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Review Article

Molecular mechanisms of wound healing: the role of zinc as an essential microelement

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Abstract

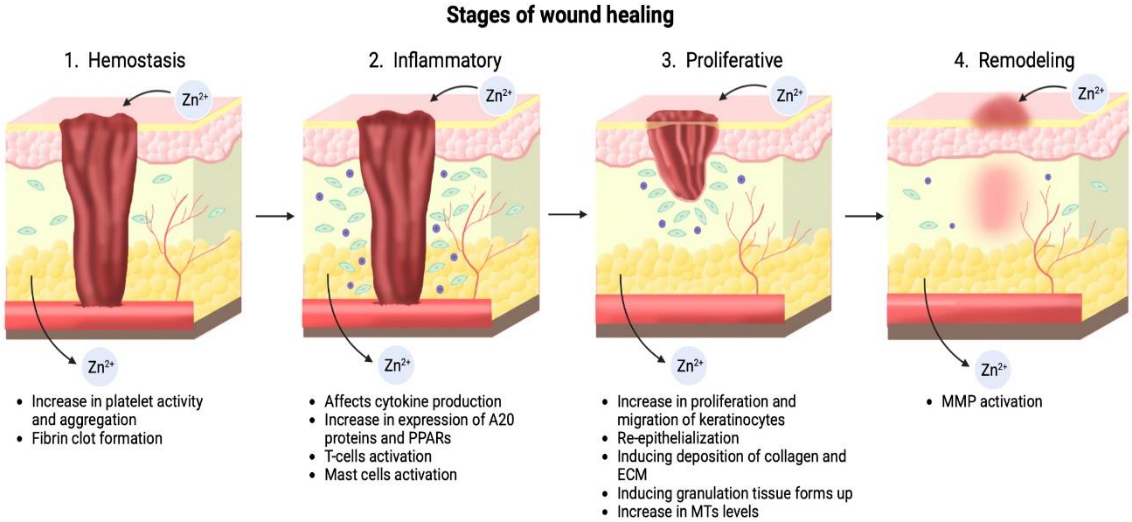
Introduction: In the course of evolution, humans developed a number of complex multi-step wound healing mechanisms which limit the infectious agents access to the bloodstream, protect the organism from blood loss, and restore skin integrity. The process of skin wound healing includes the following stages: haemostasis, inflammation, proliferation, and remodeling. These processes are possible because of modulators, growth factors, cytokines, matrix metalloproteinases and cellular receptors, as well as some trace elements like zinc.

Materials and Methods: The presented data was analyzed and compiled using all relevant articles describing the role of zinc in blood coagulation, proliferation, damaged tissues regeneration and angiogenesis.

Results and Discussion: There are some on-going studies about zinc effects on blood coagulation, proliferation, damaged tissues regeneration and angiogenesis. However, molecular mechanisms of these processes are not yet fully understood and require further study. The analysis of scientific efforts to investigate the role of zinc in wound healing molecular mechanisms is especially relevant to the understanding of treatment of skin wound injuries.

Conclusion: Wound healing is a complex multi-phase process consisting of several phases. Each stage involves metal ions, primarily zinc, which stimulates re-epithelialization, decreases inflammation and bacterial growth. The use of known zinc-based drugs is accompanied by side effects and low efficacy due to low skin absorption. These factors significantly limit use of such drugs and highlight the urgency of finding new, more effective and safe treatment. The emerging field of nanobiotechnology may provide an alternative platform to develop new therapeutic agents for the wound healing process.

Graphical Abstract



Keywords

haemostasis, inflammation, keratinocyte, metalloproteinases, platelets, proliferation, remodeling, skin, wound healing, zinc.

Introduction

The integrity of skin plays an important key role in maintaining physiological homeostasis, viability and internal organs functioning. Deep understanding of the physiology of wound healing is a theoretical base for developing new therapeutic approaches in treatment of wounds. Zinc plays an important role in wound healing processes.

Zinc is an essential micronutrient in human body. It is involved in growth and development processes, bone tissue metabolism, and functioning of nervous and immune systems (Roohani et al. 2013). Approximately 3000 zinc-dependent proteins play an indispensable role in transcription, apoptosis, deoxyribonucleic acid (DNA) repair, extracellular matrix (ECM) regulation, and antioxidant defence (Pawlak et al. 2012; Zheng et al. 2015; Cho et al. 2016; Kimura and Kambe 2016). Intracellular Zn homeostasis in mammals is regulated by two types of zinc transporters: ZnTs and ZIPs (Bin et al. 2018; Hoch et al. 2020). ZIP family members provide an inflow of Zn^{2+} from the extracellular space into cells or from the intracellular zinc ions stock into cytoplasm, increase intracellular Zn $[Zn^{2+}]i$ (Zhang et al. 2019). ZnT isoforms regulate Zn^{2+} outflow from cytosol to the extracellular space or to intracellular organelles, decreasing their cytoplasmic concentration (Fukada and Kambe 2011; Kambe 2012).

Human skin contains about 20 % of total zinc content in the body, being second only to muscle fibers and bone tissue. Zinc plays an extremely important role in the physiology of skin and its appendages. Currently, it has been demonstrated that wound healing process goes more slowly in zinc-deficient conditions (Lin et al. 2017).

Within the first twenty-four hours from injury, zinc content in the wound increases by 15–20 %, reaching its maximum of 30 % during the period of intensive granulation tissue formation and epidermis proliferation (from 8 hours to 3 days after surgery). This increase in Zn^{2+} may be attributable to recruitment of cells with high Zn^{2+} content (including erythrocytes, neutrophils, lymphocytes, and platelets), and may represent a mechanism by which Zn^{2+} is delivered to sites of vascular damage (Ahmed et al. 2021). In the late stages of healing, zinc content decreases; it points out to mitotic activity decrease and scar tissue maturation (Lin et al. 2017).

