Molecular Targets for the Novel Therapies of Inflammation and Wound Care

Palak Agrawal[1*], Sushma Singh[1], Nimisha Singh[1], Geetika Mishra[1], Maandvi Sharma[2]

[1]*Institute of Pharmacy, Shri Ramswaroop Memorial University, Lucknow-Dewa Road, Barabanki, 225003. U.P, India.*

[2]*CSIR-Indian Institute of Toxicology Research, Lucknow, 226001. U.P, India.*

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Abstract

Anti-inflammatory drugs, particularly steroidal and non-steroidal, are already the sole treatment options for inflammatory illnesses. Chronic use of these medicines has been linked to gastrointestinal, cardiovascular, as well as other serious side effects. New anti-inflammatory and wound healing drugs with selective effect and lower toxicity are desperately needed. Novel therapies acting on different molecular targets have shown promising results. Relevant studies (2003-2024) were identified through electronic searches of PubMed and Google scholar. The search used the keywords, including the following inflammation, wound care, signalling pathways, molecular targets of inflammation. Neutrophils and macrophages play a significant role in the release of mediators and phagocytosis at the site, Nf-kB signaling pathway and the JAK/Stat signaling pathway stimulate the production of mediators including IL-6, IL-1, and TNF-α, although their overproduction can have a variety of consequences. Cell therapy, MicroRNA, plasma protein therapy, COX-2 inhibitor with stem cells, combination of AMD3100 and Tacrolimus and combination of siRNAs with Plurogel for increasing wound healing time are among the approved and continuing clinical trial novel therapies mentioned. This study shows that these new therapeutics can interact with numerous targets and modify the dysregulated inflammatory pathways and mediators associated with normal and chronic wounds more effectively than standard anti-inflammatory medication treatments.

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Introduction

Inflammation is a major source of doom in today's contemporary lifestyle, as it is a common occurrence in the majority of acute and chronic disabling diseases. It is a mechanism that begins the body's healing process against invading organisms such as human infections, viruses, poisonous components, and dust particles. Most chronic illnesses are caused by infections, alcohol, hazardous radiations, cigarettes, food, and environmental contaminants, which are mostly produced by inflammation, according to large-scale studies conducted over the last several decades. Inflammation is characterized by a complex network of mediators, diverse cells, and the application of different pathways (1). Redness, swelling, heat, discomfort, joint stiffness, and loss of tissue function are all signs of inflammation. Fever, chills, fatigue/lack of energy, headaches, lack of appetite, and muscular stiffness are all possible flu symptoms (2).

Inflammations are divided into acute and chronic categories based on numerous inflammatory processes and cellular mechanisms. Acute inflammatory reactions have a preventive and defensive impact on the body when it is stimulated by invading pathogens or endogenous signals like injured cells, which cause tissue healing. It is a self-limiting process and a component of innate immunity that is triggered by immune cells and lasts for just a short period. This mechanism aids in the maintenance of tissue homeostasis as well as the resolution of acute inflammation. For instance, an acute inflammation caused by skin infection with S. aureus (3).

Chronic inflammation, on the other hand, is often referred to as uncontrolled acute inflammation, and it is responsible for a wide range of chronic inflammatory diseases, including diabetes, cancer, cardiovascular disease, eye diseases, arthritis, obesity, autoimmune disorders, asthma, Alzheimer's disease, and inflammatory bowel disease (4).

Inflammation is the cause of rheumatoid arthritis, psoriatic arthritis, and gouty arthritis, to name a few. Neurological illnesses can be caused by signaling pathway dysregulation, such as nuclear factor kappa-B (NF-kB), and STAT3 pathway, and others (5).

*** Corresponding Author:** Dr Palak Agrawal
Address: Institute of Pharmacy, Shri Ramswaroop Memorial University, Lucknow-Dewa Road, Barabanki, 225003. U.P, India.
Email: palak.hope2023@gmail.com

Anti-inflammatory drugs, mainly steroidal and non-steroidal, are the only current treatments for inflammatory illnesses. Chronic use of these medicines has been linked to gastrointestinal, cardiovascular, and renal problems, as well as other serious side effects. New anti-inflammatory drugs with selective effect and lower toxicity are desperately needed (6).

