Review Article

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Chronic wounds and current treatments

Abstract

Wound healing is a natural phenomenon that repairs injured cell tissues in the body. The process occurs in four overlapping stages, but when interrupted it leads to a chronic wound. Factors that can cause chronic wounds are oxygen and infection from outside sources. Current treatments include standard cleaning and patching of the wound. Unique treatments are also available for more serious chronic wounds in the form of therapies, fibrin sealants, and skin grafts.

Keywords: wound healing process, chronic wounds, fibrin sealants, skin grafts, chronic wound treatments

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Abbreviations: (TGF)-β, Transforming growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; EGF, epidermal growth factor, MMPs, matrix metalloproteases; ECM, extracellular matrix; FTSG, full-thickness skin grafts; STSG, split-thickness skin grafts; ADM, acellular dermal matrix; EpSCs, epidermal stem cells

Normal wound-healing process

Wound healing is a complex physiological activity that occurs in the body when cell tissue is injured.[1] The process occurs in four overlapping stages and includes many different cytokines, mediators, and the vascular system. The four stages include homeostasis, inflammation, proliferation, and tissue remodeling. The inflammation and proliferation stages overlap each other and use similar cell types. The whole wound-healing process takes a couple of days to seal the wound but years for it to completely heal.[1]

Once a wound has been created the homeostasis stage begins immediately to help control the bleeding.[2] The body begins with vascular constriction and fibrin clots to stop the bleeding. Several growth factors: (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) are released to help repair the tissue.[2] The wound healing-healing process moves onto the inflammatory stage once the inflammatory cells move to the wound. The inflammation cells are followed by neutrophils, macrophages, and lymphocytes to help prevent infection and remove anything that would hamper the wound-healing process. The proliferation stage occurs during the inflammation stage with the introduction of macrophages.[3] The macrophages are important to heal cell tissues in the wound. The proliferation stage helps repair and create new tissue for the wound. Fibroblasts and endothelial cells are released during this stage to help create new cells that were lost from the wound.[3]

The final stage of the wound-healing process is the tissue remodeling stage and is the longest stage. The process takes years to undo the last three stages.[4] The new capillaries start to return to their normal vascular density.[4] The cells created by the previous three stages are destroyed naturally through apoptosis. The wound-healing process can be delayed if the wound becomes infected or if one of the stages does not function correctly. The delay of the wound would create a chronic wound which would require outside medical assistance to treat the wound properly.[4]

Chronic wounds

Chronic wounds arise when the normal wound-healing process is disrupted.[2] The disruption occurs from many different factors. Chronic wounds can be very difficult to treat since there are different factors and types of chronic wounds to be treated. Chronic wounds generally have two important factors and four different types of ulcers created by those wounds. Oxygen is the most important factor that plays a critical role in the wound-healing process.[2] Oxygen prevents infections, induces angiogenesis, enhances fibroblast, and collagen synthesis, and promotes wound contraction.[2] Oxygen is needed for the wound-healing process and is therefore consumed and makes the wound area hypoxic. Health conditions such as old age and diabetes will hamper the vascular flow and prevent oxygen from returning to the wound area. The lack of oxygen makes the wound into a chronic wound and puts the wound-healing process on hold until enough oxygen is restored to the hypoxic wound.[2]

The second most common factor for chronic wounds is infection. The wound can be affected by contamination if it is not kept clean. The infection forces the inflammation stage to continue until the wound is completely clean from contamination. The prolonged inflammatory stage increases the level of matrix metalloproteases (MMPs) which degrades the extracellular matrix (ECM). The degradation of ECM causes the growth factors to degrade creating a very serious chronic wound.[2] Chronic wounds created by oxygen and infections can create different types of ulcers.[2]

Four major types of ulcers exist and contain different characteristics. The first type of ulcer is an arterial ulcer. The arterial ulcer is located near the ankle and is deep exposing many structures under the skin. The next type of ulcer is a diabetic ulcer. A diabetic ulcer is an open sore that is common in people who have diabetes.[4] The third is a pressure ulcer.[4] The pressure ulcer looks very boney and is caused by the lack of blood flow due to vascular constriction. The final type of ulcer is a venous ulcer. The venous ulcer is very shallow and is caused by blood flow issues. Knowing the different types of ulcers and factors gives an idea of how to use different treatments to heal a chronic wound.[4]

