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Effect of Circadian Clock on Wound Healing - Day vs Night

Sharath T P[1], Preethi G B[2*], Sahmika Sridhar[3], Narahari K V[4], Shrikrishna M Naik[5], Lakshmi Priya N S[6]

Department of Pharmaceutics, KLE College of Pharmacy, KLE Academy of Higher Education and Research, Rajajinagar, Bengaluru, Karnataka, India-560010

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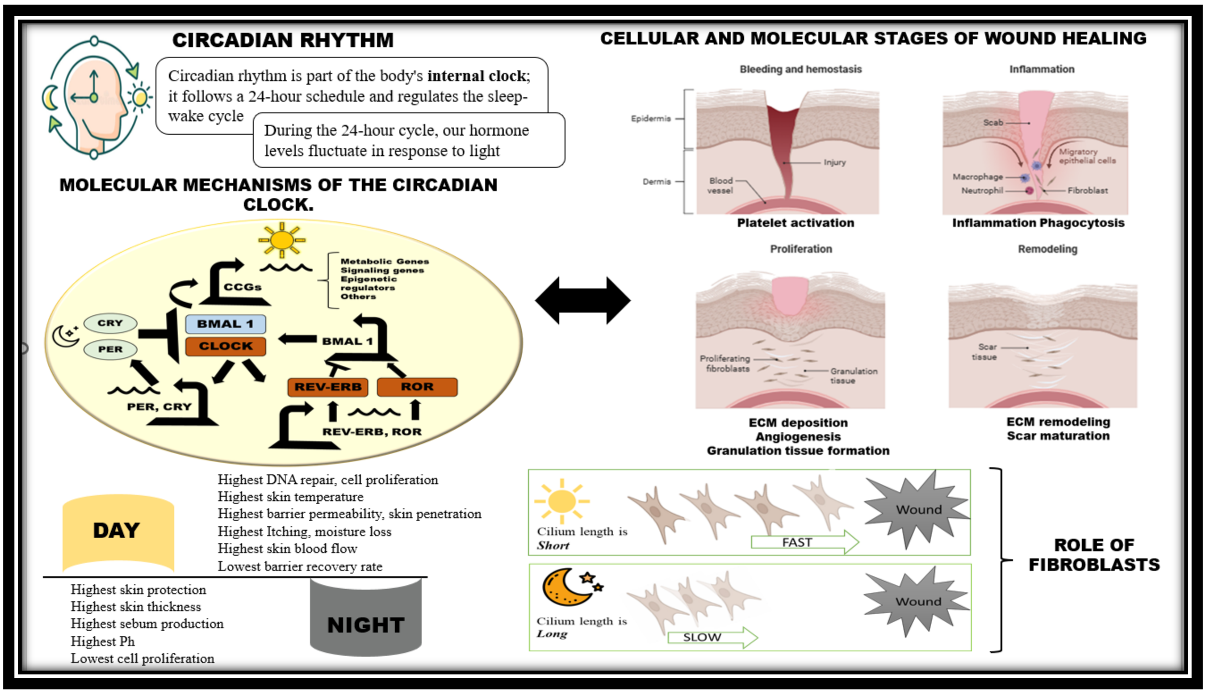
ABSTRACT:



The circadian clock is an intrinsic timekeeping system that orchestrates various physiological processes, including wound healing. This paper explores the influence of circadian rhythms on different stages of wound repair—haemostasis, inflammation, proliferation, and remodelling-highlighting the differences in healing efficiency between day and night. Recent research demonstrates that daytime injuries heal faster due to enhanced immune responses, increased keratinocyte migration, and optimized fibroblast activity. Conversely, nighttime wounds exhibit prolonged inflammation and delayed tissue regeneration due to lower cellular activity and immune function. [1,2,7]Molecular mechanisms underlying these temporal variations involve key circadian genes such as CLOCK, BMAL1, PER, and CRY, which regulate immune cell contracting the cytokine production, and extracellular matrix remodelling [5]. Disruptions to circadian rhythms—due to modern lifestyles, shift work, or sleep disorders—can impair wound healing, leading to chronic wounds and increased susceptibility to infections. [1]Clinical implications suggest that aligning medical interventions with the body's circadian rhythms, a practice known as chronotherapy, can optimize surgical outcomes and accelerate recovery. Strategies such as timing surgeries in the morning, regulating light exposure post-surgery, and developing circadian-synchronized biomaterials offer promising therapeutic avenues. [4] There are still issues, though, such as the requirement for standardized clinical procedures and individual differences in circadian reactions.Future research should focus on integrating circadian biology into precision medicine, exploring genetic influences on healing rhythms, and leveraging wearable technology for real-time circadian monitoring. [1] By harnessing the power of biological rhythms, circadian-based approaches have the potential to revolutionize wound care and regenerative medicine. [9]

Keywords: Circadian rhythms, Wound healing stages, Chronotherapy, Circadian genes (CLOCK, BMAL 1, PER, CRY), Precision medicine

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1. INTRODUCTION

The Intricate Dance of Time: Exploring the Circadian Biology

An internal clock that synchronizes biological functions with the Earth's 24-hour light-dark cycle is called the circadian clock. The term "circadian rhythms," which comes from the Latin "circa" (about) and "diem" (day), controls processes like hormone release, metabolism, immunological response, and cellular repair. The master clock, which is housed in the hypothalamic suprachiasmatic nucleus (SCN), synchronizes the peripheral clocks of the skin, liver, and heart.

At the molecular level, a transcription-translation feedback loop (TTFL) is responsible for circadian rhythms. CLOCK, BMAL1, PER, and CRY are the core clock genes that control this cycle. By encouraging the transcription of PER and CRY, which block CLOCK-BMAL1 activity, CLOCK and BMAL1 create a rhythmic cycle. Light, food, and temperature are examples of environmental signals that affect these cycles; disturbances are associated with metabolic disorders, cancer, and poor wound healing.

Hemostasis, inflammation, proliferation, and remodelling are all components of wound healing. A fibrin scaffold is formed when hemostasis starts the clotting process. The next stage is the inflammatory phase, during which immune cells release cytokines such as TNF-α and IL-1 and remove debris. This stage is impacted by circadian rhythms, which have an effect on immune cell trafficking. Fibroblasts deposit collagen during the growth phase, while endothelial cells generate capillaries; both processes are influenced by the clock. Lastly, remodelling reorganizes the extracellular matrix by substituting stronger type I collagen for type III collagen.