Up to date, the role of zinc in burn injury (Adjepong et al. 2016; Kurmis et al. 2016), subcutaneous abscess, surgical interventions (Mirastschijski et al. 2013), and bed sores (Posthauer 2014) has been also demonstrated. Zinc deficiency and its metabolism disorders are the pathogenetic link in a number of skin diseases (Gupta et al. 2014; Maxfield et al. 2022) and delay wound healing (Kogan et al. 2017). However, the mechanisms by which zinc exerts its activity have not been fully studied yet.

Wound healing stages

A wound is a disruption of anatomical continuity of skin or mucous membranes caused by an external mechanical action, with possible damage to deeper lying tissues. Wound healing process includes regeneration of the epithelial wound and formation of a scar consisting of connective tissue cells. Wounding is followed by activation of coagulation processes, and a blood clot consisting of erythrocytes, fibrin, fibronectin and complement system proteins gets formed on the wound surface. The blood clot acts as a barrier which stops bleeding and cell migration caused by growth factors, cytokines and chemokines release at the site of skin injury.

At the first stage of wound healing, vascular endothelial growth factor (VEGF) is released; it causes swelling of the surrounding tissues. After the blood clot on the outer surface gets dried, a crust forms. Then, during the first twenty-four hours, neutrophils accumulate at the wound edges and migrate to the formed fibrin clot. They secrete proteolytic enzymes, which help to initiate the wound cleansing from cellular detritus. In the period from 24 to 48 hours after the wounding, epithelial cells from its edges start migration and proliferate along the dermis surface, thus forming basement membrane components again. Then, they move to the midline of the evolving crust, and form a thin but continuous layer that closes the wound.

Three days after the wounding, macrophages replace neutrophils, granulation tissue begins to penetrate into the wound area, and well-identifiable collagen fibers appear on the wound edges. Macrophages are the main cellular components that promote angiogenesis and ECM formation, carry out tissue repair processes, cleansing from extracellular detritus, fibrin, and other foreign components. At the meantime, epithelization goes on actively, which leads to the restoration of the normal epidermis thickness.

Five days after the wounding, neovascularization process reaches its peak as the wound space gets filled with granulation tissue. Newly formed vessels become permeable to blood plasma proteins and fluids, which easily pass into the extravascular space, causing tissue swelling. Fibroblasts migration into the wound space and their subsequent proliferation occur under the influence of tumor necrosis factor (TNF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), and fibroblast growth factor (FGF), interleukin-1 (IL-1). Fibroblasts begin to produce proteins that constitute ECM, as well as collagen fibers in large quantities. After the surface cell differentiation, the epidermis mature architecture begins to form with keratinization of its surface.

During the second week, collagen accumulation and fibroblast proliferation process goes on. At this time, leukocyte infiltration of the wound area decreases, edema goes down, and vascularization decreases. As a result of collagen fiber accumulation inside the forming scar, as well as decreased number of vessels, the wound becomes whiter in appearance.

By the end of the first month, the scar consists of connective tissue free of inflammatory cells. Despite the fact that the scar is covered with normal epidermis, the skin appendages destroyed during the wounding process do not get restored. Over time, one may notice an increase in the formed scar mechanical tensile strength.

Thus, wound healing is a complex and dynamic process that can be divided into a number of phases: 1) haemostasis with coagulating fibrin clot formation (from several seconds to 1 hour); 2) inflammatory response (from several minutes to several days); 3) proliferation (begins 18–24 hours after wounding and lasts from several days to weeks); 4) matrix remodeling and scar formation (over several months) (Diegelmann and Evans 2004).

Each wound healing phase duration depends on various factors: type and size of the wound, age, physical condition, comorbidities, wound location, and treatment (Mirastschijski et al. 2013).

These phases involve a wide range of biologically active substances: reactive oxygen species (ROS), cytokines, growth factors, ECM proteins, as well as platelets, leukocytes, keratinocytes, fibroblasts, immune, epithelial, and stem cells.

The role of zinc in wound healing

At each of the wound healing stages described above, zinc plays an important biological role, which is primarily due to its effect on cell behavior and enzymatic activity regulation.

Haemostasis

Haemostasis system is based on maintaining balance between coagulation and anticoagulation systems. When a vessel is damaged, blood components pass into the wound area, and vasoactive factors get released, which leads to blood coagulation and haemostasis cascade activation.

Platelet haemostasis

Platelets are an important element of coagulation system; they release vasoactive substances, growth factors, and pro-inflammatory cytokines. Initially, little attention was paid to the role of zinc in platelet activation. The studies were mostly focused on the role of calcium ions. However, it has been known for decades that zinc also promotes platelet activity and aggregation and serves as an important haemostatic co-factor, acting as both a platelet agonist and a secondary messenger. Indeed, as far back as in the twentieth century, experiments on zinc-deficient rodents showed increased bleeding tendency, prolonged tail bleeding time and more difficult parturition (Apgar 1968; O’Dell et al. 1977; Emery et al. 1990).

It illustrates a potential role of Zn^{2+} during thrombosis and haemostasis and highlights its recognition as an intracellular and extracellular platelet regulator (Ahmed et al. 2021).

Currently, the possibility of synergistic relationship between calcium and zinc ions is assumed, but no evidence to this theory has been provided yet (Watson et al. 2016). An interesting fact is that Zn^{2+} often interacts with proteins with a higher affinity than Ca^{2+} (Dudev and Lim 2003).

Zinc ions are involved in platelet biogenesis from megakaryocytes, but these processes have not been studied yet (Mammadova-Bach and Braun 2019). Hematopoietic Zn^{2+}-finger gene (Hzf) is expressed in megakaryocyte lineage, and Hzf domain modification with zinc fingers leads to abnormal synthesis of α-granules, packing of substances into them, and platelet biogenesis (Kimura and Kambe 2016). To maintain the required level of zinc, megakaryocyte membrane contains various ZIP/ZnT transporters (Hojyo and Fukada 2016; Kimura and Kambe 2016; Hara et al. 2017; Kambe et al. 2017; Bin et al. 2018); however, to understand the molecular mechanisms of capture, storage, and release of zinc ions by platelets, further studies of zinc transporters subcellular localization and ZIP/ZnT isoforms contribution to zinc homeostasis are required (Mammadova-Bach and Braun 2019).

