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Biologic Therapeutics and Molecular Profiling to Optimize Wound Healing

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Abstract

Non-healing wounds represent a significant cause of morbidity and mortality for a large portion of the adult population. Wounds that fail to heal are entrapped in a self-sustaining cycle of chronic inflammation leading to the destruction of the extracellular matrix. Among cancer patients, malnutrition, radiation, physical debilitation, chemotherapy, and the malignancy itself increase the likelihood of chronic wound formation, and these co-morbidity factors inhibit the normal wound healing process. Current wound treatments are aimed at some, but not all, of the underlying causes responsible for delayed healing of wounds. These impediments block the normal processes that allow normal progression through the specific stages of wound healing. This review summarizes the current information regarding the management and treatment of complex wounds that fail to heal normally and offers some insights into novel future therapies [1,2].

Keywords

wound; radiation; delayed healing; malignancy

Introduction

Non-healing wounds (chronic wounds or chronic ulcers) are trapped in a constant inflammatory state due to a failure to progress through the normal stages of wound healing. This inflammation results in an abnormal wound microenvironment and results in significant, chronic disability with frequent relapse [3].

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Conflict of interest statement

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Wounds heal through four distinct yet overlapping phases: 1) hemostasis, 2) inflammation, 3) proliferation, and 4) remodeling (Figure 1; Table 1). In a chronic wound, changes associated with senescence, ischemia, and bacterial colonization transform the normal progression of healing into a self-sustaining cycle of inflammation and injury [4]. Continuous recruitment of neutrophils results in abnormally elevated levels of matrix metallo-proteinases (MMP) [5–9], especially MMP-8 and neutrophil-derived elastase. A normal wound inhibits the excess matrix metallo-proteinases MMPs through the nonspecific proteinase inhibitor, α 2-macroglobulin, and specifically by a small group of proteins called tissue inhibitors of matrix metallo-proteinases (TIMP)[5,10]; however, the abnormal MMP (degradative):TIMP (protective) ratios observed in chronic wounds lead to extracellular matrix (ECM) degradation [11–13], changes in the cytokine profile [14], and reduced concentration of proliferative factors [15, 16]. The release of reactive oxygen molecules by neutrophils both damages the wound and serves to recruit additional neutrophils. The continuous feedback loop prevents ECM deposition despite continued recruitment of fibroblasts [17–19].

Malignancy and its treatment may interfere with all four stages of wound healing through decreased tissue perfusion and hypoxia, impaired inflammatory response rates, and changes in fibroblastic proliferation. As many of the components of wound healing are involved in tumor progression, targets of chemotherapy and radiation often involve proteins related to tissue repair as well as cellular proliferation, and certainly, preoperative radiation therapy results in an increased risk of wound complications [20]. This effect may be seen on the genomic and proteomic level [21]. Malnutrition and/or obesity further complicate the process. Hypoalbuminemia and anemia have been correlated with diminished wound healing [22].

Evaluation

Chronic wounds are not subtle; however, they must be carefully evaluated to ensure maximization of treatment options and to prevent further degradation. The extent of the wound, its underlying etiology, duration, location, size, odor, appearance, and appearance of the surrounding tissue should all be documented [23,24]. Chronic ulcers are commonly divided into four categories (Table 2) [25,26]. Wounds located on an extremity are classified as non-limb threatening, limb threatening, or life threatening. Superinfection may be local (cellulitis or abscess) or systemic with signs ranging from erythema and lymphadenopathy to vital sign instability and altered mental status.

Chronic ulcers with a high bacterial load will not heal; a biopsy from the base is indicated to determine the underlying organism [27]. Radiographic films will assist in identifying subcutaneous air or a foreign body; however, if osteomyelitis is suspected, MRI or bone scans are required for evaluation. Additional evaluation of the vascular system on extremities may require venous and arterial dopplers or angiography [28].

Management

Management always aims to treat the underlying etiology; in the cancer patient population, however, this often results in competing therapeutic interests of chemotherapy and/or radiation. Advanced-staged cancer with its subsequent complications may result in a chronic state of malnutrition that further prevents adequate response to tissue injury. Nevertheless, optimization of patient care can be achieved through measures that reduce the effects of comorbidities (e.g., glycemic control and vitamin supplementation), increase perfusion, and control the inflammatory response [26,29–32].

Reduction of Bacterial Load

Regardless of the underlying cause, a clean wound bed is the minimum effort required to prevent further sequelae and reduce inflammation. Irrigation followed by debridement will reduce the bacterial load without damaging healing tissue. Utilization of appropriate wound dressings provides barrier protection against further colonization and irritation.

