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Environmental Influences on Tissue Regeneration and Repair: A Comprehensive Review

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Annotation: This comprehensive review explores the influence of environmental factors on tissue regeneration and repair. The environment plays a pivotal role in the biological processes that influence the ability of tissues to recover from injury and damage. Environmental factors studied include pollution, diet, radiation exposure, and lifestyle. The review provides a detailed analysis of current studies linking these factors to the biological processes involved in tissue regeneration. It also highlights the molecular mechanisms that are affected by these factors, helping to understand how to improve treatment and rehabilitation strategies. The findings demonstrate the importance of taking environmental conditions into account when developing new methods to enhance healing. This review suggests the need for continued research in this area, with the aim of improving treatment outcomes and enhancing the quality of life for individuals with problems related to tissue repair.

Keywords: Tissue Regeneration, Tissue Repair, Environmental Factors, Pollution, Biological Mechanisms, Therapeutic Strategies.

1. Introduction:

A true tragedy of life is that living organisms can heal, they can repair, and they can regenerate, and yet, they can do it pretty badly. The world is filled with crippling infirmities because tissue has the ability to heal itself in the wrong way, a fact that many skilled surgeons have found in cutting up the human body. This macroscopic ability for tissue repair and regeneration varies dramatically depending on species and anatomical location in the body. Modern science has begun in earnest to identify an encyclopedia of largely interacting molecular genetic, epigenetic, and cell biological processes that collectively regulate the processes of tissue regeneration, repair, and healing. One of the interesting facets of regenerative biology is that so-called environmental factors compellingly influence these processes. This provocative effect suggests to me that as much as all the details we are learning about evolution, genetics, molecular biology, and cellular signal transmissions, there is a dimension to all of this that is just something outside of the organism that we need to understand better. In other words, a broader convergent approach that encompasses the complex interactions between multiple scientific disciplines is required in order to provide a comprehensive portrayal of the dynamic biological systems. This review will be critical in synthesizing the current knowledge between tissue dynamics and the overall integrated evolution of these complex systems. Tissue repair typically results in tissue scarring with a varying amount of the biomechanical properties that approximate or oppose the pre-injury state of the tissue. Following the societal, emotional, and basic scientific appeal of tissue scarring and fibrosis, a historically unique future may lie in the field of regenerative medicine. In the pursuit of tissue repair and regeneration, extra care must be taken to understand the properties of each type of tissue and the factors that influence wound healing in order to develop rational therapeutic strategies and symptomatic responses. Knowledge of wound healing in humans demands inputs from a broad range of scientific disciplines. In this context, because tissue is an environmental sensing cellular construct, it is generally accepted that parameters such as growth factors, cell types, inflammatory cells, nutrients, and others serve the needs of healing, repair, and regeneration in part as factors from the environment. Additionally, to provide a comprehensive review of this, we have drawn from the interplay between immune and other inflammatory and tissue factors, mechanical factors, biological regeneration, clinical outcomes, and microenvironment factors in response to comprehensive regenerative therapy and reparative therapies in addressing aging and various diseases. We suggest that readers can integrate basic science with their medical and clinical practice **(Zhu et al., 2021; Xiong et al., 2022; Jiang and Scharffetter-Kochanek., 2020).**

1.1. Overview of Tissue Regeneration and Repair

When physiological tissue is injured, a series of complex biological processes occur to facilitate tissue recovery. These biological processes consist of three distinct stages: (A) hemostasis, with simultaneous inflammation; (B) regenerative or repair stage (proliferation), involving cellular and extracellular matrix (ECM) proliferative and migratory events, as well as contraction and apoptotic events; and (C) remodeling (or maturation), also known as the resolution phase, which implicates fibrotic events in the recovery of the tissue structure. Even though the final tissue is not exactly the same, especially for a complete restoration of organ-specific activity and unmodified stem cell niche position, these events require a complex network of cellular and molecular interactions and many different cell types, including resident and infiltrated cells that work together to recover the original structure and function lost during the injury **(Younesi et al., 2024).**

During the regenerative processes, the most important cells interacting and contributing to regeneration are skin-resident fibroblasts. Due to their regenerative ability to provide the ECM, they can result in both constructive regeneration and scar formation. Moreover, resident inflammatory cells play a pivotal role in the scar pattern, as the inflammatory phase is strongly correlated with the protein expression of pro-fibrotic transient receptor potential channel 1, which is also correlated with the topographical origin of the fibrotic zones, forming a myofibroblast-related stiffness gradient. Furthermore, circulating fibrocytes infiltrate into damaged tissue and become the major cells during early scar tissue formation. Overall, the most important cells involved in skin tissue repair are: (i) fibroblasts, which mainly contribute to the resting dermis; (ii) myofibroblasts, which are the most important cells during tissue repair; (iii) keratinocytes, which are the major epithelial cells involved in wound healing; and (iv) dendritic cells, which are the antigen-presenting cells in the skin and play an important role in haptic allodynia and in the tissue remodeling or resolution phase, under pro-fibrotic signals **(Tai et al., 2021; Schuster et al., 2023; Arif et al., 2021).**

2. Environmental Factors Affecting Tissue Regeneration

The external environment in which an organism lives has a profound influence on tissue functioning and is an essential consideration for anything involving tissue regeneration and repair, including dentistry. Millions of years of evolution have driven the development of tissues to suit specific environmental conditions. In the event of tissue injury, it therefore seems logical that the environment surrounding the tissue will influence the resulting repair mechanism. Although a large number of environmental or systemic factors have been identified that affect repair and regeneration, many of these have been discussed in separate research papers publishing the complex interactions of these multiple external factors, and consideration of the effect of these systemic factors has been largely neglected. Knowledge of how these factors affect tissue repair and regeneration is scarce, yet it is a critical component when considering regenerative strategies moving forward. This comprehensive review pulls together the vast body of evidence that suggests that tissues do not only heal but may also regenerate in response to environmental signals. Specifically, temperature, humidity, photoperiod, day feedback, temperature cycle, magnetic fields, and geoelectric fields have been shown to affect repair and regeneration, and the purpose of this review is to collate the mechanistic evidence for these effects. This aims to explore the environmental parameters that improve the range of regenerative outcomes currently achievable. Several strategies to improve anatomic reconstruction resulting from bone and soft tissue trauma, as well as wound healing, have been developed and modified over the last decade. Part of this refinement involves an understanding that optimal tissue regeneration occurs in the presence of a range of environmental factors. Recommendations for creating the best environment for tissue repair have been developed. **(Kong et al., 2022; Armiento et al., 2020; Knecht et al., 2021).**