2. inflammatory response mechanisms

Signaling pathways initiate the inflammation response, which is the related elevation of inflammatory mediator levels in resident tissue cells and inflammatory cells selected from the circulation. Inflammation is a prevalent pathogenetic element in many chronic illnesses, including cardiovascular, intestinal, diabetes, arthritis, and cancer. Although the precise mechanism of the first stimulus and its location in the body are aspects that influence inflammatory response mechanisms, there is a common mechanism that governs them all: 1) Pattern recognition receptor activation; 2) Inflammatory pathway activation; 3) Inflammatory marker release; and 4) Inflammatory cell recruitment (7).

2.1. activation of pattern recognition receptors

Pathogen-associated molecular patterns (PAMPs) stimulate germline-encoded pattern-recognition receptors, which trigger the inflammatory response across both immune and non-immune cells (PRRs) (8). DAMPS (danger-associated molecular patterns) are pattern-recognition receptors that may detect a variety of endogenous signals that are triggered during tissue or cell injury (9).

Toll-like receptors (TLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), C-type lectin receptors (CLRs), and NOD-like receptors are all members of the PRR family (NLRs). TLRs are the most well-known PRRs; probably ten or more members of the TLR family are being found. They are mammalian PRRs that are engaged in the activation of the inflammatory response and are particularly well-protected (10).

TLR4 is a shared receptor for both DAMPs and PAMPs, indicating that infectious and noninfectious inflammatory responses are comparable. DAMP and PAMP transmission is carried out by (MyD88), a myeloid differentiation factor-88, as well as TLRs. TLR signals trigger an intracellular signaling cascade that results in nuclear translocation of transcription factors such activator protein-1 (AP-1) and NF-kB, as well as STAT3 or interferon regulatory factor 3 (IRF3) (11).

2.2. inflammatory marker release

Markers are essential in clinical applications to distinguish between normal and pathological biological processes and to measure therapeutic response. Inflammatory markers may be linked to the origins and consequences of numerous inflammatory disorders, such as endothelial dysfunction, cardiovascular disease, and infection, and may be used to diagnose these conditions (12).

Stimuli stimulate inflammatory cells like macrophages and adipocytes, causing them to produce inflammatory cytokines like IL-1, IL-6, and TNF-α, as well as inflammatory proteins and enzymes. These molecules might be used as biomarkers for illness diagnostic, prognostic, and therapeutic decision-making (13).

2.3. activation of inflammatory pathways

Intracellular signaling pathways are activated by inflammatory stimuli, which leads to the generation of inflammatory mediators. Microbial products and inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukins (IL) including IL-1, IL-6, IL-8, and chemokines influence inflammation by interacting with TLRs, TNF receptor (TNFR), IL-1 receptor (IL-1R), and IL-6 receptor (IL-6R). Important intracellular signaling pathways, including the nuclear factor kappa-B (NF-kB), mitogen-activated protein kinase (MAPK), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways, are engaged when receptors are activated (14) (15).

3. wound care

Early in the inflammatory stage, the wound caused by local aggressiveness begins to heal. Tissue regeneration and repair processes occur after the start of the lesions, either as a consequence of trauma or as a result of a specific pathological state. When all of the stimuli combine to form one wound, it breaks the physical continuity of functioning tissues. External or internal stimuli, also physical, chemical, electromagnetic, or thermal stimuli, can be used. Furthermore, when wounds occur, they may cause harm to individual organelles or the cells as a whole (16). It involves precise control of cell migration, proliferation, matrix deposition, and remodelling, as well as inflammation and angiogenesis. Small skin wounds heal in days, but bigger injuries caused by trauma, severe sickness, or major surgery might take weeks to heal, leaving behind a fibrotic scar that can impair tissue function (17).

Growth factors cause cell proliferation, resulting in the integration of dynamic changes including, soluble mediators, blood cells, extracellular matrix formation, and parenchymal cell proliferation. Tissue healing occurs as a result of these alterations (18).