The field of chronobiology, which has its roots in ancient discoveries, rose to prominence in the 20th century after Franz Halberg coined the term "circadian." The 2017 Nobel Prize was awarded for illuminating circadian systems through the discovery of clock genes in fruit flies. By incorporating circadian biology into wound healing, it has been possible to identify daily fluctuations in tissue regeneration and immunological activity, underscoring the potential of chronotherapy—matching medical interventions with biological cycles to maximize healing.

Research gaps still exist despite advancements: few human studies, ambiguous molecular pathways, a lack of standards for chronotherapy, chronotype variability, and the impact of contemporary lifestyles. By filling in these gaps, interdisciplinary approaches may improve wound healing results and utilize circadian science's therapeutic potential. [1,2,3,4]

The circadian modulation of wound repair has been confirmed by recent human investigations, despite the fact that the majority of the fundamental circadian research has been carried out in animal models:

Surgical Timing and Outcomes: According to a study by Cable et al. (2016), patients who had daytime surgery heal wounds faster and are less likely to get infections after that compared to individuals who underwent night time surgeries.

Clinical evidence indicates that burn injuries that occur during the daytime have less scarring and faster epithelialization than those that occur at night. Human studies have demonstrated that synchronizing post-operative light exposure and medication scheduling with circadian rhythms improves immune responses and accelerates along tissue regeneration. [5,6,7]

2. Circadian Biology: A Detailed Exploration

Introduction to Circadian Rhythms

In almost each cell, circadian rhythms—which are natural, nearly 24-hour cycles—control a wide range of physiological, behavioral, and biological processes. [5] Because they synchronize biological processes with environmental cues like the light-dark cycle, these rhythms are crucial for preserving homeostasis. Molecular mechanisms, interactions between the central and peripheral clocks, regulatory genes, and their effect on metabolic and cellular processes are all involved in the coordination of these rhythms.[3] Examining molecular mechanisms, the function of central and peripheral clocks, important genes and proteins, and the effects on metabolism and cellular dynamics, this study goes into the complex architecture of circadian biology.

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1. Molecular Mechanisms of the Circadian Clock

Factor	Daytime Healing	Nighttime Healing
Platelet Activation	Rapid clot formation, high fibrin mesh density	Slower clotting, weaker fibrin structure
Immune Defense	Active immune surveillance, efficient pathogen clearance	Lower immune activity, increased infection risk
Cellular Energy	High ATP availability, active mitochondrial function	Reduced energy supply, sluggish cellular repair
Fibroblast Activity	Increased collagen synthesis, rapid wound closure	Decreased collagen production, delayed contraction
Keratinocyte Migration	Faster cell movement, efficient skin barrier restoration	Slower migration, prolonged exposure to external factors
Angiogenesis	Increased VEGF expression, robust blood vessel formation	Weaker endothelial response, sluggish capillary growth
Scarring Risk	Controlled ECM remodelling, minimal fibrosis	Excessive scarring due to prolonged tissue repair
Inflammation Duration	Shorter, well-regulated inflammatory phase	Prolonged inflammation, risk of chronic wounds

1.1 The Core Molecular Loop

At the heart of circadian biology lies a transcription-translation feedback loop (TTFL), which promotes the oscillatory behavior of clock genes and proteins. This loop forms the molecular basis of circadian rhythms in both central and peripheral clocks.

- **Core Components**:

  - **CLOCK** and **BMAL1**: These transcription factors heterodimerize and bind to E-box elements in the promoter regions of target genes such as **PER** (period) and **CRY** (cryptochrome).

  - **PER** and **CRY Proteins**: Once transcribed, they accumulate in the cytoplasm, dimerize, and inhibit CLOCK: BMAL1 activity, providing negative feedback.

  - This interplay generates oscillations in gene expression with a periodicity of approximately 24 hours. [6]

1.2 Auxiliary Loops

Additional loops enhance the robustness and precision of circadian rhythms:

- **REV-ERBα/β** and **RORα/β/γ** compete to regulate BMAL1 expression, fine-tuning the clock's amplitude and phase. [1]

- Post-translational modifications, such as phosphorylation (via casein kinases CK1δ and CK1ε), regulate the stability and localization of PER and CRY proteins. [12]

1.3 Light Entrainment

The circadian clock is reset daily by environmental cues, with light serving as the primary zeitgeber. In mammals, light signals are transmitted from the retina to the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract, inducing transcriptional changes in core clock genes. [1] [13]

2. Interactions Between Central and Peripheral Clocks

2.1 The Suprachiasmatic Nucleus (SCN)

The SCN, located in the anterior hypothalamus, is the master circadian pacemaker. It synchronizes peripheral clocks throughout the body to ensure temporal coherence.

- Light input resets the SCN, which uses neural and humoral signals to align peripheral clocks.
- SCN neurons exhibit autonomous rhythmicity and intercellular coupling, enabling robust oscillations. [1]

2.2 Peripheral Clocks

Peripheral clocks are present in almost every tissue, including the liver, heart, kidneys, and skin. While they share the same core molecular machinery as the SCN, they rely on signals from the master clock for synchronization.

- **Communication Pathways**:

  - Neural signals: Efferent pathways from the SCN modulate autonomic outputs.
  - Humoral signals: Hormones such as glucocorticoids and melatonin act as systemic entrainment cues.
  - Metabolic signals: Feeding-fasting cycles regulate peripheral rhythms, particularly in metabolic tissues. [12]

2.3 SCN-Peripheral Coordination

The hierarchical relationship between the SCN and peripheral clocks ensures systemic alignment. Disruption in this coordination, as seen in shift work or jet lag, can lead to metabolic dysregulation, inflammation, and impaired wound healing. [1]

3. Key Regulatory Genes and Proteins

3.1 CLOCK and BMAL1

CLOCK and BMAL1 are the primary transcriptional activators in the circadian system.

- CLOCK contains a histone acetyltransferase (HAT) domain, enabling chromatin remodeling.
- BMAL1 interacts with CLOCK to initiate transcription of target genes, playing a pivotal role in maintaining rhythmicity. [11] [13]

3.2 PER and CRY

PER (PER1, PER2, PER3) and CRY (CRY1, CRY2) are the main negative feedback regulators.

- **PER Proteins**: Exhibit oscillatory degradation influenced by CK1δ/ε-mediated phosphorylation.
- **CRY Proteins**: Stabilize PER complexes, prolonging the negative feedback phase. [5] [12]

3.3 Auxiliary Regulators

- **REV-ERBα/β**: Suppress BMAL1 transcription, contributing to rhythmic gene expression.
- **RORα/β/γ**: Antagonize REV-ERB activity, ensuring balanced BMAL1 levels.
- **Casein Kinases**: Regulate clock protein stability and nuclear localization. [7]

3.4 Non-Core Regulators

Emerging evidence highlights additional modulators, including:

- **NFIL3**: Integrates immune signals with circadian regulation.
- **SIRT1**: Links metabolic status to circadian control via deacetylation of clock proteins.[1]

4. Impact on Metabolic and Cellular Processes

Circadian rhythms influence a wide array of metabolic and cellular functions, underscoring their critical role in health and disease.

