e-ISSN 3050-8460
Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Microgravity in Space and its Effect on Wound Healing

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Citation: Barla NSSC, et al. Microgravity in Space and its Effect on Wound Healing. J Dermatol Res. 2026;7(3):1-8.

https://doi.org/10.46889/JDR.2026.7303

Received Date: 12-08-2026

Accepted Date: 05-09-2026

Published Date: 12-09-2026

Abstract

Wound healing in microgravity conditions presents with conflicting results despite the signals coming from individual cells which indicate otherwise. Isolated skin cells cultured in microgravity simulations show enhanced stem cell activity and increased migratory behavior, but real animal tissue and real spaceflight data refute it consistently showing delayed wound healing, slow blood vessel growth and slower fibroblast movement. This discrepancy between *in-vivo* and *In-vitro* findings is the general pattern across the research and this pattern flows to collagen biology as well, cells appear more active under microgravity but fail to rebuild overall tissue structure. A specific molecular pathway that includes Fibrous-actin (F-actin) and Yes-Associated Protein (YAP) signaling which have been identified as one of the drivers of the impairment in fibroblasts and a countermeasure drug known as Lysophosphatidic Acid (LPA) has already been tested successfully in an animal model. Real human data, including a documented postflight skin rash case and cytokine changes from the NASA Twins Study, confirm the visible signs of changes taking place at the cellular level even after the flight in human beings. The current gap in this field is detected to be the limited human data on wound healing collected in actual flight conditions. The majority of the findings still come from cell culture or animal models and a major gap remains, as no controlled study has yet directly tracked wound healing *in-vivo* in humans during spaceflight aboard the International Space Station (ISS).

Keywords: Space; Wound Healing; NASA; Fibroblasts

Introduction

Gravity is the force of attraction generated between objects with mass, the more massive an object is, the stronger its gravitational pull. Earth's mass generates a constant, predictable gravitational force at its surface, which every cell in the human body has evolved under and continuously relies on as a mechanical signal [1,2]. Conversely, microgravity talks about the condition that very weak gravitational forces, experienced by astronauts either in real spaceflight where entities are in continuous freefall around the earth or recreated on the ground using simulation devices like the Random Positioning Machine, clinostats and the hindlimb-unloaded rat model, which continuously redistribute the gravity on tissue [3-7]. Under microgravity, the redistribution of gravitational and mechanical cues can disrupt cellular and biological processes that normally operate within Earth's gravitational environment [1,6-9].

Wound healing is one of the skin's most important jobs, it relies on its cells to rapidly divide, migrate and rebuild tissue when under pressure. This happens in three phases: Inflammation, proliferation and remodeling. Inflammation occurs when the body forms a clot and sends immune cells to the site, proliferation takes place after with keratinocytes multiplying and migrating across the wound while fibroblasts rebuild the deeper connective tissue and form new blood vessels and lastly remodeling ensues with the wound closing and scarring. This entire process heavily relies on mechanical signals, which includes gravity, it is one of the constant physical forces that skin cells use to regulate their behavior, a process called mechanotransduction. When this

signal is removed (by being in space), the mechanism that drives normal healing is disrupted at multiple levels, from the stem cells that renew the skin to the mature cells that physically close the wound [3].

Understanding how microgravity affects wound healing allows us to face real and practical risks such as injuries and surgical emergencies that astronauts can confront on any mission with limited medical resources compared to on Earth. In current low-orbit missions, the major strategy for a serious wound is to stabilize the astronaut and return them back to Earth as soon as possible. This is an option that will not exist on future deep space or Mars missions, where the return back to Earth from an emergency could take months or potentially be impossible altogether. This concern is no longer purely theoretical since commercial spaceflight is scaling rapidly with many advancements in space technology. As both government and commercial programs push toward longer and more distant missions, understanding and eventually treating impaired wound healing in microgravity becomes a more prominent problem rather than a distant one. This section reviews the current evidence on how microgravity affects the cells responsible in wound healing, why isolated cell culture experiments show contradicting results from real animal and human tissue data and what is currently known about mechanisms and potential countermeasures on this topic.