Due to their active transport mechanisms, platelets are able to absorb Zn^{2+} from blood plasma and accumulate them in α-granules (Taylor and Pugh 2016; Kiran Gotru et al. 2019). Apart from α-granules that contain a significant part of zinc (Mammadova-Bach and Braun 2019), zinc is present in platelet cytosol, either bound to metallothionein (MT) or in a free state.

Mechanisms of platelet function regulation with the participation of zinc have not yet been studied. K.A. Taylor and N. Pugh (2016) presented a model that describes the mechanisms of platelet activation, which are influenced by zinc ions. According to this model, amounts of $[Zn^{2+}]i$ significantly increase after vascular damage and primary activation of platelets by collagen. It is assumed that this is caused by membrane ion channels and transporters. Also, a part of ions is released from internal storages (Taylor and Pugh 2016). Labile zinc acts as a platelet agonist: at low concentrations, it potentiates platelet response to other agonists, and at high concentrations it stimulates aggregation (Watson et al. 2016).

Zinc ions increase GpVI receptor affinity for collagen, thus inducing primary activation of platelets, release of thromboxane A_2 (TxA_2) and α-granules (Watson et al. 2016). Zinc ions also interact with protein kinase C (PKC), activating tyrosine phosphorylation for signaling proteins and a subsequent change in GpIIbIIIa glycoprotein conformation, which promotes their binding to fibrin, and clot formation (Ahmed et al. 2019).

Zinc is also a regulator of platelet granule biogenesis and release. A-granules contain fibrinogen, prothrombin, coagulation factors V, XI, XIII, von Willebrand factor (VWF), fibronectin, P-selectin, PDGF, epidermal growth factors (EGF), β-thromboglobulin, albumin, kallikrein, α-2-antiplasmin (Taylor and Pugh 2016). Dense granules contain adenosine triphosphate (ATP), adenosine diphosphate (ADP), guanosine diphosphate (GDP), serotonin, calcium, and inorganic phosphates. The content of granules enhances aggregation of platelets, maintains integrity and stimulates restoration of vascular wall and connective tissue.

Platelet activation depends on rapid phosphorylation and dephosphorylation of key signaling proteins, especially tyrosine residues. According to the study, even a slight increase in $[Zn^{2+}]i$ is able to inhibit activity of many tyrosine phosphatases and maintain phosphorylation of platelet proteins (Taylor and Pugh 2016). Tyrosine kinases that regulate protein tyrosine phosphorylation after activation of platelets, also get activated.

An important factor of platelet activation regulation are changes in intracellular level of cyclic nucleotides: cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). According to the studies, zinc prevents further cAMP synthesis by changing adenylate cyclase conformation (Klein et al. 2004). By inhibiting cyclic nucleotide phosphodiesterase (PDE), zinc ions increase cGMP levels (Wätjen et al. 2001). A decrease in cAMP and and increase in cGMP lead to a lower influence of negative regulation in platelet activation process, and promote their aggregation.

The role of Zn^{2+}-dependent signaling mechanisms on ROS formation during platelet activation has been shown (Ruttkay-Nedecky et al. 2013; Lopes-Pires et al. 2021). Since ROS regulate the storage of MTs containing zinc ions (Ruttkay-Nedecky et al. 2013), platelet incubation with MT or administration of MT to mice suppresses the aggregation response to collagen by reducing calcium ions mobilization and TxA_2 synthesis (Ruttkay-Nedecky et al. 2013) (Fig. 1).

After platelet activation, degranulation sets in; it promotes coagulation, wound healing, and inflammation.

Vascular haemostasis

Zinc released from α-granules participates in fibrin clot formation process along with calcium ions. The basic reaction is soluble fibrinogen conversion into insoluble fibrin fibers via fibrinopeptide A removal by thrombin. Fibrin fibers polymerize into protofibrils, and their cohesion, in turn, forms a fibrin fiber. Accumulation of fibrin fibers forms a network within the blood clot, which then becomes a thrombus basis.

Many factors influence the formation process, structure and properties of fibrin, and, consequently, fibrin network: ionic strength, medium pH, various exogenous substances, and medium ionic composition (calcium and zinc ion concentration). An increased thrombin activity leads to formation of a network consisting of thinner fibrin fibers, which, in turn, form an extensive network with a smaller pore diameter. Such network will be more rigid, and it will significantly increase the chances of a thrombus separation and subsequent development of thromboembolism. A decreased thrombin activity leads to formation of thicker fibers and a less extensive network with a large pore diameter. In this case, a more flexible thrombus is formed, and it can change its shape under external mechanical factors and retain its function (Weisel and Litvinov 2017).

The main modulator of mechanical rigidity is factor XIII, which contributes to fibrin fiber compaction and to formation of an elastic network together with Zn^{2+} from activated platelets (Weisel and Litvinov 2017).