4.1 Metabolic Regulation

The circadian clock governs glucose metabolism, lipid homeostasis, and energy expenditure.

- **Glucose Metabolism**:
  - Insulin sensitivity exhibits diurnal variation, with peak sensitivity during the active phase.
  - Disruption of circadian genes impairs glucose tolerance and promotes insulin resistance. [9]
- **Lipid Metabolism**:
  - Genes involved in lipid synthesis (e.g., SREBP) and oxidation (e.g., PPARα) are under circadian control.
  - Aberrant circadian rhythms contribute to dyslipidaemia and obesity. [6]

4.2 Cellular Processes

The circadian clock regulates key cellular activities, including:

- **Cell Cycle**: Synchronizes cell division with environmental cycles to prevent genomic instability.
- **DNA Repair**: Enhances nucleotide excision repair during the active phase, reducing mutation rates.
- **Immune Function**: Rhythmic cytokine production and immune cell trafficking align with circadian cues, optimizing host defense. [19]

4.3 Chronotherapy

Understanding circadian influences has led to the development of chronotherapy, where treatments are timed to maximize efficacy and minimize side effects.

- For example, chemotherapy drugs targeting DNA synthesis are more effective when administered during specific circadian phases. [14] [17]

The circadian clock is a fundamental regulator of physiological and cellular processes, integrating environmental and endogenous signals to maintain homeostasis. Its molecular mechanisms, governed by key genes like CLOCK, BMAL1, PER, and CRY, exhibit a remarkable interplay between central and peripheral clocks. [18] By orchestrating metabolic and cellular functions, the circadian system not only optimizes biological efficiency but also provides a promising framework for therapeutic innovation. [21] Further research into the circadian biology will illuminate its role in health and disease, offering novel avenues for precision medicine and chronotherapy.

3. Mechanisms of Wound Healing: A Comprehensive Exploration

Introduction to Wound Healing

Wound healing is a complex, dynamic biological process that restores the integrity of damaged tissue through a highly orchestrated sequence of cellular and molecular events. [4] This intricate process involves various cell types, signaling molecules, and extracellular matrix components, progressing through distinct yet overlapping stages: hemostasis, inflammation, proliferation, and remodeling. [18] The healing process is driven by molecular signaling pathways and cellular interactions that ensure timely and effective tissue repair.

This chapter delves into the cellular and molecular stages of wound healing, emphasizing the roles of keratinocytes, fibroblasts, and macrophages, as well as the critical contribution of immune cells in tissue repair. [23]

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1. Cellular and Molecular Stages of Wound Healing

1.1 Hemostasis

Hemostasis is the initial response to tissue injury, aiming to stop bleeding and create a temporary matrix for subsequent repair.

- **Key Processes**:
  - Vascular constriction reduces blood flow to the site of injury.
  - Platelet aggregation forms a primary plug.
  - Coagulation cascades activate thrombin, leading to fibrin clot formation.
- **Molecular Players**:
  - **Platelets** release growth factors like platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), which recruit immune and progenitor cells.[(1)]

1.2 Inflammation

The inflammatory phase is marked by the recruitment of immune cells to clear debris and pathogens.

- **Key Immune Cells**:
  - Neutrophils arrive first, releasing reactive oxygen species (ROS) and antimicrobial peptides to prevent infection.
  - Monocytes differentiate into macrophages, which phagocytose debris and orchestrate the transition to the proliferative phase. [(8)]
- **Cytokines and Chemokines**:
  - Pro-inflammatory cytokines (e.g., interleukin-1β, tumor necrosis factor-alpha) amplify immune responses.
  - Chemokines such as CCL2 and CXCL8 recruit additional immune cells. [(12)]

1.3 Proliferation

The proliferative phase focuses on tissue formation and angiogenesis.

- **Cellular Activities**:
  - Keratinocytes migrate to re-epithelialize the wound.
  - Fibroblasts proliferate and differentiate into myofibroblasts, secreting extracellular matrix (ECM) proteins like collagen. [(16) (18)]
  - Endothelial cells form new capillaries in response to vascular endothelial growth factor (VEGF) signaling.
- **Growth Factors**:
  - Epidermal growth factor (EGF) and fibroblast growth factor (FGF) stimulate cell proliferation.
  - TGF-β drives fibroblast-to-myofibroblast differentiation and collagen deposition.[(31)]

1.4 Remodeling

The final stage, remodeling, strengthens the repaired tissue and restores functionality.

- **Matrix Remodeling**:
  - Myofibroblasts contract the ECM, reducing scar size.
  - Matrix metalloproteinases (MMPs) degrade excessive ECM components, balancing synthesis and degradation. [15]
- **Scar Formation**:
  - Type III collagen is replaced with type I collagen, increasing tensile strength.
  - Angiogenesis is downregulated, leaving mature blood vessels. [17] [19]

2. Key Players in Wound Healing

2.1 Keratinocytes

Keratinocytes are essential for re-epithelialization and barrier restoration.

- **Migration**:
  - Keratinocytes migrate from wound edges, guided by gradients of EGF and integrins.
  - Activation of Rac1 and Cdc42 signaling pathways facilitates cytoskeletal rearrangements. [25]
- **Proliferation**:
  - Growth factors like EGF and keratinocyte growth factor (KGF) drive keratinocyte proliferation.
- **Cytokine Secretion**:
  - Keratinocytes release interleukins (e.g., IL-6) and VEGF, promoting angiogenesis and immune cell recruitment. [23] [27]

2.2 Fibroblasts

Fibroblasts are pivotal for ECM synthesis and wound contraction.

- **Differentiation**:
  - Fibroblasts differentiate into myofibroblasts in response to TGF-β and mechanical tension.
- **Collagen Synthesis**:
  - Fibroblasts produce collagen types I and III, glycosaminoglycans, and fibronectin.
- **Matrix Organization**:
  - Myofibroblasts organize ECM components into aligned bundles, essential for tensile strength. [26]

2.3 Macrophages

Macrophages play a dual role in inflammation and resolution.

- **M1 Macrophages**:
  - Activated by interferon-gamma, they produce pro-inflammatory cytokines and ROS.

- **M2 Macrophages**:

○ Induced by IL-4 and IL-13, M2 macrophages promote resolution by secreting anti-inflammatory cytokines (e.g., IL-10) and growth factors like VEGF. (27) (30)

3. Role of Immune Cells in Tissue Repair

3.1 Neutrophils

Neutrophils are the first responders to injury, providing essential defense mechanisms.