3.1. Role of NF-κB signaling pathway in wound healing

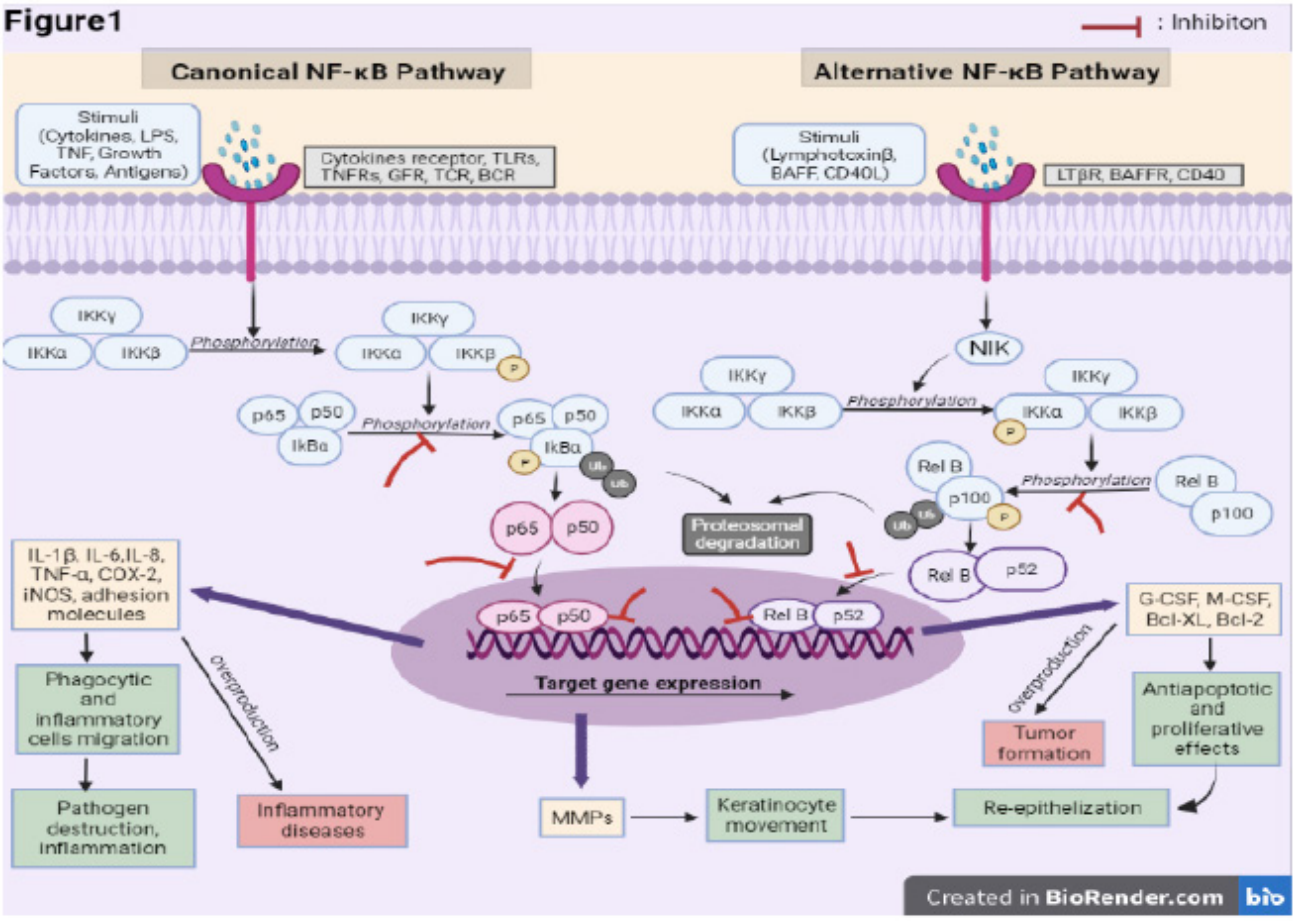
During wound healing, the traditional NF-κB pathway

is activated, resulting in the production of many cytokines, chemokines, adhesion molecules, enzymes that generate secondary inflammatory mediators, major histocompatibility complex class II antigens, and apoptosis inhibitors. In the early protective response to infections, factors including IL-1β, IL-8, IL-6, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, inducible NO-synthase, and cyclooxygenase-2 are essential. NF-κB activation, particularly in macrophages and epithelial cells, is required for phagocytic and inflammatory cells to migrate to tissues. Chronic illnesses such as rheumatoid arthritis, vascular inflammation psoriasis, vascular problems, diabetes mellitus, inflammatory bowel disease, and cardiovascular hypertrophy are caused by defects in NF-κB regulation, particularly up-regulation(19).

As NF-κB regulated genes are involved in cell proliferation (granulocyte colony-stimulating factor and macrophage colony-stimulating factor), transformation, and survival (Bcl-XL, Bcl-2) as well as anti-apoptotic and proliferative effects, can aid tumor formation and metastasis. The impact of NF-κB on the host is either protective or non-protective depending on the stimulatory environment. It is essential for re-epithelization during wound healing as it controls keratinocyte proliferation and migration. This transcription factor also regulates the production of matrix metalloproteinases, which aid keratinocyte mobility and regulate the release and stability of cytokines and growth factors for epidermal wound healing (20).