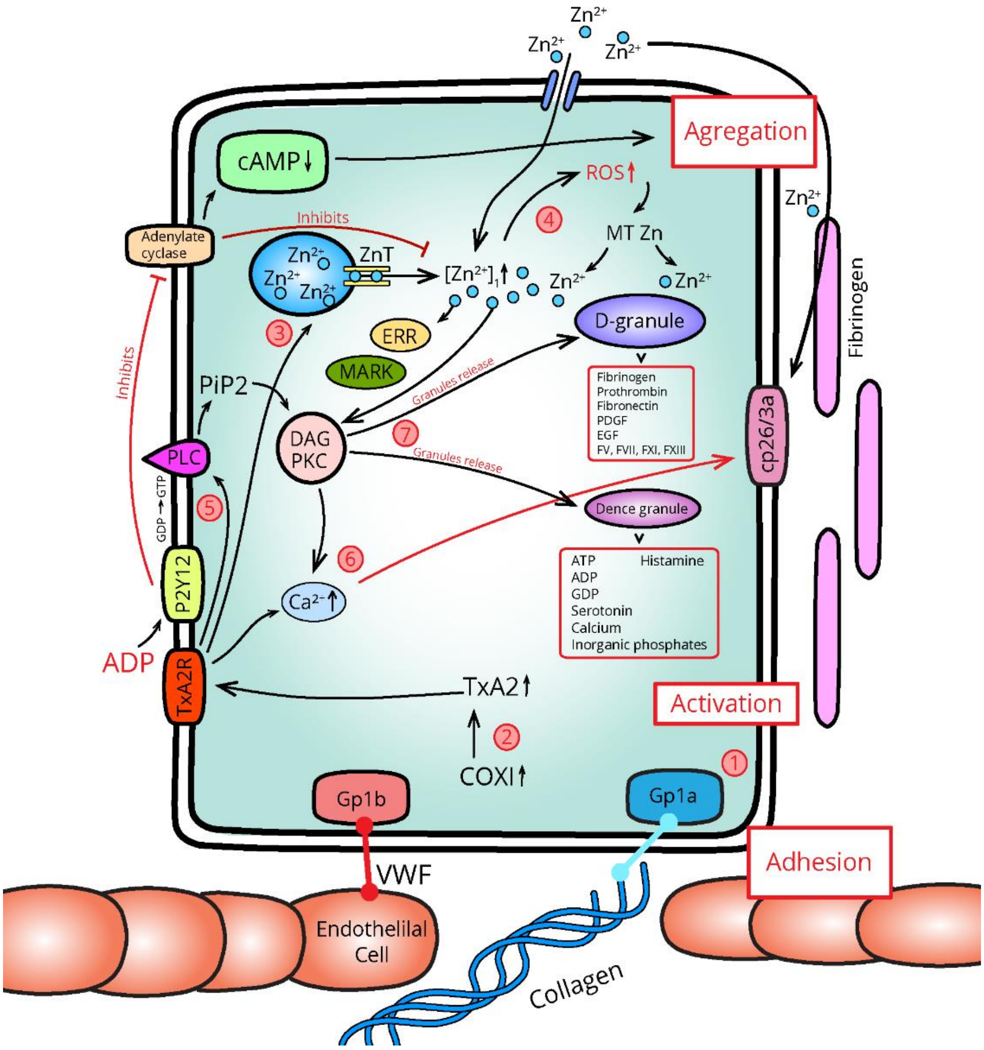


Figure 1. Adhesion. (1) Platelets respond to vessel injury by interacting with basal membrane collagen via collagen-sensitive platelet receptor glycoprotein 1a (Gp1a), and glycoprotein of endothelial and subendothelial tissue cells, von Willebrand factor (VWF), which binds to a specific receptor, glycoprotein 1b (Gp1b) via the A1 domain and to collagen via the A3 domain. **Activation.** (2) Increased activity of cyclooxygenase type 1 (COX 1) enhances TxA_2 synthesis, which results in Zn^{2+} release from intracellular stores (3). Increased ROS generation results in the reduction of thiols on MT binding Zn^{2+}, and leads to Zn^{2+} release (4). Affected by TxA_2, Gq proteins get activated (5), which leads to an increase in inositol-3-phosphate formation, an increase in Ca^{2+} content in the platelet, and a change in Gp2b/3a conformation (6). An increased content of $[Zn^{2+}]$i activates the PKC and leads to α-granule release (7). $[Zn^{2+}]$i inhibits adenylate cyclase, reducing cAMP and promoting platelet **aggregation** (8).

Much earlier studies showed that, at elevated Zn^{2+} concentrations, thrombin binding to fibrin and fibrinopeptide A cleavage decreased (Marx and Hopmeier 1986; Hopmeier et al. 1990). Accordingly, at lower ions concentrations, thrombin adsorption increased. Thus, one can conclude that Zn^{2+} participation in fibrin clot formation is focused not on fibrin formation stimulation, but on its subsequent transformations and fibrin network formation.

Zinc ions regulate several stages of coagulation. For example, they bind to factor XII, inducing conformational changes, thereby improving its susceptibility to enzymatic activation (Wang et al. 2019). Zn^{2+} binds to such neutralizing proteins as fibrinogen, high-molecular-weight kininogen (HMWK) and histidine-rich-glycoprotein (HRG), increasing their affinity for anticoagulants and is thus an important regulator of glycosaminoglycans (GAGs) neutralization and haemostasis (Sobczak et al. 2018). It has been proved that zinc deficiency disrupts coagulation cascade and fibrin formation, which leads to a bleeding time increase (Taylor and Pugh 2016).

Conformational changes in factor XII under influence of zinc ions induce the kallikrein-kinin system (Chaudhry et al. 2020). As a result, bradykinin releases and accumulates on endothelial cells surface, and it promotes adhesion of inflammatory immune cells.

Thus, zinc can promote haemostasis by virtue of several platelets aggregation modulating mechanisms, coagulation, and fibrin network formation (Mammadova-Bach and Braun 2019). Zinc acts as a haemostatic regulator after degranulation, as a platelet agonist, and also as an intracellular regulator of platelet responses (Ahmed et al. 2021). Nevertheless, this model still remains incomplete. There is a need of further studies aimed to elucidate the paths by which ions enter platelet cytosol, and zinc-induced signaling pathways.

Coagulation-induced haemostasis provides the basis for wound healing inflammatory phase and tissue formation. Haemostatic plug creates a matrix into which effector cells and ECM components migrate.

Inflammation

The inflammation stage is a complex process involving coordination between a variety of cells. The inflammatory response to wounding promotes rapid migration of keratinocytes from the wound edges and from hair follicles and sweat glands into the wound bed where matrix molecules begin to appear. Fibroblasts begin to produce new cells; ECM, EGF and transforming growth factor (TGF) initiate epithelialization. Epithelialization is a sequence of migration, proliferation and differentiation of keratinocytes and is stimulated by altered ECM proteins and cytokines (Rousselle et al. 2019). The main cytokine producers are macrophages and other immune cells.