Irrigation may be performed initially with saline or lactated Ringers using an 18 gauge needle and 60 mL syringe. Excessive pressure from devices such as power sprays may damage granulation tissue and force bacteria and debris further into the wound bed. While effective at removing superficial bacteria, skin cleansers such as hydrogen peroxide and Betadine will also kill host tissue. Debridement is commonly performed surgically; however, enzymes such as proteolytics and collagenases have been used. Both serve to reduce bacterial concentration and remove necrotic tissue [25]. Less widespread, sterile maggots are another method of debridement [33,34].

Prevention of Further Injury

The wound requires a protective barrier to allow healing to progress. Commercially available preparations include hydrocolloids, films, foams, alginates, and hydrogels. The choice of dressing will depend on the location, state of the wound, and type of wound (Table 3) [35]. Occlusive dressings such as hydrocolloids should be avoided in infective wounds that require draining. Absorbant dressings such as foams and alginates may cause damage if dry and are best suited for wounds that produce copious amounts of exudate. Wounds with good granulation tissue would benefit from moisture-providing hydrogels and hydropolymers. The Wound VAC (vacuum-assisted closure) offers an attractive alternative as it keeps the wound bed moist while removing exudates; similar to occlusive dressings, however, these negative pressure devices are contraindicated for infected wounds [36,37].

Ischemia-reperfusion injury may result from pressure or trauma. When possible, pressure relief should be initiated either through re-positioning, specialty mattresses, or scheduled turning as this will minimize additional inflammation and tissue damage [38,39]. In addition to the specific factors and situations discussed above, there are many other factors that should be considered that can impair normal wound repair (Table 4).

Other Techniques

Exogenous cytokines and growth factors can, in theory, shift the degradative: protective ratio to one more favorable to healing. Of those evaluated, only recombinant PDGF (Regranex) has shown efficacy in multi-center randomized controlled trials; however, response to this expensive therapy was limited due to the ability of proteolytic enzymes to degrade both PDGF and TGF- β [40]. In patients whose inflammation level can be kept low, healing may progress.

Bioengineered dermal replacements such as Apligraf and Dermagraft have also shown evidence of augmentation of healing [41,42]. These living cell materials contain highly active cells that produce and supply a spectrum of growth factors that can promote the repair process. However, these high-tech materials will only supplement the healing process; usage is best reserved as an adjuvant when the chronic inflammation is controlled or reduced.

The treatment of bacterial wound colonization with topical antibiotics is controversial. The line between colonization and infection has not been well defined, nor has the level at which colonization leads to an inflammatory response. Lastly, bacterial biofilms, which are resistant to topical antibiotics, theoretically serve as a source for an uncontrolled inflammatory response.

Although ubiquitous, bacterial colonization does not always lead to an inflammatory response [43]. Topical antibiotics should be reserved for wounds with a large exudative component, with oral or systemic medication only for patients with a known infectious process (e.g., cellulitis or osteomyelitis). As the organisms are generally polymicrobial, outpatient management options require broad spectrum coverage such as oral amoxicillin plus clavulanate (Augmentin) 875 mg P.O. twice a day with trimethoprim-sulfamethoxazole double strength (Bactrim DS) twice a day [44]. Intravenous antibiotics such as vancomycin 1 gm every 12 hours with piperacillin plus tazobactam (Zosyn) 3.375 gram every 6 hours may be required for severe systemic infections [44].

Although only available at select centers, hyperbaric oxygen has been shown to be an effective treatment of radiation-induced wounds [45]. The partial pressure of oxygen is increased to greater than one atmosphere to allow elevated concentrations in the blood and tissue [46]. Complications include reversible myopia, central nervous system toxicity, middle ear, dental, sinus or pulmonary barotraumas, and pneumothorax. Tension pneumothorax is the only absolute contraindication; however, relative contraindications include inability to equalize pressures and coronary artery disease.

Recently, our laboratory found that Androstenediol (AED), an immune-regulating hormone, has the ability to reverse glucocorticoid inhibition of wound healing by immunomodulation [47,48]. In addition, AED has the ability to improve outcomes from overwhelming bacterial and viral infections. Furthermore, AED stimulates host cellular and humoral immunity and can protect against lethal whole body irradiation. It is also important that there is no known toxicity associated with the administration of AED. These combined biological attributes afforded by AED may prove useful to overcome wound healing inhibition following irradiation. These studies are currently underway in our Laboratory of Tissue Repair.