- **Functions**:

○ Phagocytosis of pathogens and debris.

○ Release of ROS and neutrophil extracellular traps (NETs) to trap pathogens.

- **Resolution**:

○ Neutrophils undergo apoptosis, and macrophages clear them, marking the transition to repair. (21)

3.2 Monocytes and Macrophages

Monocytes migrate to the wound site and differentiate into macrophages, which regulate inflammation and repair.

- **Cytokine Production**:

○ Pro-inflammatory cytokines initiate repair.

○ Anti-inflammatory cytokines mediate resolution. (17)

- **Role in Angiogenesis**:

○ Macrophages secrete VEGF and FGF, supporting new vessel formation.

3.3 T and B Lymphocytes

Adaptive immune cells contribute to wound healing, particularly in chronic wounds.

- **T Cells**:

○ Regulatory T cells (Tregs) suppress excessive inflammation.

○ Helper T cells (Th2) release cytokines like IL-4 to promote repair. (14)

- **B Cells**:

○ Contribute to antibody-mediated clearance of pathogens and support fibroblast activity. (25)

4. Integration of Cellular and Molecular Dynamics

The interplay between cellular and molecular mechanisms ensures timely and effective wound healing:

- **Cytokine Networks**:

○ Balance between pro-inflammatory and anti-inflammatory signals determines repair efficiency.

- **Cell-ECM Interactions**:

○ Integrins and adhesion molecules guide cell migration and ECM remodeling.

- **Temporal Regulation**:

○ Circadian rhythms influence immune cell recruitment, cytokine release, and keratinocyte activity, highlighting the need for chronobiological approaches in wound management. (22) (25)

The mechanisms of wound healing encompass a dynamic interplay of cellular and molecular processes that restore tissue integrity. Keratinocytes, fibroblasts, and macrophages, along with immune cells, play critical roles in orchestrating hemostasis, inflammation, proliferation, and remodeling. Understanding these processes offers insights into therapeutic interventions, including biomaterials, growth factor therapies, and chronobiological strategies, to enhance wound healing outcomes.

1. Day vs. Night Differences in Immune Responses

Factor	Daytime Healing	Nighttime Healing
Platelet Activation	Rapid clot formation, high fibrin mesh density	Slower clotting, weaker fibrin structure
Immune Defense	Active immune surveillance, efficient pathogen clearance	Lower immune activity, increased infection risk
Cellular Energy	High ATP availability, active mitochondrial function	Reduced energy supply, sluggish cellular repair
Fibroblast Activity	Increased collagen synthesis, rapid wound closure	Decreased collagen production, delayed contraction
Keratinocyte Migration	Faster cell movement, efficient skin barrier restoration	Slower migration, prolonged exposure to external factors
Angiogenesis	Increased VEGF expression, robust blood vessel formation	Weaker endothelial response, sluggish capillary growth
Scarring Risk	Controlled ECM remodelling, minimal fibrosis	Excessive scarring due to prolonged tissue repair
Inflammation Duration	Shorter, well-regulated inflammatory phase	Prolonged inflammation, risk of chronic wounds

1.1 Circadian Regulation of Immune Cells

The immune system exhibits robust circadian rhythms, with leukocyte trafficking, cytokine secretion, and pathogen recognition fluctuating across the day-night cycle.

- **Leukocyte Recruitment**:

○ Neutrophil and monocyte migration is influenced by clock genes, such as **CLOCK** and **BMAL1**, that regulate the expression of adhesion molecules like ICAM-1 and VCAM-1.(18)

○ Studies demonstrate heightened neutrophil infiltration during the active phase, which correlates with enhanced microbial clearance but also increased inflammation during daytime injuries. (23)

- **Cytokine Secretion**:

○ Pro-inflammatory cytokines, including TNF-α and IL-6, peak at night, while anti-inflammatory cytokines like IL-10 are more active during the day, modulating the inflammatory phase of wound healing.

○ Temporal Variations in Pathogen Clearance Circadian rhythms affect the capacity of macrophages and dendritic cells to recognize and clear pathogens. (18)

- **Toll-like Receptor (TLR) Activity**:

○ TLR expression and downstream signaling pathways are under circadian control, influencing phagocytosis and antigen presentation.

- **ReacSpecies (ROS)**:

○ Higher ROS production at night contributes to oxidative stress, while daytime ROS is tightly regulated to minimize tissue damage during repair.

1.2 Circadian Modulation of Adaptive Immunity

The adaptive immune response is also circadian-dependent, with T-cell proliferation and antibody production showing time-of-day variations.

- **Helper T Cells (Th1 vs. Th2)**:

○ Th1-driven responses are dominant during the day, favoring microbial clearance, whereas Th2 responses peak at night, promoting tissue repair and resolution. [33]

Migration and Proliferation Rhythms

2.1 Keratinocyte Migration

Keratinocyte migration, critical for re-epithelialization, follows a circadian pattern regulated by clock genes and growth factors.

- **Role of BMAL1 and PER Genes**:

○ These clock genes modulate keratinocyte motility by regulating actin cytoskeletal dynamics and integrin expression.

- **EGF and FGF Pathways**:

○ Epidermal growth factor (EGF) signaling peaks during the day, enhancing keratinocyte migration during daytime wound healing. [32]

Fibroblasts exhibit circadian rhythms in collagen synthesis, matrix deposition, and myofibroblast differentiation.

- **Collagen Synthesis**:

○ Pro-collagen production is higher during the night, aligning with the body's rest phase, where energy is conserved for tissue repair. [7]

- Myofibroblast GF-β signaling, critical for fibroblast-to-myofibroblast transition, follows a circadian rhythm, influencing wound contraction dynamics. [1]

2.2 Angiogenesis and Endothelial Cell Migration

Angiogenesis is temporally regulated, with VEGF expression and endothelial cell activity peaking during the day.

- **VEGF Signaling**:

○ Circadian clocks in endothelial cells drive rhythmic expression of VEGF and its receptors, promoting daytime angiogenesis.

- Role of Hypoxia-Inducible Factors (HIIF activity, essential for hypoxia-driven angiogenesis, is higher at night, facilitating vessel stabilization during nocturnal repair phases. [42]

3. Chronobiological Variation genesis and Tissue Remodeling

3.1 Circadian Angiogenesis

Angiogenesis, essential for delivering nutrients and oxygen to regenerating tissue, displays marked circadian variations.

- **Endothelial Progenitor Cells (EPCs)**:

○ EPC mobilization from the bone marrow is higher during the day, correlating with enhanced capillary formation in daytime injuries.