Methodology

Sources were identified through PubMed, Google Scholar, NASA's Open Science Data Repository (OSDR), CiNii (Japanese academic database), CNKI (Chinese academic database) and UMBC's AOK Library system. Some search terms used include "microgravity wound healing," "spaceflight fibroblast," "keratinocyte microgravity," and "skin transcriptomics spaceflight," along with translated language searches, (using google translate) "микрогравитация кожа" (microgravity skin), "航天 医学 皮肤" (space medicine skin) to identify non-English literature. Sources found in other languages were translated using google translate for review.

Inclusion was based on direct relevance to skin wound healing under microgravity or simulated microgravity conditions. No date range was applied, sources varied from 1995 to a 2026 publication. Sources were excluded if they talked about spaceflight biology unrelated to skin or wound healing or if they could not be translated or verified as peer reviewed.

Results

Across almost every source reviewed, there shows a consistent contradiction between how skin cells behave in isolated culture versus how real tissue responds under microgravity. *In-vitro*, simulated microgravity increases Epidermal Skin Cell (ESC) proliferation while keeping cells from progressing all the way to becoming mature, specialised skin cells [10] and this triggers keratinocytes to go through Epithelial-to-Mesenchymal Transition (EMT), pushing them toward a migratory, wound closing state (Fig. 1) [3]. This appears to be accelerating healing, but animal studies using hindlimb-unloaded rat models show the opposite, keratinocyte migration and wound closure are delayed and dermal blood vessel growth is reduced and misdirected [3]. A more recent review establishes this same pattern extends to fibroblasts and endothelial cells, finding that even when individual cell types are only fairly affected, the breakdown in communication between keratinocytes, fibroblasts and blood vessel cells accumulate the overall healing deficit (Fig. 2) [11].

The clearest explanation for this impairment comes from research conducted on dermal fibroblasts. Simulated microgravity causes the cell's internal actin cytoskeleton to lose its normal firm structure, which causes the suppression of YAP signaling, a pathway that drives cell migration. This delays the wound closure in rats, most notably between days 4 and 6 post-wounding (Fig. 3) [7]. A related, recent study found that this same cytoskeletal breakdown also weakens the structural integrity of the cell's nucleus and increases DNA damage, prolonging the effects of microgravity beyond just migration [1]. Notably, Zhou, et al., went further than just identifying the problem, they applied the drug LPA directly to rats' wounds which were directly exposed to microgravity. This accelerated healing to almost normal speed, representing one of the only tested countermeasures identified in this body of literature. Combined stressor research adds an important caveat to all of this, when microgravity, radiation and cortisol were tested together on fibroblasts rather than in isolation, the stressors interacted instead of simply adding together, suggesting real spaceflight conditions may impair wound healing more severely than single stressor studies predict [6].

Real human and animal spaceflight data confirm that these cellular changes have measurable consequences. The NASA Twins Study found that 50 of 62 measured cytokines were significantly changed during and after a year-long mission, with a sharp

inflammatory spike immediately at the time of landing [12]. This directly correlates with another article where one astronaut developed a diffuse skin rash accompanied by a C-Reactive Protein (CRP) level over 13 times normal after landing from a 340 day mission (Fig. 4) [13]. A repeating pattern also appears in collagen biology across species, cells appear more active but fail to efficiently rebuild structure. In ISS flown mice, mast cells increased their secretory activity but did not form new collagen fibers [14], while a separate 91 day ISS mouse study found increased procollagen synthesis along with a 15% reduction in dermal thickness [15]. This same pattern appears even in the bacterial infection model, where combining simulated microgravity with a real soft tissue infection reduced dermal collagen by up to 48% compared to infection alone (Fig. 5) [5]. Not all findings point toward impairment, but the oldest study in this review, using real space shuttle rat tissue, found that microgravity accelerated fetal epidermal barrier development rather than delaying it, moreover it is a reminder that microgravity's effects likely depend on the specific tissue, cell type and developmental stage involved [16].

Additional evidence points to a broader immune and molecular dimension. Lymphocytes consistently show increased apoptosis while macrophages resist it, implying microgravity affects immune cell types differently rather than uniformly (Fig. 6) [8]. At the regulatory level, simulated microgravity has also been shown to greatly amplify circadian clock gene oscillation (Bmal1) in human keratinocytes, an effect that persists and intensifies even after cells return to normal gravity, however this specific study found no accompanying changes to cell morphology, proliferation or apoptosis within its short exposure window [17]. Real ISS skin surface measurements found a 45% decrease in a skin topography parameter, though this is more likely explained by microgravity driven fluid shifts rather than true tissue damage [18]. At the gene level, a large cross species analysis combining five NASA OSDR mouse datasets with real astronaut skin and blood samples found consistent downregulation of skin barrier genes (Filaggrin, Caspase 14) and flagged vitamin D and tretinoin as possible countermeasures worth testing [9]. Beyond the skin barrier, gravity's effects are not uniform even within a single cell lineage, pigment producing melanocytes and melanoma cells respond to increased versus decreased gravity in opposite directions and differently depending on how aggressive the cell line is [2].

