The Relationship of Wound Healing with Psoriasis and Multiple Sclerosis

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Significance: Better understanding of wound healing could lead to improved treatment(s) of multiple sclerosis (MS) and psoriasis (Pso).

Recent Advances: New concepts in the events of wound healing, such as the roles of the innate and adaptive immune systems, have generated targets for treating these debilitating diseases.

Innovation: That in MS and Pso defective wound healing is responsible for the diseases' progression has not been hypothesized to date.

Conclusion: Impaired initiation of wound repair by oligodendrocyte precursor cells or oligodendrocytes may play a role in MS, and a lack of inhibition of the proliferative phase in wound healing may explain the pathophysiology involved in Pso.

Keywords: wound healing, psoriasis, multiple sclerosis

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BACKGROUND

PSORIASIS (Pso) AND multiple sclerosis (MS) are two chronic diseases that share a number of characteristics, including symmetry of the lesions and an isomorphic response (Koebner phenomenon).¹ It was first described in Pso by the German dermatologist, Koebner, when, anecdotally, he saw a psoriatic plaque develop in the skin of a patient, a farmer, traumatized by his horse that accidentally had bitten the man in an attempt to get at the sugar the farmer kept in his trouser pocket, a treat usually fed to the horse.² The occurrence of the Koebner phenomenon in Pso and MS suggests that the etiology of both of these diseases may relate to defects in the wound healing process. In Pso, a common skin disease characterized by epidermal hyperproliferation, the dysregulation in wound healing may be due to faulty control of differentiation of the keratinocytes (KCs), resulting in an

accelerated rate of wound healing.³ By contrast, in MS, after injury the oligodendrocytes appear not to fully repair the myelin sheath that protects the nerves. This article explores these concepts.

RELEVANCE

Epidermal response to wounding

The outermost layer of the skin, the epidermis, is particularly exposed to injury. In this layer, the vast majority of cells are KCs that must respond quickly to repair any damage. Wound healing is an essential and complex process and inflammation is a necessary component of wound repair as is the activation of Toll-like receptors.⁴ To facilitate this activity, KCs synthesize a large number of cytokines including tumor necrosis factor alpha (TNF α), vascular endothelial growth factor (VEGF), and both the constitutive and inducible forms of nitric oxide synthase.⁵ KCs,

as well as another cell of ectodermal origin, the oligodendrocyte, can produce nitric oxide (NO), a gas that is important in vasodilation and immune and inflammatory responses.⁶ NO stimulates KC proliferation and enhances VEGF expression in cultured KCs and during cutaneous wound repair. NO also activates KCs' production of epidermal growth factor (EGF) receptor ligands. The synthesis of EGF by KCs results in an autocrine loop with resultant proliferation of these epidermal cells,⁷ making NO a vital component of wound healing.

Normal, resting KCs express keratin I and X. By contrast, activated KCs express keratins VI and XVI, two types of keratins that are characteristic of Pso and wound healing.⁸ Wound healing can occur in four stages: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) maturation.

Psoriasis

Pso is a common autoimmune skin disease with a genetic basis that demonstrates many of the features of wound repair, namely KC hyperproliferation, a variable inflammatory infiltrate, and neovascularization.⁹ In Pso, an elevated intracellular Ca^{++} concentration in KCs does not lead to differentiation of these cells, resulting in a statistically significant increased rate of wound healing.³

Pso is characterized by erythematous plaques covered by thick white scales. It usually occurs on the extensor surfaces of the body, but can be found on any part of the body, including the scalp and nails. In a study of psoriatic plaques, Bhushan *et al.*¹⁰ showed that VEGF, a potent stimulator of angiogenesis, and its receptors, VEGFR-1 and -2, are overexpressed by KCs in the suprabasal layers of the epidermis, as well as, by dermal fibroblasts, implying a dermally derived influence on neovascularization. Also, in individuals with Pso, serum VEGF-A concentrations are increased. This may reflect overproduction, either in the skin with overflow into the circulation or as a primary genetic aberration. VEGF expression is increased during wound repair of the skin, and treatment of murine wounds with anti-VEGF antibodies reduces the number of proliferating KCs at the leading edge of the wound.¹¹

In individuals with Pso, even the clinically normal appearing skin is reset to initiate angiogenesis if the correct stimuli are present or if there is a local reduction in angiogenesis inhibitors.¹⁰ Furthermore, Detmar *et al.*¹² concluded that in psoriatic KCs, the synthesis and secretion of VEGF-A is stimulated by $\text{TNF}\alpha$ and EGF, since receptors for these proteins are overexpressed in psoriatic skin.

In Koebner-positive psoriatic lesions, an increased amount of nerve growth factor has been

demonstrated 24 h after traumatization.¹ The synthesis of this protein becomes maximal after 2 weeks. Furthermore, cultured KCs derived from nonlesional psoriatic skin also showed a markedly increased amount of nerve growth factor compared with KCs obtained from normal skin, and this protein increases at the same time as KCs proliferation accelerates.