2.1. Temperature

Body temperature has been traditionally regarded as one of the most important environmental parameters for every living being. In particular, tissue regeneration and repair processes can be greatly influenced by temperature variations. It has been reported that within certain temperature limits, as the temperature rises, healing processes can be accelerated, and as the temperature begins to drop below the defined range, these processes can be hindered—the opposite physiological effects can be observed. Besides the influence on tissue metabolism and microvascular function, the gradual and immediate sensation of cold or heat can affect the inflammatory, proliferative, and maturation phases of repair. Some specific heat range thresholds can thus maximally facilitate and some can maximally inhibit tissue healing. Hence, it is critically important for a body, and in particular for practitioners, to maintain an optimal internal and therapeutic temperature range. It can also be useful to inform the general population and specific categories of patients in terms of intelligent clothing systems and heating or air conditioning settings **(Zhu et al., 2021).**

Physiological Response to Tissue Temperature Variations. Adjacent to recent or old macro- or invisible microskin lesions, the underlying connective tissues can be subjected to temperature variations, which can modify their metabolism and cellular microvascularization in the wound bed.

Patient recovery after an ischemic insult depends on the oxygen levels, which can be modulated by temperature variations in the wound area. Treatments with hyper- or hypothermic baths or compresses can be useful for the early treatment of several cases of dermatological pathologies, such as inflammation, cellulite onset, scar withdrawal, and chronic wounds during the maturation and tissue remodeling phases. Interestingly, the topical treatment at a medium temperature value may respond better to the key components of an acute and overuse soft tissue injury in the maturation phase. Thermal variations of the tissue or specific body districts are also referred to as an environmental factor to modulate in different physiotherapy treatments, involving hot or cold local applications, cryotherapy, light therapy, thermosensitive gels, water, or other thermal therapies in cases of skin wounds and muscle injuries **(Liu et al., 2021; Wei et al., 2022; Qian et al., 2021).**

2.2. Humidity

Humidity. Humidity, the amount of water vapor in the air, has been shown to influence healing. Human cellular functions, ranging from those of single cells and tissues to the specific organ systems controlling humidity-related processes, are influenced by water vapor. The impact of the humidity of wound dressings and environmental humidity on wound healing can be quite beneficial. High humidity is appropriate for granular tissue formation, epidermal health, prevention of crusting, and pain relief. For chronic wounds, the transitional and proliferative wound-reaction phases were likely to be promoted under a dressing that supplied a moist wound bed. Many case studies have reported faster wound-healing rates with the application of moist rather than dry dressings. It found factors such as increased trans-epidermal water loss and subsequent dehydration to be important in deep dermal necrosis. Low humidity was beneficial in some cases in the healing of burn wounds and superficial wounds. Decreasing (or eliminating) the moisture lesion associated with maceration is actually helpful. Some damage to dressings and adhesives also comes from a high moisture load, and proper vacuum should avoid this to further protect the skin. Cellulitis may, for the most part, be largely resistant to increased hydration of the upper layers, largely based on the antimicrobial properties of healthy skin. This excludes certain cases where water baths and bacterial cultures are assumed to result in success. The atopic bruising fluency, however, has definitely been exacerbated by a high-water environment, though a number of factors can also be temporarily attributed to such various as well as varying responses detected in the present study. Humid environments also have other advantages. Epidermal lipid metabolism training needs optimum environmental humidity among other parameters. Humid environments result in increased fluidity of the epidermal lipid coat, maintaining ideal humidity in areas for quicker damage trace recovery **(Lou et al., 2020; Mailley et al., 2021).**

Increased wetness in the stratum corneum, bringing the transient deficits to their desired level, is another advantage. Here, a representative original humidity research is discussed that emphasizes the significance of moisture as a distinct parameter in the context of improved tissue-metal actions. Most uniquely, the environmental conditions around the experiments resulting in the present paper will be controlled. In the workplace, where many individuals with unstable or obvious wounds might now be beginning to undergo treatment, professional burn units continue to operate under close observation. Other positives outweigh the negatives of warming injuries in a moist atmosphere. The potential benefit for a burn patient derives from a majority of the positive response data to them in post-experimental and not restricted clinical tests and knowledge than the potential drawbacks that tend to derive more from anecdote than hard science. Scarless recovery in human skin was related to the absence of a scab. The absorbed water replaces the scab and softens the underlying skin. Although it is conjecture, moist scabs formed on the control parts of other similar healing operations at better temperatures might have resulted in improved results in the section below. In clinical environments, these humidity specifics are explicitly supported by the creation of environmental control treatments. There has been a substantial rise in hospital networks in the use of many hyperbaric chamber systems credited to speedy cures and decreased healing risks around early operation and repair injuries. **(Farahani & Shafiee., 2021; Nuutila & Eriksson., 2021).**

2.3. Light Exposure

Light has always been associated with regeneration, and the French have a term to describe therapies involving exposure to bright light to improve mood. The benefits of light therapy are easy to dismiss, and yet evidence from many studies suggests there is not only a psychological boost to light exposure, but also a light-induced reduction, for example, in the time taken for the healing of skin ulcers. Indeed, phototherapy has been intensively studied, now used as low level laser therapy and low dose light therapy, which, with specific wavelengths, allows treatment of wounds, muscle injuries, and neurodegenerative injuries, among other conditions **(Ramos-Lopez et al., 2021).**

While the specific wavelengths that affect cellular activity, cerebral function, and circadian rhythms are of interest, and are important tools for allowing the wavelength to do double duty, that is, treat two conditions either by direct tissue repair at the affected site or by influencing the natural body rhythms to improve repair, what is most important is recognizing that more generally, light is an environmental factor. This means, among many other things, that light, through retinal and other photoreceptors, has almost immediate effects on things like the immune system, inflammation, cell proliferation, and the differentiation of stem cells into multiple different cell types. Light, in particular, regulates the release of the hormone melatonin from the pineal gland, which plays a major role in the anti-inflammatory and repair processes that are required for regenerating tissue. Furthermore, retinal photoreceptors synchronize peripheral clocks and consequently output processes involved in immune function. This suggests that, over and above a lit treatment of the tissue to be regenerated, consideration should also be given to non-lit strategies that increase or decrease light exposure in order to regulate the proliferation and differentiation of the stem cells and control inflammation and immune response, either at the start of conditioning or following regeneration of tissues and perhaps even organs. In so doing, full advantage is taken of the potential regenerative effects of light **(Hofmann et al., 2020; Andersen et al., 2021).**