Pro-inflammatory cytokines such as IL-1β, tumor necrosis factor-α, IL-6, T- and B-cell antigen receptors, and angiotensin II activate the conventional NF-κB pathway. Viruses, bacterial lipopolysaccharides (activation via toll-like receptors connected to the NF-κB system by various adaptor proteins), certain protozoan parasites such as Trypanosoma cruzi, ROS, laser, phorbol ester, UV, and ionizing radiation are some known inducers of this pathway. The amplification loop occurs when NF-κB starts the production of IL-6, IL-1β, and TNF-α in the nucleus and then leads to the other kind of NF-κB activation in the cytoplasm. The indirect NF-κB pathway refers to the production of IL-1 and activation of the conventional NF-κB pathway in neighboring cells. This is why an excess of NF-κB, as well as insufficient activity, can result in delayed wound healing, as well as extended inflammation, anti-apoptotic, and proliferative effects, all of which are hazardous (21).

Figure 1. Molecular targets via Nf-kb signaling pathway

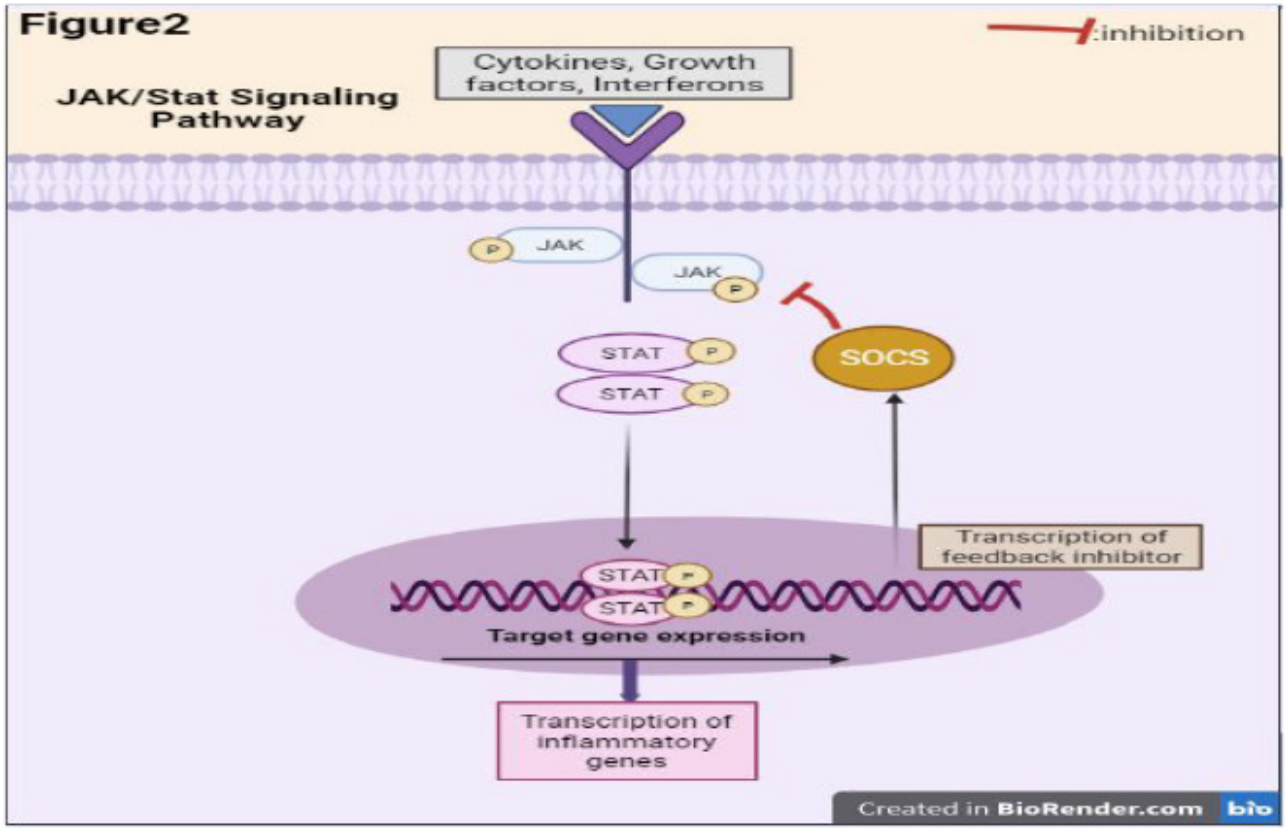


3.2. Role of JAK/STAT signaling pathway in wound healing

Growth factors and cytokines play a key role in wound healing by stimulating the activation of many signaling pathways, including JAK/STAT, through the participation of cells such as fibroblasts, keratinocytes, endothelial cells, and macrophages. Because of the disturbance in its control, persistent wounds may occur (22).

