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THE ROLE OF POLYAMINES IN THE REGENERATIVE PROCESS OF SKIN AEROBIC-PURULENT WOUNDS

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Abstract

Aliphatic polyamines (putrescine, spermidine, spermine) are organic polycations that play an important role in wound healing by stimulating several cellular mechanisms. In a human skin wound sample, the activity of the enzyme ornithine decarboxylase, which regulates the rate of polyamine synthesis, rapidly increases along the wound edges and leads to the activation of the polyamine synthesis cascade. Under the influence of polyamines, some signaling systems are also activated in wounds, which are the main pathways for the release of cellular mechanisms, and thanks to them, the healing process begins in wounds. For example, spermine induces the synthesis of urokinase-type plasminogen activator, the binding of which to the corresponding receptor at the wound margins executes the urokinase-type plasminogen activator and its receptor signaling system, which is the main driver of keratinocyte migration. Eukaryotic cell proliferation depends on precise modification of the eukaryotic initiation factor 5A1, in which spermidine plays an indispensable role. However, in addition to the significant functions performed by polyamines in the human body, polyamines are also necessary for the normal growth and development of fungi and bacteria. Small amounts of some microorganisms have a positive effect on the healing of wounds, but their increase, on the contrary, leads to the impairment of the normal course of wound healing due to their enhanced synthesis of polyamines. On the other hand, many studies show that excess ornithine decarboxylase and polyamines increase the risk of skin cancer. Suppression of polyamine synthesis by pathogenic microflora during wound healing can contribute to both rapid healing and the prevention of skin cancer.

In our study, we offer a way of inhibition of polyamine synthesis by wound microflora for rapid wound healing and prevention of subsequent cancer. The medicinal mixture "Armenicum/ Eflornithine" is a mixture of the drug "Armenicum" and α-difluoromethylornithine.

Keywords:*polyamine, putrescine, spermine, spermidine, wound, inflammation, pathogenic microflora, cancer, Eflornithine, Armenicum.*

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Wounds are defined as interruption of the anatomical, physiological integrity, and cellular composition of viable tissues, which can occur both from mechanical stimuli and as a result of physical, chemical, thermal, bacterial, and immune effects [*Mulkalwar S et al., 2015; Masson-Meyers D et al., 2020*]. The skin wound is a disruption of the integrity of the skin, with damage to the epithelial tissue of the epidermis and often changes in the function and structure of the underlying tissues [*Masson-Meyers D et al., 2020; Wang M et al., 2021*]. To restore tissue integrity, it is necessary to carry out complex and multistage tissue processes, including cell migration, proliferation, differentiation, cell interactions, synthesis of matrix components, and activation of some signaling pathways [*Masson-Meyers D et al., 2020*]. Aliphatic polyamines (putrescine, spermidine, spermine) and their derivatives play a unique role in all of this [*Moinard C et al., 2005*]. The body's response to damage i.e. primary alteration is expressed by an inflammatory response. In the case of a normal healthy reaction, it leads to the neutralization of the pathogenic factor, the limitation of the lesion, the mobilization of the body's healing mechanisms, and, finally, the restoration of damaged tissue [*Kumar R et al., 2004; Meizlish M et al., 2021*]. It is expressed by certain changes in the peripheral vascular bed, blood, and connective tissue, and in interaction with the immune, endocrine, and nervous systems, which leads to the formation of homeostatic processes in the body [*Velnar T et al., 2009; Meizlish M et al., 2021*]. However, inflammation as a general pathological process has an ambiguous (dual) character. On the one hand, it is defined by all the feature characteristics of a typical pathological process, on the other hand, it is the etiological basis of many diseases. Being a protective and adaptive process for the organism, at the same time it can also have a pathogenic significance if it's super strong or super weak. And, finally, this is not a local, but a "local ongoing" process, which is often accompanied by a systemic reaction of the body [*Velnar T et al., 2009; Wang M et al., 2021*].

