keratinocytes may undergo epigenetic alterations that lock them into a maladaptive state. These changes can be identified as part of the neopithelial molecular signature, revealing the lasting impact of inflammatory stress on epidermal renewal.

Neopithelial signatures are not purely pathological markers; they also reflect the tissue's intrinsic attempt to regenerate under unfavorable circumstances. Even within chronic wounds, small islands of well-organized neopithelium can sometimes be observed, suggesting that local microenvironments may temporarily restore the balance of growth factors and oxygen tension. These regions highlight the potential for therapeutic modulation of wound milieu to encourage stable epithelialization. Understanding the signaling pathways active within these limited zones of successful regeneration may provide clues for targeted intervention.

Recent molecular studies have revealed that chronic wound neopithelium expresses genes associated with stress response, autophagy, and aberrant differentiation. Pathways involving transforming growth factor, epidermal growth factor receptor, and nuclear factor kappa B are frequently overactivated, while pathways essential for normal keratinocyte maturation are suppressed. This duality reflects a survival-oriented cellular program that favors persistence in an inhospitable environment at the expense of functional regeneration. The recognition of these transcriptomic and proteomic profiles has opened the possibility of defining a neopithelial biomarker panel to assess healing potential and predict wound outcomes.

Another aspect of chronic wound neopithelium is its interaction with microbial colonization. The persistent exposure

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to bacterial biofilms stimulates keratinocytes to produce antimicrobial peptides and inflammatory mediators. Over time, this continuous activation alters the differentiation trajectory of the cells and contributes to a state of epithelial exhaustion. The resulting tissue is hyperproliferative yet structurally deficient, resembling psoriatic or hypertrophic epithelia in certain respects. The chronic wound surface thus represents a complex battlefield where the neoepithelium simultaneously defends against infection and attempts to restore integrity, often failing to achieve either goal completely.

Therapeutic strategies aimed at correcting neoepithelial dysfunction focus on restoring a balanced microenvironment conducive to normal keratinocyte behavior. Approaches such as growth factor supplementation, oxygen therapy, and stem cell-based treatments seek to reestablish proper signaling for migration and differentiation. Bioengineered skin substitutes that provide an organized extracellular matrix scaffold have shown promise in guiding the formation of a more stable and mature neoepithelium. Equally important is the management of inflammation and infection, which directly modulate epithelial gene expression and morphology. The ultimate objective is not

merely to accelerate closure but to promote the formation of a functional, resilient epithelium capable of long-term protection.

CONCLUSION

The concept of neoepithelial signatures in chronic wound pathophysiology encapsulates the morphological, molecular, and functional characteristics that define failed or incomplete epithelial regeneration. The disorganized cellular patterns, altered differentiation markers, and stress-induced molecular profiles represent a complex adaptation to an environment of sustained inflammation, oxidative stress, and nutritional deprivation. Understanding these signatures provides a window into the intricate interplay between the epidermis and its microenvironment during pathological healing. By decoding the signals embedded within the neoepithelial tissue, it becomes possible to design therapeutic strategies that transform dysfunctional regeneration into true tissue restoration, offering renewed hope for patients burdened by chronic, non-healing wounds.