- **Matrix Metalloproteinases (MMPs)**:

○ MMPs, which remodel the extracellular matrix for angiogenesis, exhibit peak activity in the evening, aligning with nighttime vascular repair.

3.2 Extracellular Matrix Remodeling

ECM revolving collagen deposition and cross-linking, follows circadian patterns influenced by fibroblast activity and MMP expression.

- **Collagen Cross-Linking**:

○ Lysyl oxidase, an enzyme involved in collagen cross-linking, peaks at night, enhancing tensile strength during nocturnal repair. [43]

- **Degradation vs. Synthesis Balance**:

○ Circadian ensure a balance between MMP-mediated ECM degradation during the day and synthesis at night. [21]

3.3 Scar Formation and Remodeling

Scar mat [19] remodelling are circadian-regulated processes that optimize tensile strength and minimize fibrosis.

- **TGF-β and SMAD Pathways**:

○ TGF-β signaling peaks during the night, reducing excessive fibroblast activity and scar formation.

- **Wnt/β-Catenin Signaling**:

○ Circadian control of Wnt patnces keratinocyte and fibroblast interaction, modulating scar thickness and composition. [25]

Circadian rhythms profoundly influencing, orchestrating immune responses, cellular migration and proliferation, and tissue remodeling in a time-of-day-dependent manner. Understanding these chronobiological variations provides insights into optimizing therapeutic interventions and aligning wound care with biological rhythms. Future research should focus on integrating circadian biology into personalized medicine to enhance wound healing outcomes. [27]

4. Clinical Implications of Circadian Biology on Wound Healing

Circadian biology, the study of time-dependent biological processes, has profound clinical implications for wound healing. Emerging evidence indicates that the time of day, sleep patterns, and light exposure significantly influence tissue repair outcomes. Understanding these factors can revolutionize post-surgical care, offering more personalized and effective treatment strategies. This section explores case studies, the role of sleep and light in recovery, and the integration of circadian biology into clinical settings. Patient recovery and wound healing are greatly affected by the timing of surgical procedures. According to recent studies, compared to nighttime treatments, morning surgeries lead to quicker tissue repair, less inflammation, and fewer post-operative infection rates. This is explained by the fact that immune-mediated responses, platelet activation, and cellular metabolism are all regulated by the circadian rhythm and peak during the body's active phase. [29]

1. Case Studies on Wound Healing Variations by Time of Day

1.1 Daytime vs. Nighttime Surgery Outcomes

Numerous studies have highlighted differences in surgical outcomes based on the time of day.

- **Daytime Surgeries**:

  - Patients undergoing surgeries during the daytime often exhibit faster wound healing, reduced inflammation, and lower infection rates.

  - A study by Cable et al. (2016) demonstrated that daytime-incurred wounds had enhanced re-epithelialization and reduced scar formation compared to nighttime wounds. [39]

- **Nighttime Surgeries**:

  - Surgical interventions conducted at night are associated with prolonged inflammatory responses and delayed angiogenesis, potentially due to disruptions in circadian-regulated immune function.

1.2 Chronobiological Insights from Trauma and Burns

Patients with trauma injuries incurred during the night display delayed healing due to reduced keratinocyte migration and immune cell infiltration.

- **Burns**:

  - Research on burn injuries shows better outcomes when treatment aligns with the body's active phase, as the circadian clock optimizes keratinocyte proliferation during this period. [47]

1.3 Pediatric vs. Geriatric Cases

Age-related variations in circadian rhythms further affect wound healing outcomes.

- **Pediatric Patients**:

  - Robust circadian rhythms in younger patients enhance recovery, particularly for morning surgeries.

- **Geriatric Patients**:

  - Age-associated circadian disruptions exacerbate delays in healing, necessitating interventions that reinforce circadian alignment.

2. Influence of Sleep and Light Exposure on Recovery

2.1 Role of Sleep in Immune Function

Adequate sleep is critical for optimal immune responses during wound healing.

- **Deep Sleep and Cytokine Release**:

  - Non-REM sleep phases promote the release of cytokines such as IL-1β, which are crucial for initiating the inflammatory phase. [18]

- **Impact of Sleep Deprivation**:

  - Sleep deprivation suppresses leukocyte activity and delays re-epithelialization, highlighting the necessity of quality sleep for recovery.

2.2 Light Exposure and Circadian Synchronization

Light plays a vital role in regulating circadian rhythms, which in turn affect wound healing.

- **Blue Light and Melatonin Suppression**:

o Excessive blue light exposure at night disrupts melatonin secretion, impairing processes like fibroblast proliferation and angiogenesis.

- **Therapeutic Light Exposure**:

o Morning light therapy has been shown to enhance immune responses and speed up recovery in post-surgical patients. [21]

2.3 sleep disorders and Delayed Healing

Sleep disorders, such as insomnia or obstructive sleep apnea, can significantly hinder wound healing.

- **Insomnia**:

o Insomnia prolongs the inflammatory phase and suppresses collagen deposition.[1]

- **Sleep Apnea**:

o Reduced oxygenation during sleep apnea episodes impairs angiogenesis and delays tissue remodelling.

3. Application of Circadian Biology to Post-Surgical Care

3.1 Personalized Surgery Scheduling

Aligning surgical procedures with a patient's circadian rhythm can optimize healing.

- **Morning Surgeries**:

o Preferred for procedures requiring rapid recovery, as cellular repair processes peak during the day.

- **Chronotherapy**:

o Administering medications or performing interventions at specific times enhances efficacy and reduces side effects.

3.2 Post-Surgical Light Management

Adjusting light exposure post-surgery can improve recovery outcomes.

- **Light-Dark Cycles**:

o Maintaining natural light-dark cycles in hospital settings helps synchronize circadian rhythms.

- **Red Light Therapy**:

o Emerging as a non-invasive method to enhance keratinocyte migration and reduce inflammation.

3.3 Pharmacological Interventions

Circadian-timed drug delivery has the potential to revolutionize post-surgical care.

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- **Corticosteroids**:
  - Administered in the morning to align with natural cortisol peaks, minimizing inflammation.
- **Melatonin**:
  - Supplementation at night supports immune responses and fibroblast activity. [34]

3.4 Rehabilitation and Lifestyle Adjustments

Lifestyle interventions that respect circadian biology enhance wound healing.

- **Sleep Hygiene**:
  - Strategies to improve sleep quality include maintaining regular sleep schedules and reducing evening light exposure.
- **Dietary Timing**:
  - Consuming nutrient-rich meals during active phases optimizes energy allocation for tissue repair.