Numerous studies have shown that zinc affects cytokine production by reducing nuclear factor-kappa B (NF-kB) activation (Voelkl et al. 2018). Rel/NF-κB transcription factor family regulates expression of many genes responsible for immune system functioning, inflammatory response formation, and for other biological processes. Besides, NF-κB plays a critical part in regulating survival, activation, and differentiation of innate immune cells and inflammatory T-cells (Liu et al. 2017).

Various external and internal factors can cause activation of NF-kB, for example, bacterial and viral infections, inflammatory cytokines, UV- and γ-radiation, physiological conditions (ischemia, hyperosmotic shock), and oxidative stress (ROS). NF-kB transcription factor family consists of five proteins: p65 (RelA), RelB, c-Rel, p105/p50 (NF-kB1), and p100/52 (NF-kB2). By binding to each other, they form about 15 different transcriptionally active homo- and heterodimeric complexes. In cells, NF-kB dimers stay in a complex with inhibitor of kappa B (IkB), which allows them to remain normally inactive. However, upon signaling pathway activation, these complexes are phosphorylated by IkB kinase (IKK), and it leads to NF-kB dimer activation, its nuclear translocation, and induces transcription of target genes. Activation of NF-kB signaling pathway induces the formation of molecules and mediators that regulate immunoregulatory proteins synthesis (serum amyloid, a component of C3 complement system, VCAM, ICAM, TCR α, β, MNC-1), cytokines (TNFα, IL-1, IL-6, IL-12), IkB kinases (IkBα, c-Rel, p105), granulocyte-macrophage colony-stimulating factor, and apoptosis regulators (Bcl-XL, IAPs) (Oeckinghaus and Ghosh 2009).

It is known that zinc is involved in NF-κB pathway regulation; however, its impact is rather controversial. For example, some studies report that zinc is necessary for NF-kB binding to DNA in purified or recombinant NF-kB p50 lines or T-helper cells (Zabel et al. 1991; Prasad et al. 2001).

On the other hand, it has been shown that zinc is able to inhibit activity and expression of cyclic nucleotide PDE, which results in elevation of cGMP cellular content. Zinc-mediated cGMP elevation led to cross activation of protein kinase G. By this mechanism, zinc suppresses activation of IKK and NF-κB and subsequent TNF-α production (von Bülow et al. 2007; Haase et al. 2008). Besides, it has been shown that ZIP8-mediated zinc upregulation inhibits IKK upon binding to a specific site within the kinase domain. Thus, ZIP8 negatively regulates the NF-κB pathway, indicating that the zinc-ZIP8-NF-κB axis plays crucial roles during host defense (Bin et al. 2018).

The main mechanism for suppressing zinc-induced inflammation is an increase in expression of zinc-containing A20 proteins and peroxisome proliferator-activated receptors (PPARs). Zinc finger protein A20 (also known as Tumor Necrosis Factor Alpha-Induced Protein 3 or TNFAIP3) is a central negative regulator of NF-kB. The ability of zinc to regulate A20 is determined by the presence of seven “zinc fingers” in its C-terminal domain. Little is known about the molecular mechanisms that regulate the ubiquitin-editing and NF-κB inhibitory function of A20. It is likely that A20 acts at several stages of NF-κB signaling pathway, inhibiting TNF- and TLR4-induced NF-κB activation, which ultimately leads to termination of signaling and decreases production of downstream mediators (Vereecke et al. 2009; Shembade et al. 2010).

PPAR is a family of nuclear receptors with two “zinc fingers” in the structure of DNA-binding domain (Shi et al. 2020). The PPARs consist of three main subtypes: α, β/δ, and γ. It has been found out that PPAR functions are quite extensive. Not only do they activate proliferation of peroxisomes, but also control metabolism of carbohydrates, fats and proteins in the cell, the processes of cell differentiation and apoptosis. PPARs participate in the transcriptional regulation of metabolism, inflammation, angiogenesis, and fibrotic reaction (Nakano et al. 2020.; Tobita et al. 2020). It is known that all PPAR subtypes get activated to suppress inflammation through inhibition of NF-κB (Korbecki et al. 2019; Tobita et al. 2021). (Fig. 2).