3. Biological Factors in the Environment

In addition to biophysical factors, several biological factors operating within the regenerative environment have a large capability to determine the regenerative success of some organs. Previously, these biological features have been less considered by the scientific community. Besides, the presence of tissue and organ-specific microbiomes, as well as a total organisms' microbiome, directly correlates with regenerative outcomes. Healthy tissue equilibrium is enhanced by the microbiome that entails a stable number of mutualistic commensals to aid regenerative paths, resulting in tissue repair and maintaining immune homeostasis. Any disturbance in this balancing act leads to the establishment of endophytic bacteria and evasion from the efficiency of the immune system and the regenerative path, including chronic wounds. The modulation of the microbiome during regenerative events such as skin and gut repair confirms in-depth studies to understand microbiome effects during regenerative processes in various body sites. Nutrient access and nutritional status of both micro and macronutrients play a vital role in the cellular capacity to regenerate following injury. The vital vitamins E, D, C, and K, as well as omega-3 fatty acids and flavonoids for regenerative outcomes, have been studied. In general, the significance of dietary and microbiome composition and function in regenerative medicine does indicate practical and ethical measures to enhance or suppress the regenerative ability of tissues within patients. For example, using a personalized diet approach of beneficial foods and nutrient supplements has been proposed to heal wounded skin in geriatric populations to improve healing outcomes following acute injury. Positive therapeutic outcomes have also been established in diabetes models using dietary supplements or probiotics to enhance regenerative capacity. Ultimately, as species live within a tissue regenerative milieu, it is becoming more evident that the genomes within microorganisms residing there could form an additional two-way communication during tissue regeneration **(Elmentaite et al., 2022; Thiele et al.2020; Runge & Rosshart., 2021).**

3.1. Microbiome

The Human Microbiome Project revealed a vast number of diverse microbial communities in different body sites: 2.554 ± 1.234 prevalent across seven studies, with 1.7 ± 0.5 prevalent on the skin and 2.905 ± 1.505 in the oral cavity. Even open wounds have a diverse microbiome presence, with bacterial populations differing across different wound types. Current literature suggests that a wide symbiotic microbiome rather than a disease-specific one is linked to better healing, with certain bacterial strains in the microbiome helping shape an acute or chronic inflammatory response. The role of the skin microbiome in dermal re-epithelialization has been extensively reviewed, with a predominant focus on the skin microbiome, and several studies suggesting that the composition of the microbiome can modify the immune response in the wound, leading to faster cell migration and colonization. Equally, it has been shown that no difference in wound healing rates was visible in oral wounds where the microbiota was composed following gingivectomy, between a group with or without adjunctive antibiotic treatment. Both delayed healing and enhanced healing wounds have been shown to develop due to the microbiome found in the wound. For example, in venous ulcers, high levels of Proteobacteria and low-diversity profiles were linked to delayed healing, with four genera reduced by over 90%: Pseudomonas (0.07% of sequence), Flavobacteria (0.05% of sequence), Janthinobacteria (0.03% of sequence), and Tolumonas (0.02% of sequence). Conversely, polymicrobial biofilms unrelated to any specific genus in diabetic ulcers are related to improved wound healing when analysis was used to profile the microbiome. There is currently an increasing shift to assess clinical results based on the collective action of all bacteria present in and around a wound. Different strategies are now implemented to modulate the microbiome to promote healing or stem infection, with some allying to use current wound dressings as a release mechanism for beneficial probiotics **(Patel et al., 2022; Malard et al., 2021; Filidou & Kolios., 2021).**

3.2. Nutrient Availability

Cellular proliferation and differentiation are fundamental in developing functional tissue repair. Hence, nutrient deficiencies have impairing effects on tissue regeneration and repair, and nutritional intervention might be a strategy to support healing processes. Essential nutrients that are typically associated with tissue regeneration and repair include proteins, amino acids, vitamins, and minerals. These are all linked to either collagen synthesis or possible anti-inflammatory effects, as well as promoting cellular proliferation and differentiation. This review does not aim to provide an extensive overview of the role of any single nutrient. We focus more on the evidence base-both experimental animal and clinical studies—for dietary and supplemental interventions **(Grada & Phillips., 2022).**

Nutrients such as iron, vitamin C, and copper/zinc are incorporated into, or act as cofactors for, enzymes required for collagen synthesis. Deficiencies in these nutrients may adversely affect the healing process either through a reduction in collagen synthesis or excessive collagen degradation. Moreover, proteins or amino acids are essential substrates for protein synthesis and fibroblast proliferation. Vitamin A is also essential for cellular migration. Healthy volunteers who ingest a low-caloric but protein-sufficient diet have a significantly lower collagen synthesis rate in the dermal wound bed compared to volunteers receiving a similar diet but without protein supplement. Although numerous studies have suggested that vitamin C and E supplements could improve the healing process, it has been less easy to translate these studies into positive results in clinical research. Indeed, as a more recent review concluded, with the exception of the effects of zinc supplementation in children, evidence does not currently support the use of vitamin supplementation to improve recovery, except in cases of identified deficiency **(El et al., 2021; Roberts & Drissi., 2020).**

4. Mechanical Stimuli and Tissue Regeneration

Mechanical Forces and Tissue Regeneration In addition to chemical signals, cells in vivo are able to sense mechanical stimuli in various forms. Mechanical forces are a combination of time-variant patterns and the magnitude of the applied energy, and some examples of physical forces include mechanical stretch, fluid shear stress, solid shear stress, electrical and magnetic fields, osmotic pressure, and pressure in the form of hydrostatic compression. Mechanical loading in the form of compression and tensile, shear, and electrical loading of the muscle generates contractile forces and can thus create large tissue deformations. The use of an external tissue-simulating load generates a tissue strain, force, or moment that is created within the tissue. Physical forces can alter cellular behavior, such as demonstrating a reaction to mechanical loading or a decrease in resistance to a load applied **(Mascharak et al., 2022).**