In Drosophila wound repair studies, the JAK/STAT signaling system was activated, promoting regenerative cell proliferation in conjunction with wingless (Wg) signaling (23).

Figure 2. Molecular targets via JAK/Stat signaling pathway.



Oncostatin M (OSM), a member of the IL-6 cytokine family, promoted tyrosine phosphorylation of STAT1 and STAT3 in injured intestinal epithelial cells in a time-dependent manner, with a peak after 10–30 minutes. There was a 16-fold rise in STAT5B, a 2-fold increase in STAT1 and STAT3, and a 1.5-fold increase in STAT6 (24).

When JAK/STAT signaling is controlled by SOCS proteins, it provides the greatest response. The JAK/STAT signaling system must be suppressed to treat autoimmune illnesses such as psoriasis and rheumatoid arthritis, as well as hematological malignancies such as prostate cancer (PCa) and sarcomas. In the absence of SOCS3, IL-6 functions as an immunosuppressive cytokine that lowers tumor necrosis factor (TNF) and specifically suppresses STAT3 signaling activity. SOCS4 and 5 have been related to the influence on EGF signaling via the modulation of its receptor, EGFR. The binding of EGF to EGFR activates the JAK/STAT pathway, resulting in receptor dimerization and tyrosine auto-phosphorylation, which leads to cell proliferation and migration. The study of EGFR activation by EGF and ERK 1/2 activation by TGFβ1 revealed a decrease of signaling capability in senescent fibroblast cells. MiR-7 inhibits EGFR signaling, which in turn impacts the functional pathways for cellular proliferation, migration, differentiation, and wound healing (25).

4. Novel therapies of inflammation and wound care

4.1. Growth factors

Since the 1980s, PDGF has been the only FDA-approved topical growth factor for the treatment of nonhealing wounds. In multiple randomized clinical trials, Becaplerim, a gel containing recombinant PDGF (the BB isoform), showed wound healing in diabetic foot ulcers (DFUs), and was authorized by the FDA for treatment of DFUs in 1997. In a retrospective examination of patients with neuropathic foot ulcers treated with Becaplerim, the healing rate increased by 32%. Despite good clinical trial outcomes, this therapy approach is not a first-line treatment due to its greater cost. Topical growth factor and chemokine administration is also difficult owing to the

wound's proteolytic environment, which quickly destroys given proteins. The pro-inflammatory environment causes a rise in the production of peptidases and proteases, such as MMPs, in non-healing wounds and when examined, higher levels of MMPs were seen in biopsies from DFUs compared to biopsies from non-diabetic patient's acute wounds. TIMP-2, an endogenous inhibitor of MMPs, was similarly shown to be lower in DFUs (26).

4.2. Chemokines

In db/db mice, a single injection of chemokines such as CCL2 enhanced the number of infiltrating macrophages to the site in the initial days after wounding and hastened wound healing, according to several studies. CXCL12 injections at the wound edge of genetically engineered mesenchymal stem cells (MSCs) have been shown to speed wound healing in rats. In 2012, a phase I clinical study in a pig full-thickness incisions model was started, in which non-viral gene therapy expressing human CXCL12 was injected into the wound margins. The results showed an acceleration in healing; however, the present state is uncertain. The chemokine inhibitor 35K, which suppresses the whole class of CC-chemokines, improved wound closure and neovascularization in mouse wounds, although further research is needed to determine how this strategy affects wound infections (27).

Table 1. New approaches for treatment of wound.