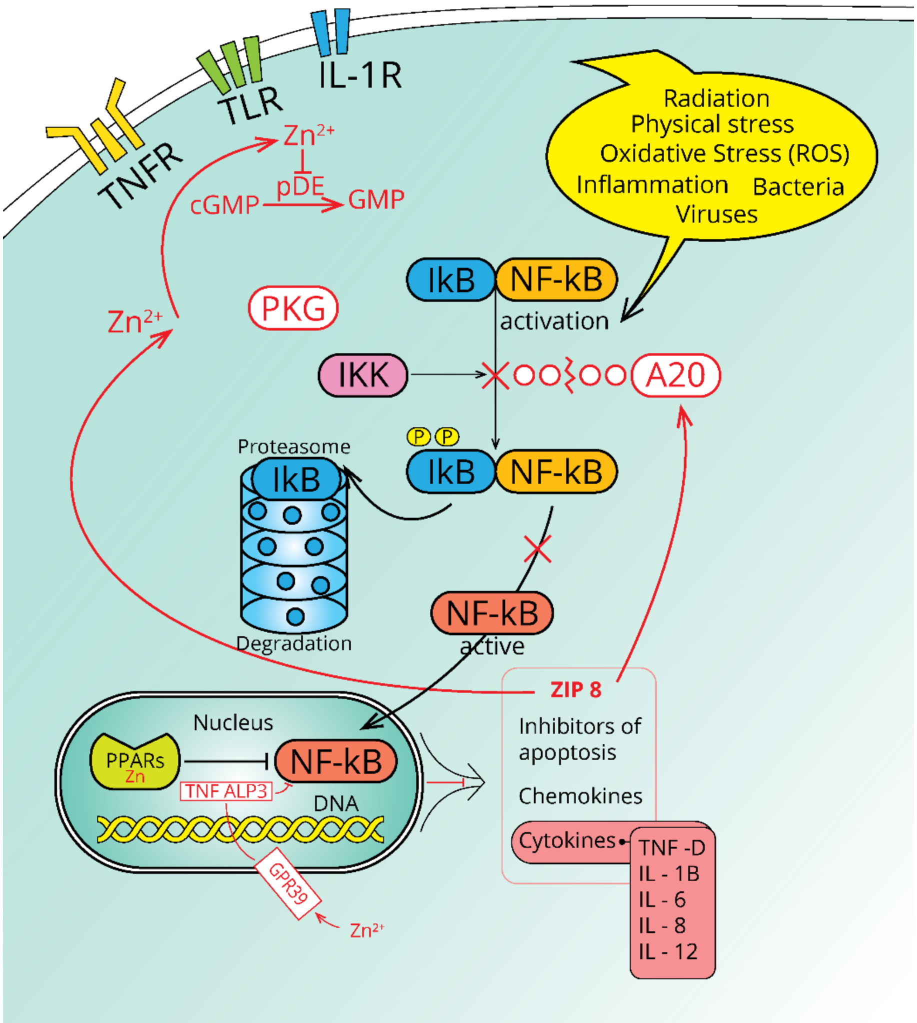


Figure 2. The role of zinc in NF-κB signaling pathway.

Besides, PPAR-α and β/δ play an important part in wound healing (Gupta et al. 2015). A model of rat alkaline corneal burn was used to demonstrate accelerated healing after topical application of ophthalmic solution of PPAR agonists; accelerated healing was achieved due to enhancement of proliferative capacity and inhibition of inflammation (Tobita et al. 2021).

An important role in wound healing belongs to the immune system, which is especially sensitive to changes in zinc levels. It is known that zinc transporters (ZIP6, ZIP8, ZIP10) are involved in many immune responses (Bin et al. 2018; Thingholm et al. 2020). For example, it has been shown that T-cell activation directs zinc influx from extracellular and subcellular sources through the ZIP6 and ZIP8 zinc transporters, respectively (Yu et al. 2011; Bin et al. 2018). ZIP6 is an important molecule in CD4 T cells (Bin et al. 2018). T-cell receptor (TCR) activation on the surface of CD4 T cells promotes their differentiation into various T-cells, including Th1, Th2, Th17, and Treg cells. TRC activation induces ZIP8 expression in human T-cells. An increased ZIP8-mediated zinc level blocks calcineurin activity, and, thereby, the phosphorylation of CREB for INF-gamma transcription. By the present time, it has been shown that ZIP8 is important for various immune cells associated with innate immunity (Bin et al. 2018).

Zinc deficiency reduces monocyte adhesion to endothelium (Lee et al. 2012), cytokine production by granulocytes, phagocytosis of macrophages, activity of cytokines secreted by T-cells and macrophages, activity of NK-cells, differentiation of T-cells, and release of certain interleukins and antibodies, and granulation of neutrophils (Kuźmicka et al. 2020).

Zinc ions are an important component of thymulin, thymopoietic hormone necessary for proliferation and differentiation of Th-cells (Prasad 2020). Besides, zinc deficiency negatively affects the expression of IL-2 and IFN-γ from Th1-cells. In turn, IL-2 deficiency reduces lytic activity of NK-cells and cytotoxic T-cells, while IFN-γ deficiency inhibits macrophage functions (Prasad 2020). Zinc deficiency also increases production of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α (Wessels et al. 2013).

It has been shown that B-lymphocytes contribute to cleaning of wounds and also produce antibodies that detect damaged tissue. Zinc deficiency caused by ZnT7 protein-disrupted transportation of ions inhibits CD145-stimulated p38 MAPK phosphorylation, which ultimately leads to inhibition of T-cell-mediated activation of B-lymphocytes.

Zinc-containing enzyme alkaline phosphatase is a marker of angiogenesis early stages, typical for post-traumatic inflammation and connective tissue proliferation. Alkaline phosphatase dephosphorylates adenosine monophosphate (AMP) with formation of adenosine, which has a pronounced anti-inflammatory effect and is important for interrupting wound process inflammation phase.

Currently, the role of mast cells (MCs) is being studied at various stages of wound healing, including inflammation, proliferation, and remodeling. Upon skin injury, they release pro-inflammatory and immunomodulatory mediators, predominantly histamine, VEGF, IL-6, IL-8, which increase endothelium permeability and vasodilation, and promote migration of monocytes and neutrophils to the injury site. MCs stimulate fibroblast proliferation phase via IL-4, VEGF, basic fibroblast growth factor (bFGF) to produce a new ECM. Mediators released from MCs (FGF-2, VEGF, PDGF, TGF-β, nerve growth factor (NGF), IL-4, IL-8) promote neoangiogenesis, fibrinogenesis, and re-epithelization (Komi et al. 2020). Currently, there is no doubt that zinc is involved in activation of mast cells and is required both for their degranulation and for production of cytokines (Nishida and Uchida 2017, 2018).

It was found that Zn and MCs induce IL-6 production from skin fibroblasts through signaling pathways mediated by the Zn G-protein-coupled receptor 39 GPR39 (Nishida et al. 2019). GPR39 is an orphan receptor bound with G protein. It is expressed in peripheral tissues including skin, intestine, and brain. To date, data have been accumulated showing that GPR39 mediates Zn-dependent signaling in keratinocytes, colonocytes, and neurons (Hershfinkel 2018).

Therefore, inflammation phase is aimed at repairing damaged tissues by activating cells and releasing inflammatory mediators, interaction between which causes local and systemic acute inflammatory response development. About 3-5 days after wounding, the signs of inflammation decrease and proliferation stage develops.