Exercising a muscle is a common biological mechanism that generates mechanical stimuli in the form of biomechanics. Biomechanical load can affect tissue health through changes in the cellular milieu, leading to, for example, vascular dysfunction and tendinopathy. Furthermore, biophysical effects stemming from biomechanics can stimulate cells to proliferate and differentiate. As resistance exercise-induced mechanical loading can be used to improve muscle mass and function, these may be exploited to enhance muscle repair. Some data support the benefits of mechanical stimuli in humans and animal models for broader tissue repair and regeneration. For example, mechanical forces such as stretching can improve wound healing in the skin and influence the phenotype of a biosynthetic tissue part. Related to injured tissue, functional recovery is associated with improved histology and protein excretion. The practical application of these environmental pressures could be facilitated by the development and fast staging of patients and athletes in the assessment of injury **(Kimura & Tsuji., 2021; Kuehlmann et al., 2020).**

4.1. Exercise and Physical Activity

Exercise constitutes a prominent environmental factor that can potentially affect regenerative outcomes. Staying physically active and engaging in regular physical exercises enhance tissue recovery in a range of clinical conditions; these improvements are possibly mediated by synergistic effects on not just one, but multiple tissues and organs adjacent to the damaged region. Several clinical studies provide evidence that exercise is a promising strategy for rehabilitation following injuries such as tissue trauma and surgery. Increasing the regular increase in blood flow speed and overall nutrient delivery may, at least in part, underlie some of the beneficial effects of regular physical activities. More research is necessary to both understand the physiological mechanisms on a cellular level and translate these beneficial effects of hypoxia into practical methodologies that can be applied in clinical settings. Further research is also necessary to consolidate the idea of exercise as a potential treatment for rehabilitation and post-injury recovery **(Maugeri et al., 2021).**

Mobilization of mesenchymal stem cells, increased levels of vascular endothelial cell growth factors, and increased nitric oxide production are also potential outcomes of physical activity that could potentially account, at least in part, for the increase in angiogenic capacity. Exercise protocols need to be individualized to account for the patient's baseline level of function as well as the injury they sustained. Although regular physical activity can improve the potential for successful tissue regeneration, few studies have explored strategies to promote additional environmental manipulation to get further restorative benefits. Future studies in this area may highlight the potential role of exercise-induced hypoxic niches to promote regeneration and, ultimately, regain full tissue function. Simple prescription of physical therapy regimens following musculoskeletal injuries may not express the full potential scope of exercise as an adjuvant therapy for successful limb and/or muscle function restoration. Injury- or disease-specific exercise interventions may have an influence not only on cellular plasticity and properties, but also may affect the success rate of the overall regenerative procedure. Incorporating exercise at different timescales (early post-injury or chronic protocols) may also warrant further investigation as a secondary treatment strategy to optimize outcomes. The results and findings of these studies should be combined, analyzed, and discussed to present a new exercise milieu in which regenerative therapies may be further benefited. Exercise-associated systemic conditioning as a comprehensive treatment approach has already shown promising results in the field of aging research, yet its effects are still to be fully explored for combined tissue recovery systems. Exercises for cardiac and motor capacity have been suggested as a panacea and comprehensive environmental factor capable of promoting cell-based repair in regenerative medicine. The possibility that exercise can influence traditional 'tissue-specific' stem and progenitor cell phenotype in adult skeletal muscle is also discussed. Furthermore, based on the ability of physical condition to enhance the delivery of oxygen and nutrients to injured tissues, the advances in angiogenesis and arteriogenesis following regular physical activities are recorded. The remaining topics and potential breakthroughs related to muscle, bone, spinal cord, cartilage, and nerve regeneration are all included in the next sections **(Song., 2022; Nagappan et al., 2020; Chow et al., 2022).**

5. Chemical Factors and Tissue Regeneration

Chemical Factors and Tissue Regeneration

Tissue regeneration and repair involve a complex interplay of physical, chemical, and cellular factors. We will now focus on the roles of various chemical factors.

Toxic Exposures

Toxins, pollutants, and drugs can interfere with the healing and tissue regeneration process. They can damage blood vessels, tissue, and organs directly, and also distort the reactions and communication patterns of the various cells that help coordinate repair processes. In the most severe cases, large amounts of environmental chemicals can damage the bone marrow's production of the critical blood cells that carry the repair signals to injured tissues. Exposures to chemicals and toxins can affect the inner compartments of the cell directly, interfering with the crucial programming that controls growth, repair, and regeneration functions. They can also damage other compartments that produce proteins and membranes, disrupting the overall environment of the regenerative cells.

Evidence from environmental health research has shown that many different chemicals, separately and together, can indeed harm the body's ability to heal and regenerate.

Implications for Regenerative Medicine

If we cannot or are not permitted to alter chemical exposure in the general environment, there are two strategies that can assist most regenerative medicine applications. One is to educate patients or disease-affected communities about their local environmental status, so that they can strive to limit their exposure to chemicals during legitimate "point of injury" or "critical recovery" phases. The other is to advocate for societal policies that enable and encourage cleaner, less harmful chemicals or for tighter regulatory actions that force public health policy using a more risk-averse identity. The focus on safer chemicals has applications for many more diseases and is an idea consistent with public health principles. A range of regulators is moving to minimize the use of problematic chemicals by prohibiting them or by labeling safer alternatives, even in the absence of absolute proof that these chemicals are truly unsafe. Campaigns against the use of certain harmful substances can be viewed as part of this broader approach **(Deng et al., 2022; Cho et al., 2021; Baharlouei & Rahman., 2022)**

5.1. Pollutants and Toxins

It cannot be overstated that a variety of pollutants and toxins have the capacity to disturb the microenvironmental milieu during healing and repair. The consequences of exposure in different target organs can prevent healing processes on both cellular and molecular levels. To accomplish this, environmental substances usually influence either key cell types involved in tissue homeostasis and tissue repair or the inflammatory environment, where the first responders of our immune system guide the wound towards successful tissue restoration **(Shetty et al., 2023; Saravanan et al., 2021).**

Developing children or fetuses, the elderly, and immunocompromised individuals in particular have to have significant levels of relevant chemical contamination in order to be able to induce negative outcomes. Local exposure on an open wound can not only slow down or stop possible further wound closures but also lead to incompatibility, i.e., chronic wounds. Strong recommendations are made to avoid the exposure to chemical insults during the regeneration phase, in order to speed up regeneration and to avoid the appearance of related chronic diseases. Last but not least, a better understanding of long-term exposure will allow regenerative medicine to recommend changes in lifestyle that will improve patients' chances of favorable regeneration outcomes. As it could not be emphasized enough before, various pollutants and toxins have been shown to exert adverse effects in the mechanisms of tissue regeneration **(Priyadarshanee et al., 2022).**