The Future

Studies by Brem et al. have shown that chronic ulcers contain subpopulations of cells with differing capacities to heal [49]. Cells from the margin of ulcers were compared to cells distant from the ulcer and found to have very unique patterns of gene expression. These new molecular strategies to investigate and understand the many complexities of chronic ulcers will provide new therapeutic approaches to treat and promote the healing of these costly problems.

Summary

In chronic wounds, the balance between tissue degradation and synthesis is shifted toward degradation, resulting in impaired wound healing. Care of the cancer patient requires treatment modalities aimed at restoring the balance with recognition that this process may be further impaired through chemotherapy, radiation, malnutrition, or the malignancy itself. Irrigation and debridement are the primary methods of initial management to break the cycle of chronic inflammation. Dressings provide a protective barrier and should match the wound characteristics to prevent further damage; negative pressure devices may help prepare the wound bed to facilitate wound healing. Other adjunctive methods include antibiotics, growth factors, hyperbaric oxygen, and skin and dermal substitutes. Great care should be taken to tailor these methods to the appropriate patient. No treatment strategy will promote healing until the wound is modulated by changing the protease-laden, inflammatory microenvironment into one that is moving forward to produce healthy granulation tissue. Then, and only then, can the wound be stimulated to heal by a variety of therapies.

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References

1. Menke N, Ward KR, Diegelmann R. Non-healing wounds. *Emerg Med Rep* 2007;28(4)
2. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. *Clin Dermatol* 2007;25:19–25. [PubMed: 17276197]
3. Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Pecoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. *Arch Dermatol* 1994;130:489–493. [PubMed: 8166487]
4. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *Plast Reconstr Surg* 2006;117(7 Suppl):35S–41S. [PubMed: 16799373]
5. Yager DR, Zhang LY, Liang HX, Diegelmann RF, Cohen IK. Wound fluids from human pressure ulcers contain elevated matrix metalloproteinase levels and activity compared to surgical wound fluids. *J Invest Dermatol* 1996;107:743–748. [PubMed: 8875960]
6. Wysocki AB, Staiano-Coico L, Grinnell F. Wound fluid from chronic leg ulcers contains elevated levels of metalloproteinases MMP-2 and MMP-9. *J Invest Dermatol* 1993;101:64–68. [PubMed: 8392530]
7. Nwomeh BC, Liang HX, Cohen IK, Yager DR. MMP-8 is the predominant collagenase in healing wounds and nonhealing ulcers. *J Surg Res* 1999;81:189–195. [PubMed: 9927539]
8. Nwomeh BC, Liang HX, Diegelmann RF, Cohen IK, Yager DR. Dynamics of the matrix metalloproteinases MMP-1 and MMP-8 in acute open human dermal wounds. *Wound Repair Regen* 1998;6:127–134. [PubMed: 9776855]
9. Lobmann R, Zacheja S, Houdek P, Moll I, Lobmann R. Expression of matrix metalloproteinases, cytokines, and connexins in diabetic and nondiabetic human keratinocytes before and after transplantation into an ex vivo wound-healing model. *Diabetes Care* 2008;31:114–120. [PubMed: 17898090]
10. Bullen EC, Longaker MT, Updike DL, Benton R, Ladin D, Hou Z, Howard EW. Tissue inhibitor of metalloproteinases-1 is decreased and activated gelatinases are increased in chronic wounds. *J Invest Dermatol* 1995;104:236–240. [PubMed: 7829879]
11. Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med* 1989;320:365–376. [PubMed: 2536474]
12. Rao CN, Ladin DA, Liu YY, Chilukuri K, Hou ZZ, Woodley DT. Alpha 1-antitrypsin is degraded and non-functional in chronic wounds but intact and functional in acute wounds: the inhibitor protects fibronectin from degradation by chronic wound fluid enzymes. *J Invest Dermatol* 1995;105:572–578. [PubMed: 7561161]
13. Grinnell F, Zhu M. Fibronectin degradation in chronic wounds depends on the relative levels of elastase, alpha1-proteinase inhibitor, and alpha2-macroglobulin. *J Invest Dermatol* 1996;106:335–341. [PubMed: 8601737]
14. Cooper DM, Yu EZ, Hennessey P, Ko F, Robson MC. Determination of endogenous cytokines in chronic wounds. *Ann Surg* 1994;219:688–691. [PubMed: 8203978]discussion 691–692.
15. Falanga V. Growth factors and chronic wounds: the need to understand the microenvironment. *J Dermatol* 1992;19:667–672. [PubMed: 1293152]
16. Bennett NT, Schultz GS. Growth factors and wound healing: Part II. Role in normal and chronic wound healing. *Am J Surg* 1993;166:74–81. [PubMed: 8392302]
17. Menke, N.; Diegelmann, R. Biochemical pathways of wound healing: implication for development of disease-specific diagnostics. In: Makowski, G., editor. *Advances in Clinical Chemistry*. Elsevier; 2006. p. 167-187.
18. Steed DL. Wound-healing trajectories. *Surg Clin North Am* 2003;83:547–555. [PubMed: 12822725] vi–vii.