An extremely strong inflammatory reaction in combination with the pathogenic microflora of the wound can lead to suppuration of the wound and local purulent diseases, which still remain an actual problem in surgery and are serious wound complications. The number of patients with purulent complications of skin and soft tissue wounds has not decreased, in fact, it is increasing, making up to 30-45% of hospitalized surgical patients [*Tretyakov A et al., 2015; Grigoryan A et al., 2022*], which is 35-60% in outpatient settings [*Grigoryan A et al., 2022*]. According to the statistics of the US Centers for Disease Control and Prevention in 2018, the incidence of postoperative purulent complications was 157,500 people, which increased the hospitalization period of patients by 11 days and required additional expenses in the healthcare system. Mortality in the intensive care unit was 11%, the main cause of which was local purulent infections after the operation [*Zabaglo M, Sharman T, 2022*]. It should be noted that in case of local purulent-inflammatory diseases, exogenous suppressors must participate in the processes of wound healing and protection of the body from pathogenic antigens to suppress the stages of inflammation and ensure its favorable outcome [*Tretyakov A et al., 2015; Grigoryan A et al., 2022*].

Inflammation as a general pathological process is carried out with the participation of a number of mediators and cellular movements and proceeds in 3 stages: alteration, exudation, and proliferation [*Velnar T et al., 2009; Wang M et al., 2021*]. And as we mentioned, polyamines of the aliphatic series (putrescine, spermine, spermidine) have their unique role in the implementation of these stages [*Moinard C et al., 2005*]. The first step in polyamine synthesis in mammalian cells is the conversion of arginine to ornithine by the arginase enzyme. Ornithine can also enter the cell from circulating blood plasma, where it is decarboxylated by ornithine decarboxylase to form putrescine [*Bae D et al.,2018*]. Ornithine decarboxylase can be inhibited by α-difluoromethylornithine (DFMO), which irreversibly binds

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

to the activated enzyme with covalent bonds. α-difluoromethylornithine depletes polyamines in vivo and in cultured cells, resulting in the growth attenuation of these cells. The fact that these effects are caused by polyamine depletion is proved by the loss of those changes in case of the addition of exogenous polyamines in the presence of DFMO [*Johnson L, McCormack S, 1999*]. Putrescine is converted to spermidine and spermine by the sequential action of spermidine synthase and spermine synthase, respectively, using decarboxylated S-adenosylmethionine as an aminopropyl group donor [*Bae D et al., 2018*]. Putrescine, spermidine, and spermine contain 2, 3, and 4 amino groups, respectively. With pK values near 10, these amino groups are protonated under physiological pH conditions and bind to negatively charged molecules such as proteins and nucleic acids. It is believed that many effects of polyamines at the cellular level are related to these connections [*Johnson L, McCormack S, 1999*].

Studies have shown that immediately after the primary alteration, a significant increase in the amount and activity of the enzyme ornithine decarboxylase, which regulates the synthesis of polyamines, is observed at the edges of the wound, which reaches its maximum amount 12 hours after receiving the wound. This increase is followed by increased levels of polyamines in damaged skin. Then the level of polyamines rapidly decreases and returns to normal rates after 48 hours [*Mizutani A et al., 1974; Johnson L, McCormack S, 1999*]. In addition to the increase in ornithine decarboxylase activity, an increase in the amount of polyamine regulatory adenosylmethionine decarboxylase 1 was also observed [*Ito D et al., 2021*]. The presence of polyamines in wounds as biologically active substances in tissues is the launch of the recovery, but it is confirmed that they can also be synthesized by the suppurative microflora, which can lead to an excess of polyamines and hyperproliferation, which often underlies tumor growth [*Gilmour S, 2007; Nowotarski S et al., 2013*]. In addition, polyamines contribute to tumor growth due to the activation of certain pro-oncogenes, which we will present later. And what processes do polyamines release in wounds during their healing?