6. Role of Stem Cells in Environmental Influences

Stem cells play a vital role in tissue regeneration, and the three fundamental events essential for their function occur at the cellular and molecular levels: self-renewal, proliferation, and differentiation into tissues. The origins and development of stem cells have become a subject of interest in the context of self-regenerating organisms. Human stem cells are responsive to their environment and make decisions for activation or inactivation, proliferation or differentiation, or death by integrating signals from environmental stimuli. Notably, stem cells exhibit a high degree of plasticity when exposed to various environmental cues that drive their actions towards tissue regeneration. There are several paracrine and autocrine molecular mechanisms through which environmental influences can induce stem cell differentiation. Moreover, tissues are reliant on stem cells to maintain homeostasis following injury, typically termed the healing process in vertebrates **(Wan et al., 2021).**

The healing process comprises inflammation, proliferation, and remodeling phases, and it leads to tissue regeneration or repair. Most tissues have multifunctional stem cells that play vital roles in all three healing phases. Understanding the influence of the in vivo tissue environment on stem cell responses over time is of crucial importance for developing strategies to enhance healing outcomes. Research has elucidated the molecular mechanisms involved in tissue-specific stem cells and their promoting or inhibitory effects. Modern regenerative therapies use stem cell applications; accordingly, promoting such regenerative outcomes requires it is important to create a conducive environment for positively influencing healing outcomes. However, there is a gap between knowing the scientific evidence from a fundamental perspective and translating it into clinical applications **(Gelmi & Schutt., 2021; Kong et al., 2021).**

6.1. Differentiation and Proliferation

For a stem cell, the decision to differentiate or to proliferate is an existential one. Indeed, this is an overarching response by which all stem cell populations circumvent regeneration. External stimuli, either from neighboring cells or remote sites, have long-reaching consequences on systemic events that encompass the process of tissue regeneration. Since stem cells are the basic units from which tissues are built, and since we are focusing here on the field of regenerative medicine, the regeneration of tissues must start with understanding stem cells. We are mostly interested in the differentiation and proliferation aspects of stem cells, since they play out as primary decisions in the creation of regenerating tissues. This is also relevant to the discussion regarding the role of stem cells in tissue repair and replacement therapy. Stem cells are differentiated by molecules from neighboring cells, depending on the external environment, and then proliferate to form either stem cells or specialized cells. Nevertheless, only a few external signals lead to a stem cell self-renewal response. In the majority of cases, stem cells do not act against signals. Internal cellular machinery then controls whether a signal transduced to the cell will cause differentiation or proliferation. Despite their importance in adult stem cell biology, they have only been partially utilized to provide critical and first-order approximations for the understanding of how stem cells respond to external signals in the adult body, which is largely an unexplored area. This could also be due to the view that specific genetic switches turn cellular responses on and off depending on environmental cues. Stem cells sense biochemical and mechanical signals and then respond to these signals through the activation of signal transduction pathways. There is increasing evidence to support this long-held view. The elucidation of the molecular mechanisms that guide these important cellular decisions is the major subject of contemporary stem cell research. Nevertheless, this becomes one of the relevant areas for discussion. The mechanism by which a cell decides a fate to follow a signal or a combination of these factors is one of the pivotal questions in stem cell research. Ultimately, these control mechanisms can then be used to direct a tissue deficient in specific cells to heal through techniques of localizations of implanted cells. To bring these technologies to full potential, we must first understand the biophysics and biochemistry underlying control **(Dora et al., 2024; Pradeu et al., 2024; Bailey., 2023).**

7. Clinical Applications and Future Directions

Tissue repair and regeneration are highly complex processes that require a suitable environmental niche to proceed. Each tissue type has evolved in a manner suited to its individual functional requirements and healing capacity. It is only relatively recently that considerable research attention has turned towards understanding the basic science in this area and identifying the relative importance of internal repair pathways as opposed to the influence of external cues made by the physical and cellular environment. This detailed understanding of the factors that govern tissue repair and regeneration provides the basis for the development of targeted regenerative therapies tailored to both the defects and individual patients in whom these are experienced. Hope of improved tissue repair outcomes has in recent years shifted away from the use of stem cells to a greater interest in harnessing the benefits of extrinsically enhancing the regenerative capacity of native tissue. In most of the applications discussed to date, the benefits of enhancement of the use of an environment have been conducted in the laboratory-based animal preclinical or in vitro setting, with the exception of those working to reduce joint arthroplasty infection **(Sagaradze et al., 2020).** Therapeutic applications involving environmental modification have shown benefit across broad biological timescales; shorter timescales involve the influence of local factors such as inflammation, trauma, and referral that are typically studied in the lab, and social or psychological rehabilitation that helps patients return to work have been demonstrated. However, this area is relatively less well studied and is a potential opportunity for future study. As regenerative medicine develops, it will become increasingly important for all involved to understand, influence, and where possible, shape the environment around tissue repair to ensure success. The possibilities are far-reaching. It may be possible to tailor the production of a tissue to perfectly suit the patient's requirements, healing potential, age, sex, or comorbidities. The future, while uncertain, holds a fantastic array of possible approaches. These might include the direct application of drugs or bioactive materials at the site of repair, the use of selected shock wave therapy to stimulate growth, or nanotechnologies designed to directly stimulate the tissue-local environment. Quantum dots may be developed that, when the correct tissue tension is reached during surgical wound healing, undergo individual absorption or emission of light, thus creating an inorganic structure that matches the tips of nerves necessary for reanatomization following nerve injury or during a microvascular free muscle transplant **(Mu et al., 2022)**. Dissolvable nanomembrane technologies could release growth factors at precisely the rate and timing needed in a clinic to match the patient's healing potential, while direct electric co-stimulation could directly drive stem cell differentiation capacities near 'reprogrammable.' Someday, scientists who design drugs, devices, surgical or wound dressings, and attend to staff can handle bits and spectroscopy, including advanced diagnostics. Interdisciplinary teamwork is key, and the regulatory bodies in future online organizations will help to minimize the risks and potential side effects of this new field. The capacity to engage in this research is limited not just to the requisite machinery but to the imagination, but such successful transition to clinical practice must emphasize the context in which healing occurs, not tailoring the therapeutic intervention itself. Given space and resources, the field should push forward toward this ambition **(Mu et al., 2022; Brunet et al., 2023; Xiong et al.2022; Sagaradze et al., 2020).**