Proliferation

Proliferation phase consists of three main processes: re-epithelialization, including keratinocyte proliferation and migration over the wound bed, granulation tissue formation, including proliferation, migration, and synthesis of ECM components by fibroblasts, and neovascularization.

At a time of wound healing, it is important to suppress the inflammatory process as early as possible and prevent it from becoming chronic. It is necessary to eliminate inflammation and promote re-epithelialization and shrinkage of wound Treg (Nosbaum et al. 2016). A number of studies have shown that zinc supplements regulate Treg signaling pathways and contribute to their induction and stability (Rosenkranz et al. 2016, 2017; Maywald and Rink 2017). Under impact of collagenases, plasminogen activators and zinc-dependent matrix metalloproteinase (MMP), fibrin clot degrades and provides space for cell growth, migration, and angiogenesis.

Re-epithelialization, i.e. reproduction of epithelial cells and subsequent settlement and closure of the wound by them, is induced. Inability to re-epithelialize is a clear indicator of chronic non-healing wounds, which fail to proceed through the normal phases of wound healing in an orderly and timely manner (Rousselle et al. 2019).

The known zinc-finger X-linked protein (ZFX) additionally promotes proliferation and migration of keratinocyte cells (Feng et al. 2021). Zinc is a necessary co-factor for normal functioning of SMAD proteins, which are the main converters of signaling molecules to TGF-β receptors. Thus, deposition of collagen and ECM is induced, and then granulation tissue forms up (Maywald et al. 2017).

By the present time it has been shown that ZIP4 is expressed in human keratinocytes, and its expression is dramatically reduced on epidermal differentiation (Bin et al. 2017), and an increase in zinc concentration from 8 h to 3 days after wounding can cause keratinocytes proliferation (Coger et al. 2019). Besides, by using immortalized human keratinocytes (HaCaT) it was found that zinc-sensitive GPR39, which is highly expressed in keratinocytes, promotes skin wound healing (Satianrapapong et al. 2020).

Keratinocytes proliferation is followed by increased levels of MTs – redox-sensitive antioxidant proteins. Regulation of oxidation-reduction reactions is essential in wound healing. About 20 % of intracellular zinc is associated with MT, and it has been shown that zinc enhances MT expression (Lin et al. 2017).

MTs are cysteine-rich 6-7 kDa proteins that regulate intracellular Zn movement based on physiological needs (Kimura and Kambe 2016). In skin, the most common are MT-1 and MT-2. Results obtained using models of normal human epidermal keratinocytes (NHEK) and in injured murine skin have shown that MTs and Zn levels increase with proliferation of keratinocytes (Bin et al. 2017).

Angiogenesis

Simultaneously with re-epithelialization, endothelial cells migrate and proliferate at the wound site to form up new blood vessels. In this way, new cells are provided with the oxygen and nutrients necessary for their life and growth. The exact role of zinc in angiogenesis regulation has not been studied yet. It is known that expression of zinc-dependent protein ZEB2 is increased in damaged cardiomyocytes. On administering a therapeutic dose of ZEB2 into cardiomyocytes, angiogenesis is induced, and the density of newly formed vascular network increases, which leads to a decreased scarring and preservation of cardiac function (Gladka et al. 2021). On the other hand, zinc deficiency stimulates migration of endothelial cells of human microvessels (Maywald and Rink 2017). The study of zinc transporter Slc39a5 role in venous angiogenesis in Danio rerio embryo model shows that its destruction leads to systemic accumulation of zinc and delayed growth and development of veins.

Remodeling

The remodeling phase comes after the complete restoration of epidermis and is aimed at replacing granulation tissue with healthier skin via re-epithelialization (Coger et al. 2019). Remodeling is a delicate balance between tissue formation and tissue degradation, controlled by proteolytic enzymes activity.

Degradation of various proteins in the ECM is an important process in tissue remodeling and repair. Degradation is carried out by various types of proteases, but the main ones are MMPs.

MMPs are a family of zinc-dependent endopeptidases, identified in various tissues (Agren and Auf dem Keller 2020) and secreted by various cell types: inflammatory cells, keratinocytes, endothelial cells, fibroblasts, vascular smooth muscle (VSM), etc. All members of the MMP family contain common domains, of which zinc is required in catalytic domain for proteolytic activation of protein (Wang and Khalil 2018).

In skin, MMPs are involved in many cellular, molecular, and biochemical processes (Sabino and Keller 2015) and modulate release of cytokines, growth factors, and other active agents that are sequestered in ECM (Krishnaswamy et al. 2017; Wang and Khalil 2018).

Human acute injury wound-healing models were used to have demonstrated that neoepithelium formation gets impaired due to MMP activity blocking (Krarup et al. 2017).

On mouse models, it was shown that MMP-1, MMP-7, MMP-9 are involved in re-epithelialization (Pilcher et al. 1997; Kyriakides et al. 2009; Hayden et al. 2011), and MMP-9 activation occurred during wound healing (Kang et al. 2017); in superficial human wounds, MMP-1 expression and activities are upregulated 100-fold.

MMPs are able to hydrolyze almost all ECM proteins, including elastin and collagen, and determine structural organization and regeneration of dermis and epidermis (Sternlicht and Werb 2001; Maret 2013; Rohani and Parks 2015). MMPs are involved in vascular tissue remodeling, cell growth, migration and differentiation, and also in tissues invasion and vascularization (Jabłońska-Trypuć et al. 2016). Besides, MMPs could influence endothelial cell function as well as VSM cell migration, proliferation, Ca^{2+} signaling, and contraction (Cui et al. 2017; Wang and Khalil 2018).

MMP activation is triggered by such processes as tissue damage, oxidative stress, inflammatory cytokines, hormones, growth factors, and UV-radiation.