In addition to regulating T cell function, polyamines may have a role in the thymotrophic effects of mediators such as prolactin. In addition, spermine, released by damaged or killed cells during local inflammation, promotes cell migration and growth. Here, polyamines have a negative regulatory effect on macrophage activation, and there is a complex relationship between NO metabolism and polyamines [*Moinard C et al., 2005*]. Initially, platelets and red blood cells increase in the wound cavity. This is followed by infiltration with polymorphonuclear leukocytes, macrophages, lymphocytes, and then fibroblasts. The order of formation of these cell types remains constant regardless of the type of damage [*Shearer J et al., 1997; Velnar T et al., 2009*]. The exudation phase is characterized by the migration of cells of the immune system to the site of injury and the release of inflammatory mediators. It is accompanied by an increase in vascular permeability [*Velnar T et al., 2009*], in which polymorphonuclear leukocytes activate the cascade of arginine metabolism in the wound. In addition to other important biologically active substances, NO also contributes to an increase in vascular permeability, the synthesis of which is carried out by arginine-induced NO synthase in phagocytes. NO synthase activity creates a cytotoxic environment that may be important for the early phase of wound healing. As the wound inflammatory process matures, an increase in arginase activity creates a favorable environment for fibroblast reproduction and collagen synthesis. Arginase, which produces ornithine and urea from arginine, was originally considered a mediator of macrophage cytotoxicity. Intensification of arginase synthesis by macrophages was induced by a pathogen-associated molecular pattern, which in this case was lipopolysaccharide of the wound microflora. It also activates phagocytes. As long as these signals persist and arginine is available, a cytotoxic environment may exist at the site of inflammation. However, it later became clear that these two arginine metabolic pathways (NO-synthase and arginase) have opposite effects, and macrophage cytotoxicity was attributed to NO-synthase. At the beginning of the injury, high concentrations of citrulline and NO were observed in the wound exudate, and the concentration of ornithine began to increase on the 3rd day. However,

wound fluids collected 3 days later contained low concentrations of NO and citrulline, indicating reduced NO synthase activity and enhanced synthesis of ornithine and polyamines from arginine for normal proliferation [*Shearer J et al., 1997*]. Thus, summarizing the abovementioned, we can conclude that at the early stage of wound formation, the arginine-NO cascade is active, the activity of which mediates a number of important events of the early stage of inflammation, including microbiostasis, vasodilation, and inhibition of platelet aggregation, and at the late stages of inflammation, the arginine-ornithine cascade is activated, which activates cell growth and proliferation via the polyamine cascade and accelerates collagen synthesis via proline synthesis. Mechanisms for terminating the activity of arginine – NO signaling cascade and initiating another are still unknown [*Shearer J et al., 1997*]. A possible option is the reduction of the synthesis of IFNγ by inflammatory cells since it is an activator of NO-synthase in the site of inflammation and its suppression by transforming growth factor (TGF-β) leads to a reciprocal increase in the amount of ornithine. In addition to the destruction of microbes and other invading organisms, the cytotoxic effect of NO can also lead to the death of polymorphonuclear leukocytes and the formation of exudate, which is particularly strong in purulent wounds [*Shearer J et al., 1997*].

Polyamines are of great importance in the proliferation phase of inflammation, where their functions are most pronounced. At this stage, polyamines are involved in cell migration, cytoskeleton rearrangement, signaling in the endothelial growth factor receptor, and are involved in the regulation of proto-oncogene activity. Notably, the depletion of polyamines by DFMO inhibited cell migration by 80%, while the administration of exogenous polyamines abolished the inhibitory effect of DFMO. Interestingly, the addition of TGF-β to "polyamine depleted" cells exposed to DFMO also restores normal keratinocyte migration [*Johnson L, McCormack S, 1999*]. In general, the proliferation of eukaryotic cells depends on the exact modification of the eukaryotic initiation factor 5A1, in which spermidine plays an indispensable role [*Pällmann N et al., 2015*]. At the initial stage of modification of this transcription factor, deoxyhypusine synthase transfers the 4-aminobutyl moiety of spermidine to the ε-amino group of Lys50, resulting in the formation of the deoxyhypusine intermediate. In the second step, hydroxylation of the deoxyhypusine residue with deoxyhypusine hydroxylase gives hypusine-containing eIF-5A. Different functional protein groups are under the control of eukaryotic initiation factor 5A1, such as those involved in cytoskeletal organization, collagen metabolism, and cell differentiation. Studies have shown that eIF5A is required for the translation of tripeptide motifs present in collagen [*Pelechano V, Alepuz P, 2017; Barba-Aliaga M. et al., 2021*]. One of the first dramatic moments in the impact of DFMO on polyamine metabolism is serious changes in the cytoskeleton, which is restored after the addition of exogenous polyamines and normal actin filaments begin to appear in the cytoskeleton [*Johnson L, McCormack S, 1999*]. Polyamines also have a significant effect on cell migration by activating a number of signaling pathways. Thus, keratinocytes, which are normally located in the basal layer of the skin and make up to 85% of the cells, after skin damage begin to activate and lose intercellular desmosomes, turning into cambial elements. After the loss of desmosomes, keratinocytes located along the edge of the wound pass from the immobile epithelial state to the mesenchymal state and secrete a special type of proteases that begin the absorption of the intercellular substance. Attention is drawn to the synthesis of urokinase-type plasminogen activator by marginal keratinocytes, which is stimulated by spermine [*Lim H et al., 2018*]. In addition, urokinase-type plasminogen activation and functional activity significantly increase endothelial cell viability, growth, and wound healing. It plays a key role in extracellular proteolysis and is believed to play an important role in modulating angiogenesis through interaction with its urokinase-type plasminogen activator receptor. The latter plays a major role in the activation of plasminogen and, when activated, promotes the "disassembly" and transformation of the extracellular matrix. Blockade of this receptor or inhibition of polyamine synthesis by DFMO results in disruption of keratinocyte migration and inhibition of wound healing. It has