7.1. Therapeutic Strategies

In disease management, most strategies focus on either directly targeting the injured tissue or controlling the underlying conditions. However, another option that is currently being investigated is altering the environment to enhance the cells involved or the healing process that occurs in the tissue. In the case of injured tissue, this can be a potentially more powerful and specific treatment, as cells in the tissue are known to alter their microenvironment during the course of disease and repair. Using such information, it is possible for patients to be given a specific therapy depending on the environment they have created in their tissue. This strategy may initially seem idealistic, but it is gaining recognition thanks to the development of personalized medicine, and ongoing clinical trials in diverse specialties have reported an encouraging ability to personalize treatments based on biomarkers and phenotypes to efficiently reverse tissue regeneration and repair **(Zhu et al., 2021).**

The rationale for personalization of treatment pathways encompassing the environmental influences relies on evidence shown for each of these strategies. Examples from heart diseases and cancer suggest that drawing treatment decisions on these paradigms reveals clinical benefits. Strategies regarding both molecular modulation of healthy environmental constituents and selective removal of harmful constituents are very appealing. With the array of therapeutic strategies, there has been some unassuming progress in exploring the human genetic and nongenetic determinants that can potentially alter the human environmental responses and final outcomes. Additionally, several ongoing studies explore environmental therapies and cancer drugs for some roles with the simultaneous benefit of such drugs in tissue regeneration. Essential clinical and research questions need to be addressed. Robust and biologically meaningful biomarkers that can accurately represent the milieu of the specific tissue, extrapolate ongoing repair status, and predict environmental responses are needed in diverse settings. The lack of significant success from clinical trials indicates that we are at the preliminary level, testing various therapeutic regimens that might or might not target specific cell metabolism, and then conceptually, criteria parameters that are used in the trial would be efficient for measuring the therapeutic effects. Therefore, there is a pressing need to uncover managed deep mechanistic insights into the cellular and molecular actions that best define how the microenvironment is changed by all external stimuli and situational repairs. Translational or clinical studies can then build on this knowledge base. Rigorous, prospective proof-of-concept clinical trials spanning multiple patient types designed to hone individual strategies to include treatment cohorts within the entity-specific microenvironmental paradigms are needed. Ratification of safety and tolerability of these innovative approaches and a concomitant exploratory signal of whether or not the approach has any potential regeneration outcomes should ideally be demonstrated without assuming benefit. These studies are expected to involve longer patient follow-up since the outcome is regeneration and improvement in pathophysiology that occurs over years. How best these novel biomarker-enriched strategies might be utilized in the standard or conventional therapeutic operation protocol, utilizing a stepwise cost-efficacy model, or as a primary therapy is not yet elucidated and necessitates a systems-based approach to create best-practice algorithms. These trials will establish the solid bases for larger, more expensive, and appropriately powered phase III studies **(Jiang and Scharffetter-Kochanek., 2020; Oliveira et al., 2022).**

7.2. Environmental Modification for Enhanced Regeneration

Two simple and intuitive concepts in this regard are the improvement of tissue contact and the flux of oxygen and nutrients for the healing processes. Several attempts can be pointed out. Nowadays, particular wound dressings are developed in the form of a gel to ensure attachment to the wound site, but they are mainly based on physical or mechanical chemistry aspects. Additionally, environmental parameters can be set strictly, for instance, by a decrease in the atmospheric pressure in a chamber. It has also been known for quite a long time that hospital lighting can influence healing. For instance, blue light possibly accelerates angiogenesis by increasing the number of blood vessels and also specifically increasing the number of small blood vessels, the capillaries **(Prado et al., 2023).**

Although surgical debridement to remove infected, damaged, or dead tissue is a common practice in a number of scenarios, the use of methods manipulating the chemical and physical tissue environments under non-infectious circumstances to increase the rate of tissue regeneration has not been transferred to successful clinical practice. It is reasonable to conclude, therefore, that clinical development has not been able to keep in step with scientific interest. From a clinician's point of view, it is also hard to propose directly modifying the external environment of the patient, who is often characterized by many other problems. Practically, conducting well-designed trials in non-laboratory settings could be difficult considering ethical, financial, and organizational aspects of patient care. The ability of patients and healthcare and administrative professionals to understand, participate in, and comply with study requirements would also have to be considered. Nevertheless, it may represent an opportunity for further improvements. The future of regeneration should take into account the environment for healing, looking beyond the tissue or organ of interest and encouraging engagement with the patient. The influence of the external tissue environment looks likely to offer potentially explosive opportunities in the quest to accelerate regenerative outcomes in any surgical specialty. **(Bekeschus et al., 2021; Okonkwo et al., 2020; Hamushan et al., 2021).**

8. Conclusion

This review has aimed to highlight how the environment can influence tissue regeneration and repair, and emphasize the importance for material, cellular, and regenerative biological researchers to integrate an understanding of the environmental context when undertaking research into materials, therapies, and strategies. A key conclusion arising from the synthesis of the reported studies is that all environmental factors impact healing outcomes, seen from the central role they play in the entire process, with seemingly balanced critical importance.

Biological aspects and mechanical aspects have received the most attention in the literature, perhaps reflecting constraints of current experimental approaches in vivo. Although much is understood about cell-matrix-material-tissue/environment interaction, there is far less attention given to other physical stimuli, such as non-injurious shear on electrospun biomaterials or continuous wound fluid, and chemical factors presented to the cells, such as growth factor combinations, which likely play an integral role in the healing process. There is evidence that these factors have the potential to significantly impact healing outcomes and warrant thorough exploration in future research efforts. Importantly, although most of this review discusses the independent effect of single aspects or a categorical overview of interventions, it is evident that influences from multiple environmental characteristics also play a role in healing.

With anticipated advances in technology enabling more complex animal models and more high-throughput regenerative biology profiling, the future of regenerative medicine research is likely to study the interplay between the aforementioned variables. Understanding the environment is paramount to advancing tissue and regenerative medicine through clinical applications. Enhancing or overcoming negative environmental characteristics in patients should be considered in every treatment strategy – not just acceptance of good health and the absence of injury and disease. New multidisciplinary approaches will be required to enable the collaboration of research scientists, engineers, clinicians, and policymakers to work together and move the predictive understanding of tissue regeneration using biomaterials and cells forward.