4. Future Directions

4.1 Integration into Hospital Protocols

Hospitals can adopt circadian-aware protocols to improve patient outcomes.

- **Surgical Timing Guidelines**:
  - Recommendations to conduct surgeries during optimal circadian windows.
- **Lighting Systems**:
  - Circadian-adjusted lighting in recovery wards to support biological rhythms.

4.2 Research Frontiers

Further studies are needed to explore:

- The molecular pathways linking circadian disruptions to delayed healing.
- The role of genetic polymorphisms in circadian genes on individual healing capacities.

The interplay between circadian biology and wound healing offers promising avenues for improving surgical outcomes and recovery processes. [4] From timing surgeries to optimizing post-operative care through light exposure and sleep regulation, integrating chronobiology into clinical practice can revolutionize patient care. [9] Future research and clinical protocols must prioritize circadian-aligned strategies to harness the full potential of the body's biological rhythms.

5. Therapeutic Applications in Circadian Biology and Wound Healing

The field of circadian biology has opened transformative possibilities for therapeutic applications in wound healing. Chronotherapy, targeted pharmaceutical interventions, and innovations in biomaterials are emerging as pivotal approaches to enhancing tissue repair processes. These strategies leverage the circadian rhythms of cellular and molecular processes to optimize healing outcomes [15]. This section delves into chronotherapy, circadian-targeted pharmaceuticals, and time-regulated biomaterials, offering a comprehensive view of their roles in advancing wound care.

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1. Chronotherapy in Wound Healing

1.1 Defining Chronotherapy

Chronotherapy refers to the alignment of therapeutic interventions with the body's circadian rhythms to maximize efficacy and minimize side effects.

- **Importance**:

○ Cellular processes such as immune responses, angiogenesis, and fibroblast activity exhibit diurnal variations, making timing critical in therapeutic interventions [42] chronotherapy ensures optimal cellular responses at specific times, leading to improved wound outcomes.

1.2 Timing of Surgical Interventions

Research indicates that the timing of surgeries significantly affects healing outcomes.

- **Morning Surgeries**:

○ Morning surgeries have been shown to enhance keratinocyte proliferation, reduce inflammation, and promote angiogenesis due to peak circadian activity of repair cells. [1]

○ Time Risks: Procedures performed during the night correlate with delayed epithelialization and increased infection rates, often due to circadian misalignment of immune responses.

1.3 Chronotherapy in Drug Administration

The circadian timing of medication plays a vital role in enhancing therapeutic efficacy.

- **Antibiotics**:

○ Antibiotic delivery timed to peak immune activity improves infection control and reduces wound complications.

- **Anti-inflammatory Agents**:

○ Administering corticosteroids in the morning aligns with natural cortisol rhythms, enhancing anti-inflammatory effects. [14]

○ **Potential Pharmaceutical Interventions Targeting Circadian Pathways**

2.1 Overview of Circadian-Targeted Drugs

Circadian-targeted drugs are designed to modulate biological rhythms and optimize healing processes.

- **Mechanisms**:

○ These drugs influence key circadian proteins (e.g., CLOCK, BMAL1, PER, CRY), which regulate cellular repair, immune responses, and metabolism. [23] [28]

○ Melatonin Supplementation: Melatonin, a circadian hormone, plays a critical role in wound healing.

- **Mechanisms**:

○ Enhances fibroblast activity, regulates oxidative stress, and promotes angiogenesis.

- **Applications**:

○ Effective in patients with disrupted circadian rhythms, such as shift workers or those with sleep disorders. [9]

- Corticosteroid Timing: Corticosteroids, when administered in alignment with circadian rhythms, exhibit enhanced efficacy.

- **Morning Administration**:

- Reduces prolonged inflammation while minimizing side effects.

- **Clinical Trials**:

- Studies have shown that timing corticosteroid injections improves scar outcomes in surgical patients. [36] [17]

- Targeting Circadian Clock Genes: Emerging drugs aim to modulate clock genes directly to accelerate wound healing.

- **PER2 Activators**:

- Promote keratinocyte migration and immune cell activity.

- **BMAL1 Modulators**:

- Enhance fibroblast proliferation and extracellular matrix deposition. [29]

- **Innovations in Biomaterials for Time-Regulated Release of Growth Factors**

3.1 Role of Biomaterials in Wound Healing

Biomaterials are engineered substances designed to support tissue repair by delivering therapeutic agents.

- **Advantages**:

- Localized delivery minimizes systemic side effects.

- Time-regulated release aligns with circadian repair cycles [37] biomaterials. Chrono-biomaterials are a novel class of materials designed for time-regulated drug delivery.

- **Mechanisms**:

- Incorporate circadian-responsive polymers that release drugs or growth factors based on time-of-day signals.

- **Applications**:

- Used for delivering growth factors, such as VEGF, to promote angiogenesis during peak circadian activity.

3.2 Hydrogenation Release Properties

Hydrogels embedded with circadian-responsive nanoparticles are gaining traction.

- **Mechanisms**:

- These hydrogels adjust drug release rates in response to biological cues, such as changes in pH or temperature.

- **Examples**:

- Hydrogels loaded with PDGF (platelet-derived growth factor) exhibit accelerated wound closure by synchronizing with circadian phases of cell proliferation. [16]

Smart wound dressings integrate sensors and chrono-responsive materials for dynamic wound management.

- **Features**:
  - Monitor circadian changes in wound environments (e.g., temperature, humidity).
  - Deliver antimicrobial agents or growth factors at optimal circadian times.
- **Clinical Trials**:
  - Remonstrate improved healing in chronic wounds, such as diabetic ulcers, using circadian-synchronized dressings. [34]

4. Case Studies applications

4.1 Chronotherapy Success Stories

Clinical cases illustrate the potential of circadian-aligned therapies.

- **Case 1**:
  - A 2018 study showed that patients receiving melatonin-aligned treatments experienced 30% faster wound healing in surgical sites compared to conventional care. [5]
- **Case 2**:
  - Smart hydrogeneration VEGF during diurnal peaks reduced healing times in chronic wound patients by 40%. [1]

4.2 Challenges and Future Directie advances, several challenges remain in circadian-based wound therapies.

- **Standardization**:
  - Lack of standardized protocols for circadian-aligned interventions.
- **Personalized Medicine**:
  - Need for tools to assess individual circadian rhythms and tailor therapies accordingly. [15]

Then biology into therapeutic strategies for wound healing holds immense potential. Chronotherapy, circadian-targeted pharmaceuticals, and innovations in biomaterials represent the forefront of this transformative field. By aligning interventions with biological rhythms, clinicians can achieve faster recovery times, reduced complications, and improved patient outcomes. Continued research and clinical application of these strategies will pave the way for a new era in wound management and care. [15]

6. Challenges and Future Directions in Circadian Medicine and Wound Healing

Circadian medicine, while groundbreaking, faces significant challenges that must be addressed to fully harness its potential in wound healing. Ethical considerations, limitations in current methodologies, and areas for future research are integral to advancing the field. This section delves into these aspects, offering a roadmap for future exploration and application.