Treatments

Treating a chronic wound depends on the severity and the size of the wound in question.[5] The first is to clean the wound.[5] A typical chronic wound is treated with alcohol or a saline solution to clean it.[5] Serious chronic wounds with dead and inflamed skin would require debridement. The wound is cleaned by removing excess skin with tweezers and cleaned with a high-pressure water jet. The chronic is patched using a dressing. The dressings are used to remove excess fluid from the wound and prevent further infection. The different types of dressing include gauze, films, foam, hydrogel, hydrocolloid, and dressings containing silver or alginates. Wounds with poor circulation require a compression stocking or bandages to help improve blood flow through the wound.[5]

Certain therapies are available if the chronic wound is still infected after initial treatment. Hyperbaric oxygen therapy has the patient in a special oxygen chamber with high pressure. The pressure from the oxygen will increase the concentration of oxygen inside the patient and improve the blood supply in the infected area. Negative pressure wound therapy is another treatment. A dressing connected to a pump is applied to a wound and pumps liquid out of the wound. The treatment creates negative pressure on the top of the wound.[5]

A new type of treatment that is emerging is the use of fibrin to stop bleeding and seal the wound.[6] Fibrin is a special hemostatic protein that helps the hemostasis stage of the wound-healing process by stopping blood leakage.[6] Fibrin products are special because they can control the release of growth factors which are important for the wound to continue the wound healing process.[7] Previous studies have shown that fibrin is an excellent delivery of keratinocyte growth factors and epidermal growth factors to the wound to help with the coagulation cascade.[8,9] The structure of fibrin is made of two sets of Aalpha-chains, Bbeta-chains, and two y-chains connected by disulfide bridges.[10] In order for the fibrin to complete coagulation it must remove the fibrinopeptide from the terminal segments of the Aalpha-chains and Bbeta-chains.[10] The fibrin is then converted into monomers which form a network of fibrin fibers The network is stabilized by thrombin during fibrin polymerization and helps cross-link the fibers into a clot.[11] The fibrin can crosslink due to transglutaminase reactions between two y-chains or between a y-chain and an alpha-chain. The cross-links can form a fibrin clot that can be used to help seal chronic wounds.[12]

The only fibrin sealant product on the market is TISSEEL.[6] The product uses fibrin proteins to mimic blood clotting and restore the wound-healing process. The product is very versatile with its different applicators and has precise placement due to its design. Grifols is currently in phase III of a clinical trial on its own fibrin sealant.[13] The fibrin product is a dual-component fibrin sealant that contains human fibrinogen, human thrombin, and calcium chloride.[14] The combination of these products creates a cross-linked fibrin clot that mimics the final steps of blood clotting in the wound-healing process.

Fibrin products are a great way for doctors to seal small chronic wounds, but not for larger wounds.[5] Doctors use what are called skin grafts to seal large wounds that fibrin sealants cannot close. Skin grafts are created from human cells and synthetic materials.[15] Currently, there exist two types of skin grafts: full-thickness skin grafts (FTSG) and split-thickness skin grafts (STSG). An FTSG procedure has the surgeon fully remove all the epidermis and dermis from one part of the body and place it on the wound area to seal the large wound.[16] The graft heavily depends on the ingrowth of capillary tubes so that vascular activity can occur.[16] FTSGs do not need to change the chronic wound site to fit with the skin graft. The main problem with FTSGs is that they are very susceptible to graft failure and have limited sources. The risk of graft failure and limited supply makes doctors choose STSGs over FTSGs.[16]

STSGs are created by having surgeons remove the epidermis and only a fraction of the dermis.[17] The STSGs can be obtained from many different sources such as autograft, homograft, allograft, and xenograft.[17] The procedure for the STSGs has the surgeon place the graft over the wound to close it. The multiple sources give STSGs an advantage over FTSGs because of the limited options FTSGs have. The main disadvantage of STSGs is that they are more fragile and have a high chance of shrinking.[18] The cause for the disadvantages is the lack of dermis taken from the donor section. Despite all the shortcomings STSGs remain the doctors' first choice for most skin graft procedures.[18]

Exciting new research is currently being conducted with STSGs to help make skin grafts more durable for patients. The research involves combining STGS with an acellular dermal matrix (ADM) to remove the previous constraints STSGs had. The main problem in this experiment is that ADM causes delayed vascularization, which defeats the purpose of skin grafts.[19] The researchers combat this problem with epidermal stem cells (EpSCs). The EpSCs are rare stem cells but can heal wounds very fast and leave little to no scarring compared to other wound-healing stem cells.[20] The group did the experiment on mice and used different combinations of STSGs, EpSCs, and ADM to see their effects on wound healing. The experiment showed that the combination of STSGs, ADM, and EpSCs in mice can do a one-step repair on a full-thickness wound with little shrinkage and more durability.[18]