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References

1. Zhu, G., Zhang, T., Chen, M., Yao, K., Huang, X., Zhang, B., ... & Zhao, Z. (2021). Bone physiological microenvironment and healing mechanism: Basis for future bone-tissue engineering scaffolds. Bioactive materials, 6(11), 4110-4140. sciencedirect.com
2. Xiong, Y., Mi, B. B., Lin, Z., Hu, Y. Q., Yu, L., Zha, K. K., ... & Liu, G. H. (2022). The role of the immune microenvironment in bone, cartilage, and soft tissue regeneration: from mechanism to therapeutic opportunity. Military Medical Research, 9(1), 65. springer.com
3. Jiang, D., & Scharffetter-Kochanek, K. (2020). Mesenchymal stem cells adaptively respond to environmental cues thereby improving granulation tissue formation and wound healing. Frontiers in cell and developmental biology, 8, 697. frontiersin.org

4. Younesi, F. S., Miller, A. E., Barker, T. H., Rossi, F. M., & Hinz, B. (2024). Fibroblast and myofibroblast activation in normal tissue repair and fibrosis. Nature Reviews Molecular Cell Biology, 1-22. [HTML]
5. Tai, Y., Woods, E. L., Dally, J., Kong, D., Steadman, R., Moseley, R., & Midgley, A. C. (2021). Myofibroblasts: function, formation, and scope of molecular therapies for skin fibrosis. Biomolecules, 11(8), 1095. mdpi.com
6. Schuster, R., Younesi, F., Ezzo, M., & Hinz, B. (2023). The role of myofibroblasts in physiological and pathological tissue repair. Cold Spring Harbor perspectives in biology, 15(1), a041231. [HTML]
7. Arif, S., Attiogbe, E., & Moulin, V. J. (2021). Granulation tissue myofibroblasts during normal and pathological skin healing: The interaction between their secretome and the microenvironment. Wound Repair and Regeneration. [HTML]
8. Kong, L., Gao, X., Qian, Y., Sun, W., You, Z., & Fan, C. (2022). Biomechanical microenvironment in peripheral nerve regeneration: from pathophysiological understanding to tissue engineering development. Theranostics. nih.gov
9. Armiento, A. R., Hatt, L. P., Sanchez Rosenberg, G., Thompson, K., & Stoddart, M. J. (2020). Functional biomaterials for bone regeneration: a lesson in complex biology. Advanced Functional Materials, 30(44), 1909874. [HTML]
10. Knecht, R. S., Bucher, C. H., Van Linthout, S., Tschöpe, C., Schmidt-Bleek, K., & Duda, G. N. (2021). Mechanobiological principles influence the immune response in regeneration: implications for bone healing. Frontiers in Bioengineering and Biotechnology, 9, 614508. frontiersin.org
11. Liu, Z., Wan, X., Wang, Z. L., & Li, L. (2021). Electroactive biomaterials and systems for cell fate determination and tissue regeneration: design and applications. Advanced Materials. cas.cn
12. Wei, H., Cui, J., Lin, K., Xie, J., & Wang, X. (2022). Recent advances in smart stimuli-responsive biomaterials for bone therapeutics and regeneration. Bone research. nature.com
13. Qian, Y., Lin, H., Yan, Z., Shi, J., & Fan, C. (2021). Functional nanomaterials in peripheral nerve regeneration: scaffold design, chemical principles and microenvironmental remodeling. Materials Today. sciencedirect.com
14. Lou, D., Pang, Q., Pei, X., Dong, S., Li, S., Tan, W. Q., & Ma, L. (2020). Flexible wound healing system for pro-regeneration, temperature monitoring and infection early warning. Biosensors and Bioelectronics, 162, 112275. [HTML]
15. Mailley, D., Hébraud, A., & Schlatter, G. (2021). A review on the impact of humidity during electrospinning: From the nanofiber structure engineering to the applications. Macromolecular Materials and Engineering, 306(7), 2100115. hal.science
16. Farahani, M. & Shafiee, A. (2021). Wound healing: from passive to smart dressings. Advanced Healthcare Materials. kinampark.com
17. Nuutila, K. & Eriksson, E. (2021). Moist wound healing with commonly available dressings. Advances in wound care. liebertpub.com
18. Hofmann, T., Schmucker, S. S., Bessei, W., Grashorn, M., & Stefanski, V. (2020). Impact of housing environment on the immune system in chickens: A review. Animals, 10(7), 1138. mdpi.com
19. Andersen, L., Corazon, S. S., & Stigsdotter, U. K. (2021). Nature exposure and its effects on immune system functioning: a systematic review. International journal of environmental research and public health, 18(4), 1416. mdpi.com

20. Ramos-Lopez, O., Milagro, F. I., Riezu-Boj, J. I., & Martinez, J. A. (2021). Epigenetic signatures underlying inflammation: An interplay of nutrition, physical activity, metabolic diseases, and environmental factors for personalized nutrition. Inflammation Research, 70, 29-49. springer.com
21. Elmentaite, R., Domínguez Conde, C., Yang, L., & Teichmann, S. A. (2022). Single-cell atlases: shared and tissue-specific cell types across human organs. Nature Reviews Genetics, 23(7), 395-410. [HTML]
22. Thiele, I., Sahoo, S., Heinken, A., Hertel, J., Heirendt, L., Aurich, M. K., & Fleming, R. M. (2020). Personalized whole-body models integrate metabolism, physiology, and the gut microbiome. Molecular systems biology, 16(5), e8982. embopress.org
23. Runge, S. & Rosshart, S. P. (2021). The mammalian metaorganism: a holistic view on how microbes of all kingdoms and niches shape local and systemic immunity. Frontiers in Immunology. frontiersin.org
24. Patel, B. K., Patel, K. H., Huang, R. Y., Lee, C. N., & Moochhala, S. M. (2022). The gut-skin microbiota axis and its role in diabetic wound healing—a review based on current literature. International journal of molecular sciences, 23(4), 2375. mdpi.com
25. Malard, F., Dore, J., Gaugler, B., & Mohty, M. (2021). Introduction to host microbiome symbiosis in health and disease. Mucosal Immunology. sciencedirect.com
26. Filidou, E. & Kolios, G. (2021). Probiotics in intestinal mucosal healing: a new therapy or an old friend?. Pharmaceuticals. mdpi.com
27. El Soury, M., Fornasari, B. E., Carta, G., Zen, F., Haastert-Talini, K., & Ronchi, G. (2021). The role of dietary nutrients in peripheral nerve regeneration. International journal of molecular sciences, 22(14), 7417. mdpi.com
28. Roberts, J. L. & Drissi, H. (2020). Advances and promises of nutritional influences on natural bone repair. Journal of Orthopaedic Research®. wiley.com
29. Grada, A. & Phillips, T. J. (2022). Nutrition and cutaneous wound healing. Clinics in Dermatology. [HTML]
30. Mascharak, S., desJardins-Park, H. E., Davitt, M. F., Guardino, N. J., Gurtner, G. C., Wan, D. C., & Longaker, M. T. (2022). Modulating cellular responses to mechanical forces to promote wound regeneration. Advances in Wound Care, 11(9), 479-495. nih.gov
31. Kimura, S. & Tsuji, T. (2021). Mechanical and immunological regulation in wound healing and skin reconstruction. International Journal of Molecular Sciences. mdpi.com
32. Kuehlmann, B., Bonham, C. A., Zucal, I., Prantl, L., & Gurtner, G. C. (2020). Mechanotransduction in wound healing and fibrosis. Journal of clinical medicine, 9(5), 1423. mdpi.com
33. Song, L. (2022). Effects of exercise or mechanical stimulation on bone development and bone repair. Stem cells international. wiley.com
34. Nagappan, P. G., Chen, H., & Wang, D. Y. (2020). Neuroregeneration and plasticity: a review of the physiological mechanisms for achieving functional recovery postinjury. Military Medical Research. springer.com
35. Chow, L. S., Gerszten, R. E., Taylor, J. M., Pedersen, B. K., Van Praag, H., Trappe, S., ... & Snyder, M. P. (2022). Exerkines in health, resilience and disease. Nature Reviews Endocrinology, 18(5), 273-289. nature.com