been established that the main role in wound healing is played by the glycosylated form of the urokinase-type plasminogen receptor, which proteolyzes the damaged components of the cytoskeleton by three extracellular domains of the receptor (D1-D3). This receptor is also activated upon stimulation with spermidine, and studies have shown that topical administration of spermidine increases the activity of glycosylated form of the urokinase-type plasminogen receptor, which in turn activates urokinase-type plasminogen, promoting the breakdown of plasminogen. In turn, it activates plasmin. Plasmin activates matrix metalloproteinases and induces proteolysis of the damaged matrix [*Ito D et al., 2021*].

Polyamines also have a great influence on the formation of new tissues. They are a substrate for transglutaminases. These Ca2+-dependent enzymes catalyze the formation of isopeptide bonds between proteins and primary amines and their activity is enhanced by several mediators such as TGF-β. These transglutaminases are involved in many intracellular and extracellular processes that occur during healing (apoptosis, osteogenesis, cell signaling, etc.).

Of course, the role of polyamines in wound healing and their inflammatory process is not limited to their influence on the above steps, polyamines affect both regulatory genes and proto-oncogenes at the gene level. Polyamines stimulate translation in several ways, one of which is by changing the structure of mRNA, which allows the synthesis of proteins encoded by genes that lack the Shane Dalgarno sequence. Proteins, the synthesis of which is directly stimulated by polyamines also include transcription factors and kinases, which, in turn, can enhance gene expression of other proteins [*Pegg A, Casero R, 2011*]. Spermidine appears to bind to a G-C-rich double-stranded mRNA region close to the Shine Dalgarno sequence of OppA mRNA. This causes a conformational change in the Shine Dalgarno sequence and the AUG start codon, which facilitates interaction with the 30S subunits of the ribosome. Spermidine has also been found to stimulate the association of Met-tRNAf with 40 S ribosomal subunits. This is also associated with a change in the mRNA structure caused by spermidine [*Igarashi K, Kashiwagi K, 2000*]. Thus, polyamines regulate the synthesis of proteins responsible for cell migration and transformation, which underlies wound healing.

The exchange of polyamines by pathogenic and opportunistic microflora of the wound is extremely important. Small amounts of some microorganisms have a positive effect on wound healing, and their increase, on the contrary, leads to disruption of the normal course of the wound process. At the initial stage of wound formation, the wound cavity is populated by skin commensals, then colonization changes with time, gram-positive microorganisms appear in the wound, yet in deeper wounds, the microflora can contain both aerobic and anaerobic representatives. Some pathogens of purulent skin diseases, such as Cl.sporogenes, E.coli, Proteus Vulgaris, actively exchange polyamines [*Edwards R, Harding K, 2004*]. These microbes actively synthesize and absorb polyamines from the wound, for which they have special systems for the exchange of polyamines necessary for their growth (polyamines stimulate the growth of bacteria, such as E. coli), reproduction, and bioactivity, the formation of biofilm conglomerates, and also for the production of biologically active substances unique to bacteria (for example, siderophores). Spermidine is especially important in this context. Being a classic representative of polyamines, its activity in the above processes was higher in the studied bacteria compared to the rest [*Igarashi K, Kashiwagi K, 1999; Michael A, 2018*]. E. coli has many polyamine genes. About half of them encode enzymes involved in the biosynthesis or degradation of polyamines, while the rest are genes for the mechanisms of polyamine transport. They occupy about 0.6% of the total number of E. coli genes and chromosomes. This observation indirectly supports the idea that polyamines and polyamine regulation play an important role in E. coli [*Igarashi K, Kashiwagi K, 1999*], and a decrease in the synthesis of the latter may be vital for the bacterium. In E. coli, such genes are specC and speF in the synthesis of putrescine from ornithine, speA and adiA in the synthesis of agmatine from arginine, and ldcC and cadA in the synthesis of cadaverine

