The Role of the Skin Microbiome in Chronic Wound Healing: a Co-evolutionary Hypothesis

Tiffany J. Kim, BA[1,2]; Aneeq S. Chaudhry, BA[2]; Angelica Bartler, MS[1,2]; Emily U. Thai, BS[2]; Marlynn P. Lopez, MS[2]; Spencer Green, BS[2]; Robert D. Galiano, MD[2]

[1]Chicago Medical School, North Chicago, IL, [2]Department of Plastic Surgery, Northwestern Feinberg School of Medicine, Chicago, IL

Background

Millions of patients suffer from chronic wounds, leading to reduced quality of life and rising healthcare costs.[1,2] Despite antibiotics and proper surgical care, many chronic wounds fail to fully heal. Biofilms are frequently implicated, acting as barriers to treatment and immune defense.[1,2] These wounds persist but rarely progress to life-threatening infection, suggesting an adaptive host-microbe balance that favors low virulence and chronicity over mortality. This review synthesizes current evidence to propose that bacterial populations and host defenses have co-evolved adaptations to support sustained, localized infections.

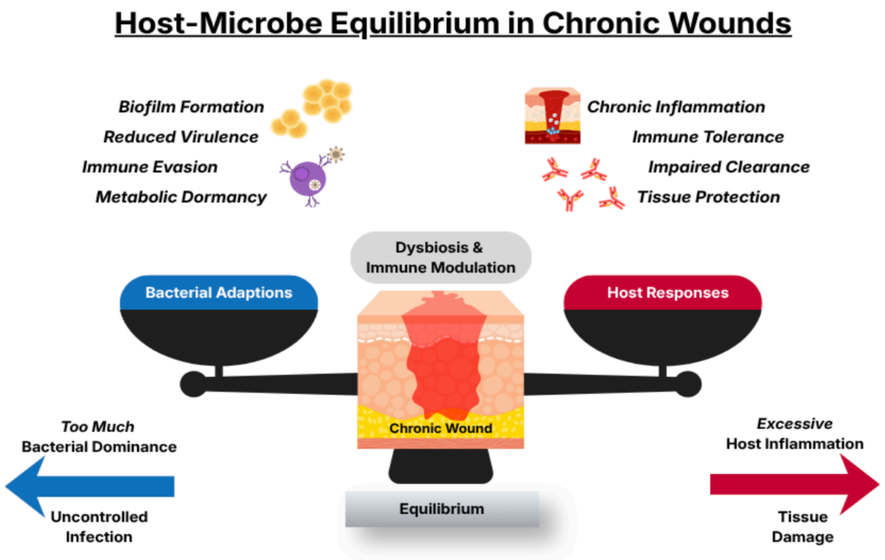
Methods

- A comprehensive literature review of PubMed and Scopus (1990-2025) was conducted using search terms: “skin microbiome,” “chronic wounds,” “biofilm,” “immune evasion,” and “immune response to chronic wounds.”
- Peer-reviewed English studies on the interaction between the skin microbiome and immune defenses in chronic, non-healing wounds were included. Case reports and studies limited to acute wounds were excluded.
- Relevant articles were screened and thematically synthesized on bacterial adaptations, host immune responses, and the pathological host-microbe equilibrium in chronic wounds.

Bacterial Adaptations

- In chronic wounds, bacterial populations adopt adaptations favoring long-term survival by forming impenetrable biofilms, attenuating host immunity, downregulating metabolism of acute virulence factors, and coordinating pathogenic activity through quorum sensing.[3,4]
- Ex) *P. aeruginosa* **alters its gene expression** during transition from acute infection (24 hrs) to chronic biofilm infection (5+ days).[3,4]
- **Before biofilm formation (days 1-4):**
  - ↑ TCA cycle, motility genes, Type III secretion system genes, and iron acquisition genes (acute virulence)
- **After biofilm formation (after day 5):**
  - Above genes downregulated
  - ↑ Anaerobic respiration, denitrification, mixed acid fermentation, and fatty acid degradation pathways
- Bacteria downregulate harmful virulence pathways and **shift towards low-grade inflammation and persistence**, which:
  - Avoids triggering overwhelming immune destruction
  - **Maintains a stable niche (chronic wound)**

Host-Microbe Equilibrium



- **Chronic wounds exist in a state of host-microbe equilibrium.**
- Chronic wounds are characterized by a dynamic interplay between microbial persistence and host immune dysregulation.
- **Shifts toward bacterial dominance** → uncontrolled infection and systemic spread
- **Shifts toward host immune dominance** → excessive tissue damage and inflammatory escalation
- **An optimal balance between bacterial adaptations and host immune responses sustains localized, chronic infections.**
- This equilibrium reflects a co-evolutionary process in which bacterial survival strategies and host immune responses have mutually adapted, resulting in sustained, localized infection.
- **This framework helps explain why chronic wounds neither heal nor frequently progress to systemic disease.**
- Viewing chronic wounds as stable host-microbe ecosystems, rather than mere sites of infection, can open new avenues for effective therapies.

Host Immune Adaptations

- Chronic wound environments reflect a shift in host immunity toward **containment over clearance**.
- Chronic wounds have persistent **innate immune activation:**[5-7]
  - ↑ Neutrophil and macrophage recruitment
  - ↑ Pro-inflammatory cytokine release (IL-1B, TNF-α, IL-6)
  - ↑ MMPs and ROS
- **Adaptive immunity** plays a limited role in chronic wound healing.[5-7]
- Leukocytes are plentiful in chronic wounds, but ↓ **phagocytosis, chemotaxis, and bactericidal activity.**[7]
- Additionally, many chronic wounds do not outwardly display clinical signs/infection, despite high bacterial burden.[7]
- This data may suggest a **functionally constrained immune state**:
  - Maintains antimicrobial pressure
  - Limits excessive tissue damage
- These features are consistent with an **adaptive, tolerance-based response:**
  - Persistent but regulated inflammation
  - Reduced bactericidal efficiency
  - Localized control of infection

Conclusion

- Chronic wounds exist in a **stable pathological equilibrium** between bacterial populations and host immunity.
- **Bidirectional interactions** between microbes and the immune system sustain persistent, localized infection.
- This co-adaptive state explains why chronic wounds **fail to heal yet rarely progress to systemic disease.**
- Future therapies would benefit from disrupting this pathologic equilibrium to promote healing of chronic wounds.

References