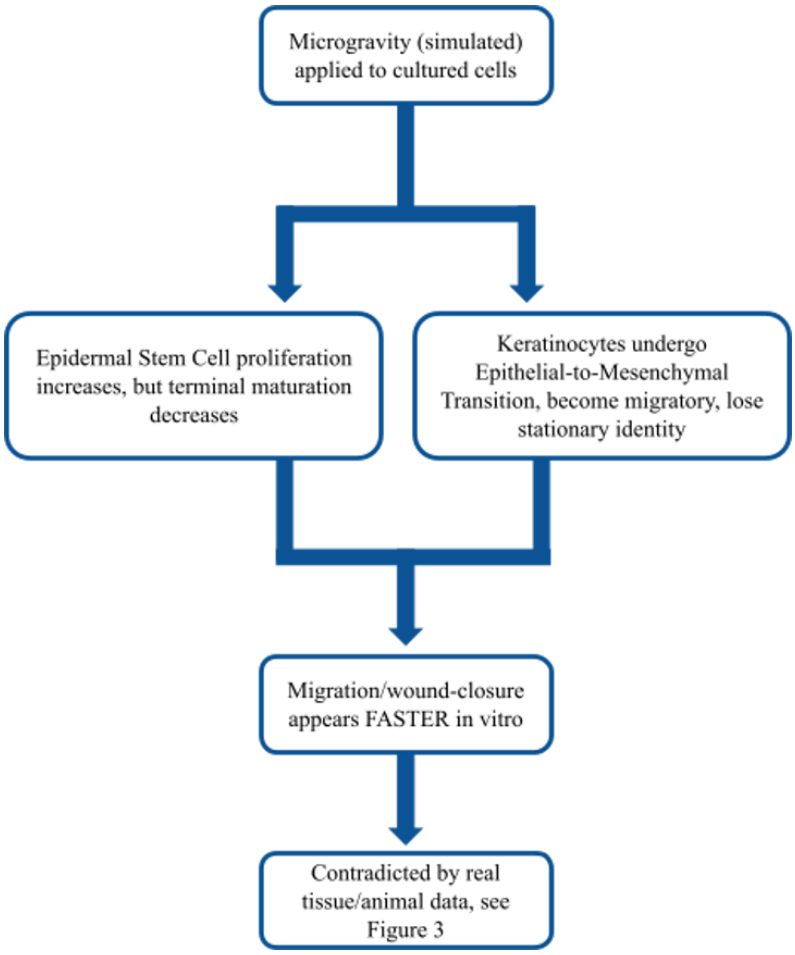

Figure 1: *In-vitro* Effects in the Epidermis [3,10,17].

Measure	Isolated Cells (In Vitro)	Real Tissue / Living Animal / Human
Keratinocyte Migration	↑ Enhanced (EMT-driven)	↓ Delayed (hindlimb-unloaded rat model)
Apoptosis	Inconsistent / some ↓	No detectable apoptosis in real ISS-flown human skin
Dermal blood vessel growth	–	↓ Reduced, misdirected
Net wound healing outcome	Appears accelerated	Impaired

Figure 2: The Core Contradiction [3,11].

