International Journal of Clinical and Experimental Medicine Research, 2023, 7(4), 696-700
https: //www.hillpublisher.com/journals/ijcemr/
ISSN Online: 2575-7970
ISSN Print: 2575-7989

Dynamics of Microbial Communities in Chronic Wounds and Their Role in Wound Healing

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How to cite this paper: Linxuan Zou, Xingkai Wang, Zhe Zhang, Tianke Yang, Junwei Zong. (2023) Dynamics of Microbial Communities in Chronic Wounds and Their Role in Wound Healing. *International Journal of Clinical and Experimental Medicine Research*, 7(4), 696-700.
DOI: 10.26855/ijcemr.2023.10.032

Received: September 30, 2023
Accepted: October 29, 2023
Published: November 30, 2023

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Abstract

Chronic wounds, such as diabetic foot ulcers, pressure sores, and venous stasis ulcers, have long posed a challenge in the medical field. The healing process of these wounds is influenced by various factors, among which the role of the microbial community is increasingly recognized. This review delves deep into the dynamic changes in the microbial community of chronic wounds and elucidates the critical role of microbes in the process of wound healing. The microbial community is closely associated with various stages of the wound healing process, including inflammation, cell proliferation, and cell migration. In particular, the inflammatory response, which is directly linked to microbial infection, subsequently affects the rate of wound healing. Microbial interventions, such as the use of antibiotics and probiotics, are gradually emerging as vital strategies for the treatment of chronic wounds. However, with the escalating issue of antibiotic resistance, probiotic therapy is showcasing its unique advantage as an alternative strategy. In conclusion, this article provides readers with a thorough and comprehensive understanding of the microbial community in chronic wounds. It also highlights new avenues for future research and treatment.

Keywords

Microbial Communities, Chronic Wounds, Wound Microenvironment

1. Introduction

Chronic wounds, including diabetic foot ulcers, pressure ulcers, and venous leg ulcers, pose one of the significant challenges faced by the global healthcare system. It's estimated that over 6.5 million people in the US alone grapple with various types of chronic wounds, imposing substantial economic burdens on the healthcare system [1]. Despite the availability of multiple treatment strategies, such as drug therapy, Maggot Debridement Therapy (MDT), and surgical intervention, the treatment of chronic wounds remains fraught with challenges. Among these, microbial infections and the dynamic shifts in the microbiome stand out as one of the pivotal factors influencing the success rate of chronic wound treatment [2].

In recent years, an increasing number of studies have begun focusing on the intricate relationship between the microbiome and chronic wounds [3]. The microbiome not only plays a role in the inception and persistence of wound infections but also wields significant influence over the wound healing process. For instance, certain symbiotic microbes may expedite natural wound healing by inhibiting the growth of pathogens. Yet, how the dynamic shifts in the microbiome influence the healing of chronic wounds and how to efficiently intervene microbiologically to enhance therapeutic outcomes remain hot topics and challenges in current research [4].

The aim of this review is to delve deep into the dynamic changes in the microbiome within chronic wounds and their foundational and clinical impacts on wound healing [5]. We will commence by introducing the basics of chronic wounds and the microbiome, followed by a comprehensive analysis of the microbiome's composition its dynamic shifts, and their associations with various types and stages of chronic wounds. In conclusion, we will discuss the advancements in microbial interventions and their potential applications in treating chronic wounds.

By presenting this review, our goal is to equip clinicians and researchers with a holistic and profound perspective, aiding in a better understanding of the significance of the microbiome in chronic wound therapy and exploring new therapeutic avenues.

2. Basic Concepts of Chronic Wounds and the Microbiome

Chronic wounds refer to injuries that haven't fully healed over 3 months, and their healing processes often get delayed or interrupted. Common types of chronic wounds include diabetic foot ulcers, pressure ulcers, and venous leg ulcers [3]. Diabetic foot ulcers often result from inadequate blood sugar management, infections, or ill-fitting footwear. Pressure ulcers arise from prolonged unrelieved pressure causing damage to the skin and underlying tissues. Venous leg ulcers typically associated with the malfunction of the lower leg veins. The diagnosis of chronic wounds typically relies on medical history, physical examination, and possibly further diagnostic tests. Pinpointing the type and cause of the wound is paramount since different types may necessitate distinct treatment strategies [1].

The microbiome, often referred to as the microbiota, encompasses the aggregate of microbes in a specific environment, including bacteria, fungi, viruses, and other microorganisms. Within the human body, each region harbors its distinct microbiome [6]. These microbes interact with their host, profoundly impacting the health and disease states of the host.