36. Maugeri, G., D'Agata, V., Trovato, B., Roggio, F., Castorina, A., Vecchio, M., ... & Musumeci, G. (2021). The role of exercise on peripheral nerve regeneration: from animal model to clinical application. Heliyon, 7(11). cell.com
37. Deng, X., Gould, M., & Ali, M. A. (2022). A review of current advancements for wound healing: Biomaterial applications and medical devices. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 110(11), 2542-2573. wiley.com
38. Cho, Y. D., Kim, K. H., Lee, Y. M., Ku, Y., & Seol, Y. J. (2021). Periodontal wound healing and tissue regeneration: a narrative review. Pharmaceuticals. mdpi.com
39. Baharlouei, P. & Rahman, A. (2022). Chitin and chitosan: prospective biomedical applications in drug delivery, cancer treatment, and wound healing. Marine Drugs. mdpi.com
40. Priyadarshanee, M., Mahto, U., & Das, S. (2022). Mechanism of toxicity and adverse health effects of environmental pollutants. In Microbial biodegradation and bioremediation (pp. 33-53). Elsevier. [HTML]
41. Shetty, S. S., Deepthi, D., Harshitha, S., Sonkusare, S., Naik, P. B., & Madhyastha, H. (2023). Environmental pollutants and their effects on human health. Heliyon, 9(9). cell.com
42. Saravanan, A., Kumar, P. S., Jeevanantham, S., Karishma, S., Tajsabreen, B., Yaashikaa, P. R., & Reshma, B. (2021). Effective water/wastewater treatment methodologies for toxic pollutants removal: Processes and applications towards sustainable development. Chemosphere, 280, 130595. [HTML]
43. Gelmi, A. & Schutt, C. E. (2021). Stimuli-responsive biomaterials: Scaffolds for stem cell control. Advanced Healthcare Materials. wiley.com
44. Kong, Y., Duan, J., Liu, F., Han, L., Li, G., Sun, C., ... & Liu, H. (2021). Regulation of stem cell fate using nanostructure-mediated physical signals. Chemical Society Reviews, 50(22), 12828-12872. [HTML]
45. Wan, X., Liu, Z., & Li, L. (2021). Manipulation of stem cells fates: the master and multifaceted roles of biophysical cues of biomaterials. Advanced Functional Materials. [HTML]
46. Dora, D., Szőcs, E., Soós, Á., Halasy, V., Somodi, C., Mihucz, A., ... & Nagy, N. (2024). From bench to bedside: an interdisciplinary journey through the gut-lung axis with insights into lung cancer and immunotherapy. Frontiers in Immunology, 15, 1434804. frontiersin.org
47. Pradeu, T., Thomma, B. P. H. J., Girardin, S. E., & Lemaitre, B. (2024). The conceptual foundations of innate immunity: Taking stock 30 years later. Immunity. cell.com
48. Bailey, E. (2023). Identifying Practice Guidelines for Cranial Electrical Stimulation With Adolescents With Opioid Use Disorder. [HTML]
49. Mu, R., de Souza, S. C., Liao, Z., Dong, L., & Wang, C. (2022). Reprograming the immune niche for skin tissue regeneration–from cellular mechanisms to biomaterials applications. Advanced Drug Delivery Reviews, 185, 114298. [HTML]
50. Brunet, A., Goodell, M. A., & Rando, T. A. (2023). Ageing and rejuvenation of tissue stem cells and their niches. Nature Reviews Molecular Cell Biology, 24(1), 45-62. nih.gov
51. Sagaradze, G. D., Basalova, N. A., Efimenko, A. Y., & Tkachuk, V. A. (2020). Mesenchymal stromal cells as critical contributors to tissue regeneration. Frontiers in cell and developmental biology, 8, 576176. frontiersin.org
52. Oliveira, A., Simões, S., Ascenso, A., & Reis, C. P. (2022). Therapeutic advances in wound healing. Journal of Dermatological Treatment, 33(1), 2-22. [HTML]
53. Bekeschus, S., von Woedtke, T., Emmert, S., & Schmidt, A. (2021). Medical gas plasma-stimulated wound healing: Evidence and mechanisms. Redox biology. sciencedirect.com

54. Okonkwo, U. A., Chen, L., Ma, D., Haywood, V. A., Barakat, M., Urao, N., & DiPietro, L. A. (2020). Compromised angiogenesis and vascular Integrity in impaired diabetic wound healing. PloS one, 15(4), e0231962. plos.org
55. Hamushan, M., Cai, W., Lou, T., Cheng, P., Zhang, Y., Tan, M., ... & Ju, J. (2021). Postconditioning with red-blue light therapy improves survival of random skin flaps in a rat model. Annals of Plastic Surgery, 86(5), 582-587. [HTML]
56. Prado, T. P., Zanchetta, F. C., Barbieri, B., Aparecido, C., Melo Lima, M. H., & Araujo, E. P. (2023). Photobiomodulation with blue light on wound healing: a scoping review. Life, 13(2), 575. mdpi.com