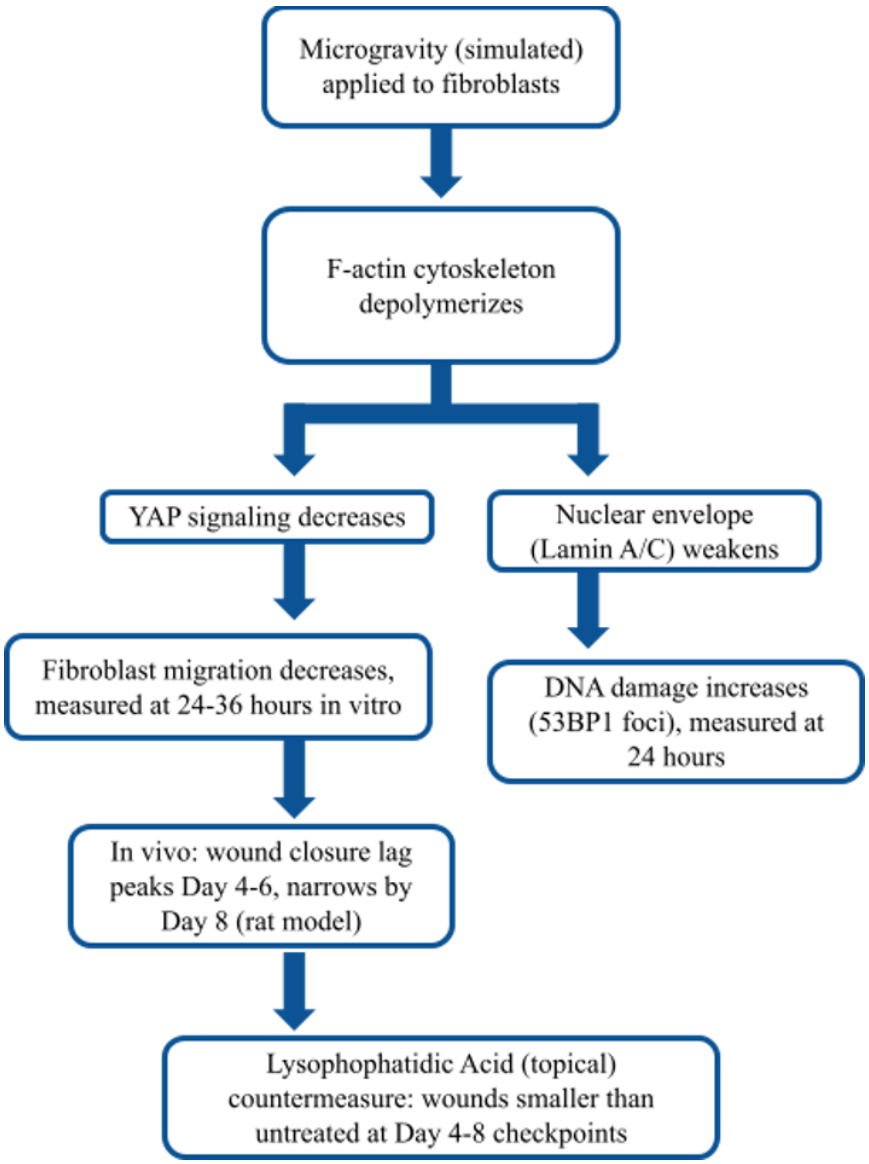

Figure 3: Dermal (Fibroblast) Pathway, Mechanistic Chain [1,7].

Finding	Detail
Cytokine dysregulation	50 of 62 measured cytokines altered pre/in/post-flight (Twins Study)
Acute landing inflammation	CRP spikes 1→19 mg/dL; ↑CCL2, ↑IL-1RA
Clinical correlate	Scott Kelly case: diffuse rash/skin hypersensitivity ~10 hrs post landing, CRP >13x normal, resolved ~6 days
Collagen breakdown	↑ Urinary COL1A1/COL3A1 during flight
Persistence	Some immune gene changes remain altered 6 months post-flight

Figure 4: Real Human Spaceflight, Systemic Picture [12,13].

Source	Activity Signal	Net Structural Outcome
Mice	Mast cells secrete MORE	Fails to build new fibers
ISS Mice	Procollagen synthesis ↑42%	Dermis thins by 15%
Human	Urinary collagen breakdown ↑	Structural remodeling, not clean buildup
Rats + Infection	–	Collagen bundle area ↓43–48%

Figure 5: ECM/Collagen, A Repeating Pattern Across Species [5,12,14,15].

Cell Type	Effect of Microgravity
Lymphocytes	Apoptosis ↑, proliferation ↓ (most reproducible immune finding)
Macrophages	Resistant to apoptosis (lack 5-LOX expression)
Keratinocytes	Inconsistent / limited data

Figure 6: Immune / Apoptosis Divergence by Cell Type [8].