from lysine. Therefore, the presence of E. coli in the wound can significantly affect the number of polyamines, which will lead to their hyperreaction in all the pathogenic circles listed above. The result can be tissue hyperproliferation, often leading to tumor growth. The fungal microflora can coexist with the bacterial microflora and promote the growth and spread of bacteria. The fungi most frequently isolated from wound exudate belong to the genera Candida and Trichosporon, but the pathogenic microflora may also include representatives of Cladosporidium, Pneumocystis, Microsporum and many other genera that actively exchange polyamines [*Boyle S et al., 1988; Kalan L, Grice E, 2018*]. Wounds infected with Pneumocystis carinii contained putrescine and spermidine, as well as traces of spermine [*Lipschik G et al., 1991*]. The latter, in combination with bacterial microflora, can also cause an excess of polyamines.

And why does an excess of polyamines lead to tumor growth? The point is that polyamines stimulate the expression of proto-oncogenes c-fos and c-myc, which are involved in the process of wound healing [*Moinard C et al., 2005*]. Excessive exposure to polyamines can lead to skin damage.

The use of polyamine cascade inhibitors was proven effective in the treatment of non-melanoma cancer in high-risk individuals [*Gilmour S, 2007; Novotarsky S et al., 2015*]. Although the mechanism by which polyamines promote skin oncogenesis is not fully understood, high levels of polyamines stimulate epidermal hyperproliferation, alter the differentiation status of keratinocytes, increase neovascularization, and increase the synthesis of extracellular matrix proteins in the wound. It gradually becomes clear that high levels of polyamines activate not only epidermal epithelial cells, but also stromal cells under the skin, promoting the development and progression of skin tumors [*Gilmour S, 2007*]. The p-53 protein, a transcription factor that regulates the cell cycle, also plays an important role in polyamine carcinogenesis. Studies have identified the spermidine/spermine-N1-acetyltransferase-1 gene as a target for p53 transcription. This is further evidence of a link between polyamine metabolism and carcinogenesis. Spermidine/spermine-N1-acetyltransferase-1 is a rate-limiting polyamine catabolism enzyme that plays an important role in the conversion of spermidine and spermine to putrescine [*Ou Y et al., 2016*]. Other mechanisms of carcinogenesis of polyamines, which we have not considered, are not excluded. However, in the case of the presence of each of them, the expected result is the same, for the prevention of which we propose the use of polyamine cascade inhibitors.

During wound healing, in order to avoid hyperproduction of polyamines by pathogenic microflora, it is necessary to limit their synthesis. It is recommended to use the domestic drug mixture "Eflornithine", the main active ingredient of which is DFMO, an inhibitor of ornithine decarboxylase. Eflornithine is a mixture of the drug "Armenicum" with antibacterial action and DFMO. Exposure to the ornithine decarboxylase inhibitor (DFMO) in cell culture results in almost complete elimination of putrescine and spermidine and arrest of cell proliferation, with little effect on spermine levels, leaving a cytostatic rather than cytotoxic effect [*Pegg A, Casero R, 2011*]. On the other hand, the 2nd component of the drug mixture that we're studying "Armenicum" activates regenerative-proliferative processes. By activating the synthesis of fibronectin, in the early period of the local inflammatory process, it promotes the synthesis of type I and III collagens, which are then transformed into collagen fibrils. An increase in the amount of fibronectin, in turn, suppresses eNOS. As a result, the cytotoxic effect of high levels of NO is also reduced. Armenicum also reduces the level of somatostatin in the blood serum (therefore, the suppression of the synthesis of type I and III collagen by somatostatin is eliminated). Moreover, it increases the level of prolactin in the blood serum (activation of B-lymphocyte populations, synthesis of antibodies against dead tissues and existing microorganisms). It has a bactericidal effect on existing gram-positive and gram-negative bacteria [*Zilfyan A et al., 2016*].

Thus, it can be assumed that the medicinal mixture "Eflornithine" should be used for wound healing. And one of the goals of our study is to find out what amounts of this drug suppress pathogenic microflora, while simultaneously promoting wound healing.

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