1. Ethical Considerations in Circadian Medicine

1.1 Patient-Centric Approaches

Circadian interventions often require precise timing, which could conflict with patient preferences and lifestyles.

- **Ethical Dilemma**:
  - Aligning medical procedures with circadian rhythms may inconvenience patients with work or personal commitments. [9] [42]
- **Proposed Solutions**:

- Incorporate patient feedback into circadian therapy schedules while ensuring medical efficacy.

1.2 Equity in Access

Not all healthcare systems have the resources to implement circadian-based treatments.

- **Resource Disparities**:
  - High-tech interventions like smart wound dressings may not be accessible in low-income regions. [37]
- **Addressing Inequities**:
  - Develop cost-effective circadian solutions, such as simplified scheduling for drug delivery.

1.3 Informed Consent

Patients must understand the implications of circadian medicine.

- **Educational Gap**:
  - Patients often lack awareness of circadian biology, making informed consent challenging.
- **Solutions**:
  - Educate patients about circadian principles during consultations to facilitate informed decision-making.

1.4 Research Ethics

Ethical considerations in circadian research include:

- **Animal Studies**:
  - Use of nocturnal models (e.g., rodents) may not fully translate to human circadian rhythms.
- **Clinical Trials**:
  - Challenges in standardizing trial protocols across populations with diverse circadian patterns. [18]

2. Limitations in Current Methodologies

2.1 Inconsistent Circadian Assessment

Current tools for assessing circadian rhythms lack standardization.

- **Challenges**:
  - Variability in metrics used to measure circadian phases, such as melatonin levels, body temperature, or gene expression.
- **Recommendations**:
  - Develop universal guidelines for circadian assessments in clinical and research settings. [5]

2.2 Limited Chronotherapy Studies

Chronotherapy in wound healing remains underexplored.

- **Gaps**:
  - Few studies investigate the timing of interventions like drug delivery or surgical procedures in wound management.
- **Suggestions**:
  - Increase funding for clinical trials focusing on circadian-aligned therapies. [30]

2.3 Challenges in Translating Research

Findings from animal models often fail to translate into human medicine.

- **Species Differences**:
  - Rodents are nocturnal, complicating the extrapolation of data to diurnal humans.
- **Solutions**:
  - Invest in human-based circadian research, such as wearable monitoring devices.[27]

2.4 Integration of Chronobiology in Medical Training

Healthcare professionals lack formal training in circadian biology.

- **Issues**:
  - Limited awareness among clinicians about the role of circadian rhythms in healing.
- **Suggestions**:
  - Incorporate circadian medicine into medical curricula to bridge this knowledge gap. [14]

3. Proposed Research Directions and Studies

3.1 Advanced Chronotherapy Applications

Explore innovative ways to align treatments with circadian rhythms.

- **Examples**:
  - Develop personalized drug delivery systems that synchronize with individual circadian phases.
  - Investigate the timing of surgical interventions to maximize healing. [28]

3.2 Wearable Technology for Monitoring

Integrate wearable devices into circadian medicine.

- **Potential Applications**:
  - Devices that monitor physiological indicators (e.g., heart rate, body temperature) to determine circadian phases.
  - Provide real-time feedback for therapy timing adjustments. [9]

3.3 Epigenetics and Circadian Medicine

Study the epigenetic regulation of circadian genes and their role in wound healing.

- **Focus Areas**:
  - Investigate how environmental factors like light exposure or diet affect circadian gene expression.
  - Explore the potential of epigenetic drugs to reset disrupted circadian rhythms.[11]

3.4 Chronobiological Biomarkers

Identify biomarkers to personalize circadian interventions.

- **Examples**:
  - Hormonal markers like cortisol and melatonin.
  - Molecular markers such as CLOCK and BMAL1 expression levels. [21]

3.5 Societal Impact Studies

Understand the broader implications of circadian medicine.

- **Topics**:
  - Effects of shift work on wound healing and recovery.
  - Public health strategies to align societal schedules with circadian biology. [35]

3.6 AI and Machine Learning Integration

Leverage AI to analyze complex circadian datasets.

- **Applications**:
  - Predict optimal intervention times based on patient data.
  - Automate circadian monitoring in clinical settings. [6]

3.7 Global Collaboration

Foster international cooperation in circadian medicine research.

- **Benefits**:
  - Pooling resources to conduct large-scale studies.
  - Sharing knowledge across diverse populations to enhance generalizability. [10] [14]

4. Future Directions

4.1 Personalized Circadian Medicine

Tailor treatments to individual circadian rhythms using precision medicine approaches.

- **Approach**:
  - Integrate genetic, lifestyle, and environmental data to customize care plans. [9]

4.2 Circadian Synchronization Programs

Develop community-based initiatives to promote circadian health.

- **Examples**:
  - Education campaigns on the importance of sleep and light exposure.
  - Workplace programs to minimize circadian disruption in shift workers. [5]

4.3 Regulatory Frameworks

Establish guidelines for circadian-based therapies.

- **Focus Areas**:
  - Standardize protocols for circadian interventions.
  - Ensure safety and efficacy through rigorous testing. [2]

4.4 Cross-Disciplinary Research

Encourage collaboration between chronobiologists, clinicians, and engineers.

- **Benefits**:
  - Integrating diverse expertise to develop innovative solutions for circadian challenges. [1]

Circadian medicine offers transformative potential for wound healing, but significant challenges remain. Ethical considerations, methodological limitations, and gaps in research highlight the need for a concerted effort to advance the field. By addressing these issues and fostering innovation, the integration of circadian biology into clinical practice can revolutionize wound care and improve patient outcomes globally. Continued research, collaboration, and education will be key to overcoming these challenges and realizing the full potential of circadian medicine.