S.No.	Name of compound	Company	Composition/ Mode of action	Stage of Development	References
1.	BioChaperone PDGF-BB	Adocia	Recombinant PDGF-BB Angiogenesis and cell proliferation in diabetic foot ulcers	Phase III	(31)
2.	ChronSeal	Kringle Pharma	rhHGF HGF agonist	Phase II	(32)
3.	DSC-127	Derma Sciences	NorLeu3 -A(1 -- 7) Angiotensin agonist	Phase III	(33)
4.	EXC-001	Pfizer	Nucleic acid Reduce CTGF expression	Phase II completed	(34)to determine effects on reducing the severity of subsequent scars. Methods: In a randomized, double-blind, within-subject, placebo-controlled study, 23 female subjects (aged 28 to 55 years
5.	Galnobax	NovaLead	Esmolol b1-adrenoreceptor agonist	Phase II	(35)
6.	NanoDOX	Nanotherapeutics	Doxycycline MMP inhibitor	Phase II	(36)
7.	HO-03-03	Heal-Or	Peptide PKCα activation, delta inhibition	Phase II	(37)
8.	LL-37	Pergamum	Cathelicidin LL-37 LL-37 is implicated in wound healing	Phase II	(38)
9.	Nexagon	CoDa Therapeutics	Anti-connexin oligonucleotide Downregulates proteins that form gap junctions	Phase II	(39)and a great deal is known about extracellular communication within the wound site via cytokines [1, 2]. Here we show that direct cell-cell communication through connexin 43 (Cx43
10.	RGN-137	RegeneRx Biopharmaceuticals	Thymosin b4 synthetic analog Modulates MMP expression; stimulates angiogenesis	Phase III	(40)

PDGF: Platelet-derived growth factor; VEGF: Vascular endothelial growth factor; TGF-b2: Transforming growth factor beta2; MMP: Matrix metalloproteinases; rhHGF: recombinant human hepatocyte growth factor; CTGF: connective tissue growth factor; PKCα: Protein kinase Cα

4.3. Cell therapy

In rats, wound therapy with Mesenchymal Stromal Cells (MSCs) resulted in an increase in anti-inflammatory IL-10, a decrease in the number of inflammatory cells, and a drop in pro-inflammatory cytokines IL-1 and TNF-α. MSC therapy has also been shown to cause macrophage polarization from M1 to M2 in several investigations. The therapeutic potential of topically administered autologous and allogeneic MSCs in chronic wound healing and second-degree burns is still being investigated in phase I or II clinical studies. Macrophages were cultivated with TNF-α and IFN-γ and injected into the wound bed of rats with streptozotocin-induced hyperglycemia for cell therapy wound treatment. As a result, wounds treated with macrophage injections healed faster than those that were not treated. Wounds of healthy or db/db mice were treated with IL-4- or IL-10-activated macrophages in another research, which did not enhance healing in healthy mice and even delayed wound healing in db/db animals (28).

4.4. Combination of AMD3100 and tacrolimus

In mice and rats, it has been observed that when AMD3100 and tacrolimus are combined, the healing period of a surgical incision is reduced by one-quarter. Other uses for these two medicines have previously been authorized by the FDA. They also help to decrease scar tissue around the incision. The promise of the two medicines for wound healing in animals was found by chance while experimenting to find strategies to avoid liver transplant rejection. AMD3100 transports stem cells from the bone marrow to the circulation, allowing them to be collected and preserved for cancer patients undergoing chemotherapy. Tacrolimus, on the other hand, suppresses the immunological response. In their investigation, the researcher and his colleagues discovered that this combination of medicines not only reduced liver graft rejection but also improved wound healing in mice. AMD3100 pushes bone marrow stem cells into the circulation, whereas tacrolimus activates cells in wound sites to release chemicals that attract stem cells (29)
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4.5. Combination of siRNAs with PluroGel

Dr. Sharp and colleagues found in 2015 that an enzyme known as fidgetin-like 2 (FL2) stops skin cells from migrating towards wounds to repair them. He reasoned that lowering FL2 levels would allow healing cells to get at their location more quickly. As a result, he and his colleagues created small interfering RNA molecules (siRNAs) that target the FL2 gene and block it. When siRNAs were encapsulated in nanoparticles and sprayed on skin wounds in mice, the wounds healed quicker than the ones that were not treated. Dr. Sharp used PluroGel, a protective gel that keeps wounds moist and has antibacterial characteristics when applied to bandages and other wound dressings, boosts the siRNAs' wound-healing capacity in the current study. Dr. Sharp also included the siRNAs in collagen microparticles, a naturally occurring protein that quickly releases its siRNA "cargo" when it comes into contact with the skin. Mice were given the FL2-siRNA/PluroGel combination via skin excisions or burns. For comparison, mice treated with PluroGel alone and mice treated with PluroGel with siRNA that did not target the FL2 gene were utilized in experiments including both types of skin injuries (30).

Conclusion

Overall, this study shows that these new therapeutics can interact with numerous targets and modify the dysregulated inflammatory pathways and mediators associated with normal and chronic wounds more effectively than standard anti-inflammatory medication treatments, which have significant adverse effects.

Conflict of interest

The author claims they have no financial or other conflicts of interest.

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