19. Robson MC, Hill DP, Woodske ME, Steed DL. Wound healing trajectories as predictors of effectiveness of therapeutic agents. *Arch Surg* 2000;135:773–777. [PubMed: 10896369]
20. Siegel HJ, Long JL, Watson KM, Fiveash JB. Vacuum-assisted closure for radiation-associated wound complications. *J Surg Oncol* 2007;96:575–582. [PubMed: 17999398]
21. Liu X, Liu JZ, Zhang E, Li P, Zhou P, Cheng TM, Zhou YG. Impaired wound healing after local soft x-ray irradiation in rat skin: time course study of pathology, proliferation, cell cycle, and apoptosis. *J Trauma* 2005;59:682–690. [PubMed: 16361913]
22. Kolb BA, Buller RE, Connor JP, DiSaia PJ, Berman ML. Effects of early postoperative chemotherapy on wound healing. *Obstet Gynecol* 1992;79:988–992. [PubMed: 1579328]
23. Tintinalli, JE.; Ma, OJ.; Cline, DM. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*. McGraw Hill; 2004.
24. Marx, JA.; Hockberger, RS.; Walls, RM. *ROSEN'S EMERGENCY MEDICINE: Concepts and Clinical Practice*. 6th Edition ed. Philadelphia, PA: MOSBY ELSEVIER; 2006.
25. Weiss EA. Surgical management of cutaneous ulcers and pressure sores. *Arch Surg* 2000;135:874.
26. Garcia AD, Thomas DR. Assessment and management of chronic pressure ulcers in the elderly. *Med Clin North Am* 2006;90:925–944. [PubMed: 16962850]
27. Bowle PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. *Clin Microbiol Rev* 2001;14:244–269. [PubMed: 11292638]
28. Sumpio BE. Foot ulcers. *N Engl J Med* 2000;343:787–793. [PubMed: 10984568]
29. London NJM, Donnelly R. ABC of arterial and venous disease: ulcerated lower limb. *BMJ* 2000;320:1589–1591. [PubMed: 10845973]
30. Watkins PJ. ABC of diabetes: the diabetic foot. *BMJ* 2003;326:977–979. [PubMed: 12727775]
31. Sarkar PK, Ballantyne S. Management of leg ulcers. *Postgrad Med J* 2000;76:674–682. [PubMed: 11060140]
32. de Araujo T, Valencia I, Federman DG, Kirsner RS. Managing the patient with venous ulcers. *Ann Intern Med* 2003;138:326–334. [PubMed: 12585831]
33. Nigam Y, Bexfield A, Thomas S, Ratcliffe NA. Maggot therapy: the science and implication for CAM Part II-Maggots combat infection. *Evid Based Complement Alternat Med* 2006;3:303–308. [PubMed: 16951714]
34. Nigam Y, Bexfield A, Thomas S, Ratcliffe NA. Maggot therapy: the science and implication for CAM Part I-history and bacterial resistance. *Evid Based Complement Alternat Med* 2006;3:223–227. [PubMed: 16786052]
35. Seaman S. Dressing selection in chronic wound management. *J Am Podiatr Med Assoc* 2002;92:24–33. [PubMed: 11796796]
36. Shirakawa M, Isseroff RR. Topical negative pressure devices: use for enhancement of healing chronic wounds. *Arch Dermatol* 2005;141:1449–1453. [PubMed: 16301393]
37. Jones SM, Banwell PE, Shakespeare PG. Advances in wound healing: topical negative pressure therapy. *Postgrad Med J* 2005;81:353–357. [PubMed: 15937199]
38. Reddy M, Gill SS, Rochon PA. Preventing pressure ulcers: a systematic review. *JAMA* 2006;296:974–984. [PubMed: 16926357]
39. Maciejewski ML, Reiber GE, Smith DG, Wallace C, Hayes S, Boyko EJ. Effectiveness of diabetic therapeutic footwear in preventing reulceration. *Diabetes Care* 2004;27:1774–1782. [PubMed: 15220265]
40. Yager DR, Chen SM, Ward S, Olutoye OO, Diegelmann RF, Cohen IK. The ability of chronic wound fluids to degrade peptide growth factors is associated with increased levels of elastase activity and diminished levels of proteinase inhibitors. *Wound Repair Regen* 1997;5:23–32. [PubMed: 16984454]
41. Marston WA, Hanft J, Norwood P, Pollak R. Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003;26:1701–1705. [PubMed: 12766097]
42. Mathias SD, Prebil LA, Boyko WL, Fastenau J. Health-related quality of life in venous leg ulcer patients successfully treated with Apligraf: a pilot study. *Adv Skin Wound Care* 2000;13:76–78. [PubMed: 11074990]