7. Conclusion

1. Summary of Findings

Therapeutic Strategy	Optimal Timing (Based on Circadian Rhythms)	Expected Benefit
Surgical Procedures	Morning (6 AM – 12 PM)	Faster healing, reduced inflammation, lower infection risk
Post-Surgical Light Therapy	Daytime exposure to natural light	Enhances immune responses, promotes collagen synthesis
Melatonin Supplementation	Nighttime (9 PM – 12 AM)	Regulates oxidative stress, improves fibroblast function
Corticosteroid Administration	Morning (7 AM – 9 AM)	Reduces excessive inflammation, aligns with natural cortisol peak
Growth Factor Therapy (e.g., VEGF, PDGF)	Late afternoon (3 PM – 6 PM)	Optimized angiogenesis and fibroblast activation
Wound Dressing Changes	Morning (8 AM – 11 AM)	Lower risk of infection due to peak immune activity

1.1 Circadian Biology and Wound Healing

The exploration of circadian biology has revealed its profound influence on the physiological processes underlying wound healing. From the molecular mechanisms involving core clock genes such as **CLOCK**, **BMAL1**, **PER**, and **CRY**, to the intricate interactions

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between central and peripheral clocks, the circadian rhythm orchestrates key cellular functions that drive tissue repair and regeneration. (17) (25)

- **Stages of Wound Healing**:

○ **Hemostasis**: Initial clot formation is influenced by circadian variations in platelet function and vascular tone.

○ **Inflammation**: Immune responses, particularly macrophage activity, are modulated by circadian-controlled cytokine release.

○ **Proliferation**: Fibroblast migration and keratinocyte proliferation exhibit time-dependent rhythms, optimizing cellular repair mechanisms.

○ **Remodeling**: Collagen deposition and angiogenesis are enhanced during certain circadian phases, improving wound tensile strength. (40)

1.2 Day vs. Night Differences

Daytime and nighttime rhythms distinctly affect immune responses, cellular migration, and tissue remodeling. These differences have been substantiated by experimental studies highlighting:

- Superior wound healing during specific circadian phases due to heightened cellular activity.
- Reduced repair efficiency in disrupted circadian environments, such as in shift workers or individuals with sleep disorders. (43)

1.3 Clinical Implications

Circadian rhythms significantly impact clinical outcomes in wound healing and recovery:

- **Surgical Interventions**:

○ Timing surgeries to align with optimal circadian phases can improve healing and reduce complications.

- **Postoperative Care**:

○ Light exposure and sleep management post-surgery play crucial roles in patient recovery. (30)

2. Emphasis on Integrating Circadian Science into Clinical Practice

2.1 Personalized Medicine

Circadian biology provides a framework for precision medicine, tailoring interventions to individual rhythms:

- **Chronotherapy**: Aligning drug administration with circadian cycles enhances therapeutic efficacy and minimizes side effects. (12)

- **Scheduling Surgeries**:

○ Morning surgeries have demonstrated better outcomes due to heightened physiological resilience during this phase. (19)

2.2 Education and Awareness

Healthcare professionals require training on the principles of chronobiology to integrate these insights into clinical decision-making:

- **Medical Curricula**:

○ Introduce circadian medicine modules to educate future clinicians.

- **Patient Awareness**:
  - Provide guidance on maintaining circadian health through regular sleep schedules and exposure to natural light. [24]

2.3 Technological Advancements

The development of wearable circadian monitors and time-regulated drug delivery systems can revolutionize wound care:

- **Real-Time Monitoring**:
  - Devices tracking circadian markers, such as melatonin or cortisol, can guide treatment timing.
- **Smart Biomaterials**:
  - Innovations in biomaterials allow for the circadian-aligned release of growth factors and other therapeutic agents. [14]

3. Vision for Future Research in Wound Healing and Regenerative Medicine

3.1 Expanding Chronotherapy Studies

Future studies should focus on:

- **Optimal Timing**:
  - Identifying the best circadian phases for interventions, such as surgery and medication.
- **Population Variability**:
  - Accounting for individual differences in circadian rhythms, influenced by genetics, lifestyle, and environment. [18]

3.2 Exploring Molecular Mechanisms

Further investigation is needed into the molecular pathways linking circadian biology to wound healing:

- **Epigenetic Regulation**:
  - How circadian genes are epigenetically modified during wound healing and repair.
- **Gene Therapy**:
  - Leveraging circadian gene manipulation to accelerate healing. [37]

3.3 Addressing Disruptions in Circadian Rhythms

Research should address the consequences of circadian misalignment:

- **Shift Work and Healing**:
  - Evaluate the long-term effects of irregular sleep and activity patterns on tissue repair.
- **Interventions**:
  - Develop strategies to mitigate circadian disruption, such as light therapy or pharmacological resetting of the clock. [15]

3.4 Integration with Regenerative Medicine

Circadian science can complement advances in tissue engineering and regenerative medicine:

- **Stem Cell Therapies**:
  - Investigate how circadian timing influences the efficacy of stem cell-based treatments.
- **3D Bioprinting**:
  - Explore the application of circadian principles in designing bioengineered tissues. [2]

3.5 Multidisciplinary Collaboration

Collaborative efforts across fields such as chronobiology, clinical medicine, and bioengineering are essential to advance circadian applications:

- **Research Networks**:
  - Establish global initiatives to pool resources and expertise.
- **Clinical Trials**:
  - Conduct large-scale studies to validate circadian-based therapies. [5]

4. Challenges and Opportunities

4.1 Addressing Ethical Concerns

Integrating circadian principles into clinical practice raises ethical considerations:

- **Access and Equity**:
  - Ensuring all patients benefit from circadian-aligned care.
- **Informed Consent**:
  - Educating patients about the rationale and potential outcomes of circadian interventions. [42]

4.2 Overcoming Methodological Limitations

Challenges in standardizing circadian assessments and interventions must be addressed:

- **Uniform Metrics**:
  - Develop standardized tools for measuring circadian phases in clinical settings.
- **Data Integration**:
  - Leverage AI to analyze circadian data and personalize treatment. [14]

4.3 Funding and Resource Allocation

Promoting circadian research requires increased funding and institutional support:

- **Government Initiatives**:
  - Encourage policies supporting circadian studies in wound healing.

- **Industry Collaboration**:

  - Partner with biotech companies to develop circadian-aligned therapeutics. (7)

Circadian biology offers transformative potential for wound healing and regenerative medicine. By aligning clinical practices with circadian rhythms, healthcare providers can enhance recovery outcomes and reduce complications. However, addressing challenges such as ethical considerations, methodological limitations, and funding gaps is crucial to unlocking this potential. Future research and interdisciplinary collaboration will be instrumental in realizing the vision of circadian-integrated healthcare, paving the way for a new era in medicine. The fusion of chronobiology with cutting-edge technologies and regenerative approaches promises not only to advance wound care but also to redefine the broader landscape of clinical medicine.

4.4 Future Research Paths:

Individualized Chronotherapy Protocols: Matching treatments to each patients individual circadian rhythms.

Advanced Biomaterials: Developing wound barriers that react to the clock to promote optimal healing.

Validating the effectiveness of circadian-aligned medicines in a variety of groups through large-scale clinical trials.

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