MMP family main enzymes are collagenases capable of hydrolyzing native collagen. Collagenolytic enzymes are effective proteolytic complexes due to their ability to break down collagen, which is the main component of wounds and scars. Studies have shown that collagenases affect the reparation process, for instance, they activate cellular migratory, proliferative and angiogenic responses to injury *in vitro*, and promote wound closure *in vivo* (Sheets et al. 2016). In relation to collagenases, apart from proreparative activity, there has been shown a decrease in pro-inflammatory polarization, for instance, increased production of anti-inflammatory cytokines IL-10 and TGF-β, and decreased levels of pro-inflammatory cytokines TNF-α and IL-1β.

During the remodeling phase, wound re-epithelialization takes place, and the dermis regains its strength.

Oxidative stress

ROS play a morbid role at all stages of wound regeneration. For instance, during the inflammatory phase, not only pro-inflammatory cytokines and proteolytic enzymes, but also neutrophils and macrophages start to release large amounts of ROS. To date, the role of ROS signals in angiogenesis has been well studied (Bretón-Romero and Lamas 2014). Moderate levels of H_2O_2 regulate production of VEGF, a key angiogenic growth factor in keratinocytes, and make angiogenesis speed up. ROS are also involved in epithelialization; they trigger activation of EGF and keratinocytes growth factor (KGF) receptors and induce TGFα production in fibroblasts. At the same time, an excessive amount of ROS slows angiogenesis down. Some enzymes involved in signaling pathways, such as phosphotyrosine phosphatase, have sulfhydryl residues that are very sensitive to oxidative modification and undergo oxidative inactivation. Thus, an excessive amount of ROS indicates an unbalanced redox homeostasis and impairs wound healing.

Antioxidant effect of zinc is manifested through various mechanisms: competition with iron (Fe) and copper (Cu) ions for binding to cell membranes and proteins that displace these redox metals; binding to SH sulfhydryl groups of bio-molecules protecting them from oxidation; activation of antioxidant proteins, molecules and enzymes, for example, glutathione, catalase, SOD; binding to MT, which is very rich in cysteine and is an excellent exchanger of·OH ions (Prasad 2014).

Zinc treatment of wounds

Currently, zinc-containing preparations (zinc sulfate, zinc oxide, zinc hyaluronate, zinc pyrition) are widely used in skin lesions of various types. Zinc sulfate is known to have antiseptic, astringent, drying, antimicrobial effects. However, experimental studies show that, exhibiting anti-inflammatory and antibacterial activity, this drug does not affect re-epithelialization (Larsen et al. 2017).

FDA-approved microbicidal zinc pyrithione agent (ZnPT) is used worldwide in antiseptic products, local antimicrobials and cosmetics. However, a study of epidermal keratinocyte and human melanocyte cultures demonstrated the vulnerability of cells to zinc pyrithione with strong expression of shock response genes and depletion of ATP levels (Lamore et al. 2010).

Almost 30 years ago, it was shown that topical administration of ZnO to murine skin increases keratinocyte mitosis (Jin et al. 1994) and the ability of MMPs to enhance collagen degradation in necrotic wounds (Agren 1993; Mirastschijski et al. 2004), which is beneficial in wound healing.

By present, it has been demonstrated that topical zinc treatment reduces the size of wounds and enhances epithelialization in surgical wounds in rabbits and rats (Abdullah et al. 2019). A rat study proved a positive (biochemical, biomechanical and histological) effect of cream with zinc oxide and composite silver nanoparticles on wound healing (Kantipudi et al. 2018).

The above-mentioned low-molecular zinc compounds due to their low bioavailability cannot provide the necessary microelement concentration in the right place, but they require a long take-up time and have pronounced side effects. Recent advances in drug delivery with zinc oxide nanoparticle (ZnO-NPs) technology has received considerable attention for the treatment of wounds due to their effective cell penetration, immunomodulation and antimicrobial ability (Xiong 2013; Oyarzun-Ampuero et al. 2015).

Currently, hydrogel membranes were developed based on poly vinyl alcohol, starch, and chitosan hydrogels with ZnO-NPs (Baghaie et al. 2017). Bioactive films with zinc oxide based on β-glucans and proteins extracted from barley are used for wound healing (Cleetus et al. 2020; Razzaq et al. 2021). Innovative ZnO-NPs also based on unprocessed human amniotic membrane antimicrobial proteins/peptides, growth factors, and signaling molecules, metabolites nanofiber mats composed of a combination of chitosan, polyvinyl alcohol and zinc oxide have great promise for applications in chronic wounds (Ahmed et al. 2018).

ZnONPs are biocompatible, permeable to the dermis and epidermis, and have exhibited remarkable regenerative abilities *in vivo* through re-epithelialization, keratinocyte migration along with collagen fiber deposition, and tissue granulation (Mendes et al. 2022).

The preparation of ZnONPs exhibits antimicrobial activity against Gram-negative and Gram-positive bacteria (Augustine et al. 2014; Díez-Pascual and Díez-Vicente 2015). One of the main mechanisms of action of ZnONPs is a slight increase in the production of ROS (especially H_2O_2), which stimulates the migration and proliferation of fibroblasts (Augustine et al. 2014; Sharma et al. 2016). When in ideal doses and size, ZnONPs demonstrated anti-inflammatory and antioxidant properties (Manuja et al. 2020). ZnONPs are highly compatible with fibroblast cells and enhance the growth of these cells, promoting cell adhesion and migration (Kaushik et al. 2019). However, in-depth pharmacodynamic and toxicological studies are needed for wider use of zinc nanoparticles (Pati et al. 2016; Lin et al. 2017).

Conclusion

Wound healing is a complex multi-phase process consisting of several phases, each involving metal ions, primarily zinc. Topical zinc may stimulate re-epithelialization, decrease inflammation and bacterial growth. The use of known zinc drugs is accompanied by side effects and low efficacy due to low skin absorption, which significantly limits their use and highlights the urgency of finding new, more effective and safe drugs. The emerging field of nanobiotechnology may provide an alternative platform to develop new therapeutic agents for the wound healing process.

Conflict of interests

The authors have no conflict of interests to declare.

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