3. The Impact of Microbial Communities on Wound Healing

Wound healing is a complex, multi-step biological process that involves the collaborative action of various cells, extracellular matrix, growth factors, and enzymes. Microbial communities play a pivotal role at all stages of wound healing, from the initial inflammatory response to the remodeling phase of the wound [7].

When a wound becomes infected, inflammation serves as the body's primary defense against microbial invasion. In this process, neutrophils and macrophages quickly gather at the infection site. These cells release an abundance of inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which are crucial in neutralizing invading microbes [8]. However, persistent inflammatory responses and excessive cytokine release can damage surrounding healthy tissue, obstructing wound healing.

For instance, Staphylococcus aureus which forms biofilms can produce a variety of toxins. These toxins activate the host's inflammatory pathways, leading to the excessive production of inflammatory cytokines like IL-8 and IL-6 [9]. This chronic inflammatory state not only damages cells but also hinders the normal wound-healing process.

Microbes present in the wound can directly or indirectly influence the surrounding skin cells. Some beneficial skin microbes, like certain strains of Bacillus, can release growth factors, promoting the proliferation of skin cells, such as keratinocytes and fibroblasts [10].

Conversely, some pathogenic microbes can release cytotoxins, which can disrupt cell migration, proliferation, and division. For example, Pseudomonas aeruginosa can produce a molecule called "exotoxin A," which can bind to receptors on the host cell membrane, resulting in cellular dysfunction and death [11]. Another common skin pathogen, Streptococcus, can damage host cells by releasing superoxides and enzymes [12].

The relationship between microbial communities and wound healing is inextricable. Understanding how these microbes interact with host cells and their microenvironment, and how these interactions affect the biological processes of the wound, is vital for developing novel and effective wound treatment strategies [13]. By deeply studying these mechanisms, we can better understand the causes of wound infections and delayed healing, thereby developing targeted treatments to improve patient outcomes and quality of life.

4. Interactions Between Microbes and the Wound Microenvironment

Microbial communities play a crucial role in chronic wounds, and their interaction with the wound microenvironment affects the wound-healing process. A deep understanding of this interaction is essential for designing treatment strategies and optimizing clinical outcomes.

Firstly, the wound microenvironment is a complex biological system consisting of various cells, nutrients, growth factors, and signaling molecules. Through their interactions with these components, microbial communities can significantly influence the wound microenvironment. For instance, microbes can produce metabolic byproducts, such as short-chain fatty acids, acids, bases, and other organic compounds, through various metabolic pathways, altering the wound's pH, oxygen concentration, and nutrient content [14].

Anaerobic bacteria, like Clostridium, are a crucial part of the wound microbial community. In anoxic conditions, these microbes proliferate extensively and produce short-chain fatty acids, like butyrate and acetate, through fermentation metabolism [15]. These organic acids can lead to a decrease in wound pH, creating an acidic environment. This acidic environment not only inhibits the growth of other beneficial microbes but may also affect wound cell functions, disrupting the microbial balance and thus delaying the healing process [16].

Additionally, some bacteria within the microbial community can form biofilms, a tightly interacting biological structure composed of multiple microbes. Microbes within the biofilm are more resistant to antibiotics and immune system clearance than those dispersed on the wound [17]. Consequently, biofilm formation may lead to persistent microbial infections, further hindering wound healing [18].

Moreover, interactions between microbes and wound cells can also influence the wound microenvironment. For instance, certain pathogenic microbes can release toxins that disrupt cell membranes, causing cell death [19]. This not only results in tissue damage at the wound site but can also induce inflammatory responses, further delaying healing [20].

In summary, the interaction between microbes and the wound microenvironment is a multifaceted process involving various biological and non-biological factors. Understanding the mechanisms of these interactions is crucial for devising effective treatment strategies and optimizing clinical outcomes. Achieving this goal requires in-depth research into the interactions between microbes and the wound microenvironment and how these interactions influence the wound-healing process.

5. Microbial Interventions

In recent years, microbial interventions have emerged as a focal point in the treatment of chronic wounds. These interventions aim to modify the microbial community of the wound to promote healing.

Traditionally, the treatment strategies for chronic wounds have largely relied on broad-spectrum antibiotics to suppress or eradicate infections. However, frequent or improper use has exacerbated the issue of antibiotic resistance. Furthermore, antibiotics might also disrupt beneficial microbial communities, thus affecting the natural healing process of the wound [21]. Hence, principles of selection and application are crucial for the use of antibiotics. This mandates clinicians to carry out bacterial cultures and antibiotic susceptibility tests to ensure targeted treatment [22].