Conclusion

The wound-healing process is a complicated multi-step process that contains some overlap between the stages. Interruption of the wound-healing process will cause a normal wound to turn into a chronic wound. A chronic wound could be caused by many different lifestyle factors such as obesity, diabetes, and age but all contain some root causes. Important root causes for chronic wounds are oxygen deficiency or bacterial infection. Chronic wounds are normally treated by disinfecting the wound with alcohol or a saline solution and patching with the appropriate dressing. Serious chronic wounds will require additional treatment and therapies. Hyperbaric oxygen treatment and negative pressure wound therapy are examples of therapies that can be used to treat chronic wounds. Alternative products exist to help with chronic wounds such as the fibrin sealant TISSEEL. The sealant allows the precise application of fibrin proteins to help stop bleeding from chronic wounds and seal them. The proteins mimic the final steps of blood clotting to seal the wound and continue the wound-healing process. Skin grafts are another treatment that closes the wound to help prevent infection and close the wound. New research has improved skin grafts so that they are more durable and repair the wound in a one-step process.

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Conflicts of interest

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References

1. Wallace HA, Basehore BM, Zito PM. Wound Healing Phases. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.

2. Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89(3):219–229.

3. Peng–Hui Wang, Ben–Shian Huang, Huann–Cheng Horng, et al. Wound healing. *J Chin Med Assoc*. 2018;81(2):94–101.

4. Bowers S, Franco E. Chronic Wounds: Evaluation and Management. *Am Fam Physician*. 2020;101(3):159–166.

5. What are the treatment options for chronic wounds? InformedHealth.org. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006.

6. Reinertsen E, Skinner M, Wu B, et al. Concentration of fibrin and presence of plasminogen affect proliferation, fibrinolytic activity, and morphology of human fibroblasts and keratinocytes in 3D fibrin constructs. *Tissue Eng Part A*. 2014;20(21–22):2860–2869.

7. Whelan D, Caplice NM, Clover AJ. Fibrin as a Delivery System in Wound Healing Tissue Engineering Applications. *Journal of Controlled Release*. 2014;196:1–8.

8. Geer DJ, Swartz DD, Andreadis ST. Biomimetic Delivery of Keratinocyte Growth Factor upon Cellular Demand for Accelerated Wound Healing *in Vitro* and *in Vivo*. *Am J Pathol.* 2005;167(6):1575–1586.

9. Zhou W, Zhao M, Zhao Y, et al. A Fibrin Gel Loaded with Chitosan Nanoparticles for Local Delivery of RhEGF: Preparation and in Vitro Release Studies. *J Mater Sci Mater Med*. 2011;22(5):1221–1230.

10. Laurens N, Koolwijk P, de Maat MP. Fibrin structure and wound healing. *J Thromb Haemost*. 2006;4(5):932–939.

11. Weisel JW, Francis CW, Nagaswami C, et al. Determination of the topology of factor XIIIa–induced fibrin gamma–chain cross–links by electron microscopy of ligated fragments. *J Biol Chem*. 1993;268:26618–26624.

12. Scott EM, Ariens RA, Grant PJ. Genetic and environmental determinants of fibrin structure and function: relevance to clinical disease. *Arterioscler Thromb Vasc Biol.* 2004;24:1558–1566.

13. Nenezić D, Ayguasanosa J, Menyhei G, et al. A prospective, single–blind, randomized, phase III study to evaluate the safety and efficacy of Fibrin Sealant Grifols as an adjunct to hemostasis compared with manual compression in vascular surgery. *J Vasc Surg.* 2019;70(5):1642–1651.

14. Oyama H, Kito A, Maki H, et al. Repair of carotid blow–out using a carotid sheath in a patient with recurrent thyroid cancer. *Nagoya J Med Sci*. 2012;74(1–2):193–198.

15. Stang Debra. Skin Graft Surgery. Healthline. 2018.

16. Ramsey ML, Walker B, Patel BC. Full Thickness Skin Grafts. [In: StatPearls]. Treasure Island (FL): StatPearls Publishing; 2023.

17. Braza ME, Fahrenkopf MP. Split–Thickness Skin Grafts. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.

18. Wang Z, Xu H, Yang H, et al. Single–stage transplantation combined with epidermal stem cells promotes the survival of tissue–engineered skin by inducing early angiogenesis. *Stem Cell Res Ther*. 2023;14(1):51.

19. Urciuolo F, Casale C, Imparato G, et al. Bioengineered skin substitutes: the role of extracellular matrix and vascularization in the healing of deep wounds. *J Clin Med.* 2019;8:2083.

20. Przekora A. A concise review on tissue engineered artificial skin grafts for chronic wound treatment: can we reconstruct functional skin tissue *in vitro*? *CELLS–BASEL.* 2020;9:1622.