43. Howell-Jones RS, Wilson MJ, Hill KE, Howard AJ, Price PE, Thomas DW. A review of the microbiology, antibiotic usage and resistance in chronic skin wounds. *J Antimicrob Chemother* 2005;55:143–149. [PubMed: 15649989]
44. Gilbert, DN.; Moellering, RC.; Eliopoulos, G. *The Sanford Guide to Antimicrobial Therapy*. 36th ed. Sperryville, VA: Antimicrobial Therapy Inc.; 2006.
45. Neovius EB, Lind MG, Lind FG. Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck: a review of the literature and a report of 15 consecutive patients. *Head Neck* 1997;19:315–322. [PubMed: 9213110]
46. Pitkin AD, Davies NJH. Hyperbaric oxygen therapy. *CEACCP* 2001;1:150–156.
47. Feeser V, et al. Modulation of the deleterious effects of glucocorticoids on wound healing by immune regulating hormones. *Acad Emerg Med* 2007;14:S147–S148.
48. Feeser V, et al. Immune-regulating androstene hormones and their ability to reverse glucorticoid-inhibited wound closure shock. 2007;27:62.
49. Brem H, Stojadinovic O, Diegelmann RF, Entero H, Lee B, Pastar I, et al. Molecular markers in patients with chronic wounds to guide surgical debridement. *Mol Med* 2007;13:30–39. [PubMed: 17515955]

Figure 1.
Comparison of the phases of normal wound healing with the appearance of specialized cells.

Table 1

Phases of Wound Healing

Phase	Primary Cell Type Recruited	Function
Hemostatic	Platelets	Provisional fibrin matrix and recruits inflammatory cells
Inflammatory	Macrophages Neutrophils	Preparation of the wound bed by killing bacteria and removing devitalized tissue as well as recruiting fibroblasts
Proliferative	Fibroblasts	Stable extracellular matrix formation
Remodeling	Fibroblasts	Mature scar formation

Table 2**Stages of Tissue Breakdown**

I	Non-blanchable erythema of intact skin.
II	Partial-thickness skin loss involving the epidermis, dermis, or both. Superficial and may present as an abrasion, blister, or shallow crater.
III	Full-thickness skin loss involving damage to subcutaneous tissue that may extend down to, but not through, fascia. Presents clinically as a deep crater with or without undermining of adjacent tissue.
IV	Full-thickness skin loss with extensive damage to muscle, bone, or supporting structure. Extend all the way to bone and are likely to have deep seated soft tissue infections or osteomyelitis.

Table 3

Wound Dressings

Dressing	Type	Function and Use
Hydrocolloids	Occlusive	Autolytic debridement through endogenous proteolytic enzymes; not for use with infected wounds
Films, Foams, Alginates	Occlusive	Wounds kept moist through fluid entrapment; may result in skin tears and tissue maceration
Foams	Absorbant	Not as adherent as films; may need secondary dressing for reinforcement
Alginates	Absorbant	Made from seaweed; best for highly exudative wounds as may cause damage if dry in wound bed
Hydrogels	Hydrophilic polymers	Best for wounds that have formed granulation tissue

Table 4
Factors That May Impair Normal Wound Healing

Age
Co-Morbidities
Cardiac
Congestive Heart Failure
Connective Tissue Disease
Diabetes Mellitus
Hepatic
Hypertension
Renal
Lifestyle
Illicit Drug Use
Nutrition
Obesity
Smoking
Therapeutic Modalities
Chemotherapy
NSAIDs
Radiation
Steroids