In recent years, as our understanding of the role of microbial communities in health and disease deepens, researchers have begun exploring strategies to modulate these communities to treat various conditions, including chronic wounds. Probiotics and prebiotics, as tactics to balance microbial equilibria, have shown immense potential in this domain [23].

Probiotics are a collection of live microorganisms beneficial to the host. Their principal functions include competing with pathogenic microbes for nutrients and adhesion sites or producing antimicrobial agents, thereby suppressing or excluding the growth and activity of pathogenic microbes [24]. Moreover, probiotics can modulate the host's immune response, provide essential nutrients, and enhance the host's resilience to detrimental external factors. In wound treatment, probiotics primarily [25]:

Form Biofilms: Some probiotics can create biofilms on wounds, a structure that can deter the adhesion and proliferation of pathogenic microbes. This biofilm formation acts as a physical barrier, making it challenging for pathogens to infiltrate the wound.

Produce Antimicrobial Agents: Many probiotics can generate antimicrobial peptides or other types of antimicrobial substances. These compounds can directly kill or inhibit pathogenic microbes, thus safeguarding the wound from infections.

Regulate Host Immune Response [26]: Probiotics can modulate the host's immune response by producing specific signaling molecules like short-chain fatty acids. This can assist in mitigating excessive inflammatory reactions, consequently promoting wound healing.

Prebiotics are food ingredients that are nearly indigestible for the host but can be utilized by probiotics. They promote the growth and activity of probiotics, thereby aiding in maintaining the balance of the microbial community. In wound treatment, prebiotics mainly function through:

Promote Probiotic Growth: Prebiotics offer a nutrient source for probiotics, enabling their rapid proliferation on the wound, thereby excluding or inhibiting pathogenic microbes.

Enhance the Wound Microenvironment: Decomposition of products of prebiotics, such as short-chain fatty acids, can help adjust the pH of the wound, crafting a microenvironment conducive to healing.

In summary, microbial interventions have charted a new direction for chronic wound treatment. As technology advances and research deepens, we anticipate the development of more effective and personalized therapeutic strategies.

6. Discussion

When discussing the relationship between chronic wounds and their microbial communities, it's essential not only to understand their fundamental knowledge and dynamic changes but more importantly, to elucidate how their interactions affect wound healing and to explore effective microbial intervention strategies. This section will summarize and delve deeper into the aforementioned research.

Firstly, chronic wounds present a complex biological environment where the dynamic changes in microbial communities closely relate to the degree of wound healing. Data extracted from different types of chronic wounds (e.g., diabetic foot ulcers, pressure sores, and venous leg ulcers) suggests that each wound type possesses its unique microbial characteristics. This microbial diversity might be influenced by various factors such as the patient's health status, age, gender, and lifestyle [27]. Importantly, as wound healing progresses, these microbial communities also change.

Secondly, microbial communities are associated not only with wound infections but also with healing. Some microbes might stimulate inflammatory responses, slowing healing, while others might promote wound repair. For example, certain probiotics can modulate the host's immune response, accelerating wound healing. This interaction offers a fresh perspective on understanding wound repair mechanisms and suggests future therapeutic strategies.

However, current research on microbial interventions is still in its infancy. While antibiotics can be effective in certain scenarios, the problem of antibiotic resistance is undeniable. The application of probiotics and prebiotics requires further clinical validation. Nonetheless, they still offer hope for chronic wound treatment.

Yet, existing studies have limitations. Most are based on small sample observations and lack large-scale clinical validation. Accurately assessing the effect of microbial interventions and devising personalized treatment strategies for each patient are challenges requiring further research.

Looking ahead, we aim to develop more effective and personalized therapeutic strategies. This demands a profound understanding of the functionalities of wound microbial communities and their interactions with the host. Only then can we truly realize effective treatment for chronic wounds.

7. Conclusion

Chronic wounds, especially common types like diabetic foot ulcers, pressure sores, and venous leg ulcers, remain a significant challenge in the medical field. Our deepening understanding of the role of microbial communities in wound healing offers a novel therapeutic perspective and strategy. The dynamic changes in wound microbial communities are closely related to the wound healing process, and their balanced state plays a decisive role in influencing inflammation, cell function, and the microenvironment.

Moreover, microbial interventions, such as antibiotic applications and probiotic and prebiotic treatments, show potential advantages. However, as the issue of antibiotic resistance becomes increasingly prominent, seeking alternative methods and strategies becomes paramount. The application of probiotics offers a new direction, but further research is needed to ensure its efficacy and safety.

In conclusion, the microbial communities of chronic wounds not only unravel the intricate mechanisms of wound healing but also provide invaluable insights for future treatment strategies. We look forward to future studies unveiling more effective and safe therapeutic methods, promising a brighter healing prospect for patients.

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