Discussion

The evidence reviewed here consistently points out to one fundamental problem: Wound healing depends on mechanical and biological signals that microgravity disrupts and once those signals are lost, the cellular machinery responsible for healing, from stem cells to fibroblasts to collagen building cells, behaves differently and less effectively than it would on Earth. This raises a concrete question that the current literature has not yet directly answered. If the core issue is a missing mechanical signal, could

that signal be recreated locally at the wound site itself instead of requiring a solution for the entire body? One possibility worth looking into is direct mechanical substitution. If a laceration in space required suturing, applying constant and controlled pressure over the wound could create a localized microenvironment that mimics the mechanical loading that is normally given by Earth's gravity, potentially reactivating the mechanotransduction pathways like the F-actin/YAP signaling identified by Zhou, et al., that microgravity suppresses. It is important to note that whole sample hypergravity through centrifugation has already been tested on dermal fibroblasts in ground based research and found to delay migration and reduce mechanosensitive structures like the focal adhesions so wound specific mechanical loading depicts the untested extension of this idea [19].

A second, more speculative possibility comes from the nature of gravity itself. Gravity is generally a force generated by mass, but cells do not sense this mass directly, instead they sense pressure, tension and mechanical strain, converting that into an electrochemical response inside the cell. This brings up the question of whether different physical input like localized electromagnetic field or pulsed electromagnetic stimulation applied directly over a wound could potentially substitute for the missing mechanical indicator. Outside of skin biology, pulsed electromagnetic field therapy is already used clinically to promote healing in non union bone fractures [20]. If a similar approach could be shown to activate YAP signaling or similar pathways in skin cells, it could offer a non-invasive alternative that does not require direct pressure on a healing wound.

A third approach could be pharmacological rather than mechanical. Since LPA has already been shown to restore YAP activity and increase the rate of healing in a rat model and vitamin D and tretinoin have separately been flagged as potential countermeasures through gene expression analysis, a logical next step could be testing whether directly supplementing wounds with growth factors already known to drive keratinocyte and fibroblast activity like Epidermal Growth Factors (EGF), Keratinocyte Growth Factors (KGF) and Transforming Growth Factors-Alpha (TFG-α) could avoid the signaling blocks that microgravity creates instead of needing to restore the mechanical signal at all [7,9].

Lastly, a less explored approach emerges from connecting a finding already in this review to research outside of spaceflight literature. On Earth, actin driven cell migration is under circadian control, wounds sustained during the body's active phase heal about 60% faster than those sustained during the rest phase, because the circadian clock steadily times when actin based migration machinery is most active [21]. Ranieri, et al., found that microgravity greatly alters circadian clock gene expression in keratinocytes, an effect that becomes even more noticeable upon arrival to gravity. If this circadian rhythm disruption also affects fibroblasts, it raises a question of whether the F-actin breakdown identified by Zhou, et al., and Ikeda, et al., is solely a direct mechanical consequence of lost gravitational loading or compounded by a concurrent loss of the circadian timing signal that would normally coordinate actin activity for optimal healing. If astronauts are facing this kind of double disruption, then stabilizing an astronaut's circadian rhythm through light exposure or scheduling, independent of any mechanical or pharmacological countermeasure, could by itself significantly improve wound healing outcomes in space. These four approaches listed above have not been directly tested for wound healing in microgravity as of this review. But each is grounded in a specific mechanism identified in the literature above and each offers a concrete, testable direction for future research, which matters most as missions are growing longer and returning an injured astronaut to Earth becomes more challenging with the increase in distance and time.

Conclusion

Microgravity interrupts wound healing at almost every level, from stem cells and fibroblasts to blood vessels and collagen structure and this disruption is consistently more severe in real tissue compared to isolated cell studies. A specific molecular mechanism (F-actin/YAP signaling) and a tested countermeasure (LPA) offer the clearest path toward an actual treatment, but this is rat model evidence and not human data. Building on this mechanism, several untested but mechanistically grounded countermeasures, localized mechanical loading, electromagnetic simulation, targeted growth factor delivery and circadian rhythm stabilization, represent solid directions for future research rather than confirmed solutions. The most pressing gap in this field is the absence of controlled, in-flight human wound healing data, a gap that will only become more imperative as missions grow longer and evacuation back to Earth becomes less practical.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement
This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement
The authors have no acknowledgments to declare.

Data Availability Statement
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement
The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement
Not applicable.

Authors' Contributions
All authors contributed equally to this paper.

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