Both KCs and oligodendrocyte precursor cells express the N-methyl-D-aspartate receptor, a cell surface receptor that regulates Ca^{++} influx.^{13,14} Activation of this receptor leads to Ca^{++} entry and resultant differentiation of normal KCs, as well as, the differentiation of normal oligodendrocyte precursor cells.¹⁵ The differentiation of oligodendrocyte precursor cells results in the remyelination of nerve cells.¹⁶

KCs also express the muscarinic acetylcholine receptor (mACh-R), as well as the nicotinic acetylcholine receptor (nACh-R),^{17,18} and activation of the nACh-R reduces the rate of wound healing.¹⁹ By contrast, benztropine, an inhibitor of the parasympathetic nervous system, inhibits the activation of the mACh-R, and can improve wound healing. Activation of the nACh-R reduces TLR-2-mediated migration of KCs, as well as, the production of proinflammatory cytokines and antimicrobial peptides. Activation of the mACh-R is needed for maintenance of epithelial progenitor cells.²⁰ Furthermore, benztropine stimulates oligodendrocyte precursor cells' differentiation and remyelination in an animal model of MS.^{21,22} The skin-related events appear to mimic the events occurring in the central nervous system (CNS) when damaged nerves are remyelinated. That the nervous system plays a role in Pso is suggested by the finding that severing of a nerve in one area of the body leads to healing of the psoriatic plaques in this area while the plaques on the contralateral side do not improve (Farber, E., personal communication). Furthermore, injecting Botox, a medication that blocks the ACh-R, into a psoriatic plaque results in clearing of only that lesion.^{23,24}

For unknown reasons, individuals with Pso have a significantly higher risk of developing MS and the more severe the Pso is, the more likely the individual will develop MS.²⁵ Furthermore, $\text{TNF}\alpha$ inhibitors can worsen the symptoms of MS and can even induce this disease.²⁶ Also, these drugs can induce Pso.²⁷ As previously mentioned, Pso shares many common characteristics with MS. For example, both diseases demonstrate slight itching, as well as symmetry of the lesions, stress-induced flare of the disease, exacerbation of the disease(s) after stopping corticosteroid treatment, and the Koebner phenomenon. This phenomenon includes provocation of the disease(s) by stress and stress

has been reported to be a provoking factor for the first and subsequent flares of MS.²⁸ Therefore, it seems possible that both Pso and MS may be due to abnormalities in the wound healing process. Thus, in Pso, the proliferation of KCs does not stop when the wound has re-epithelialized and in MS healing/remyelination does not start or does not progress to complete healing.

When an individual who has MS is treated with benztropine, the skin shows changes only in those areas of the body that were previously affected by the MS.²⁹ Initially, in these areas, erythema occurs. Then, the areas become purple, followed by white discoloration, due to vasoconstriction, and edema and scale/flakes. Finally, the skin in these areas turns sky blue. These changes in the skin suggest that similar abnormalities may also occur in the CNS of individuals with MS who are treated with benztropine.

Multiple sclerosis

MS is a disease that affects the CNS and, except for pruritus, does not affect the skin. Clinically, MS is characterized by decreasing motor strength, numbness, and sensitivity to heat. The latter symptom is due to increased malfunction of the nerves' potassium channels when the body temperature rises.

In MS, release of NO by oligodendrocyte precursor cells causes differentiation of these cells but does not lead to remyelination.¹⁶ Similarly, in the KCs comprising a psoriatic plaque, NO does not induce differentiation. As previously stated, elevated intracellular Ca^{++} also does not result in the differentiation of psoriatic KCs.

Since in MS the damage to the myelin sheath occurs in a "sterile" environment, that is, foreign pathogens such as bacteria and viruses do not enter the CNS. Therefore, in this disease, the innate immune system would not be activated, and the later stages of wound healing, proliferation, and maturation would not be initiated. Alternatively, the defect in the wound healing response in MS could relate to a failure in the switch of the resident macrophages from the inflammatory to the anti-inflammatory phenotype.³⁰ By contrast, in areas of the skin that express the psoriatic phenotype, one of the antimicrobial peptides, LL-37, is highly expressed, and, therefore, the wound healing response would likely be initiated.³¹

The many similarities in the pathophysiology documented in Pso and MS, as well as in wound healing, suggest that further basic research in these two autoimmune diseases may lead to a better understanding of wound healing. Furthermore, these

KEY FINDINGS

- Psoriasis (Pso) and multiple sclerosis (MS) share a number of features.
- Pso is related to abnormal wound healing.
- MS also may be related to abnormal wound healing.

insights may, in turn, suggest novel therapies for Pso and MS.

SIGNIFICANCE

The importance of the factors involved in wound healing and their relationship with the symptoms in two autoimmune diseases MS and Pso are discussed. An understanding of the cellular and molecular mechanisms that lead to wound healing may improve the selection of novel targets for the treatments of these two diseases. Also, knowledge of the early events in the development of psoriatic plaques in the skin in Pso may lead to better treatment(s) of wounds.

CLINICAL PROBLEMS ADDRESSED

In both MS and Pso, wound healing is abnormal and wounding can trigger expression of the disease(s). A striking difference between these diseases is that whereas $\text{TNF}\alpha$ inhibitors usually improve Pso, these inhibitors worsen the symptoms of MS. Moreover, development of MS can be a side effect of $\text{TNF}\alpha$ therapy for Pso and, paradoxically, these inhibitors can rarely initiate/induce Pso.

SUMMARY

Pso appears to be the result of a genetic abnormality in the inhibition of the wound healing response. By contrast, in MS, the opposite occurs: repair of the myelin sheath is not initiated or stops before the wound healing process is completed.

FUTURE DIRECTIONS

Both Pso and MS have a number of symptoms in common. Many of these symptoms are features of wound healing. Currently, impaired wound healing in, for example, diabetic ulcers causes considerable morbidity and mortality. Thus, foot ulcers occur in 15% of individuals with diabetes, leading to a large number of lower leg amputations. A better understanding of the pathophysiology of wound healing may lead to more targeted therapies.

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Vera B. Morhenn, MD, is a retired dermatologist who until her recent move to the San Francisco area worked/volunteered in the Division of Dermatology, UC San Diego and the VA Hospital in San Diego.

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Abbreviations and Acronyms

CNS = central nervous system
 EGF = epidermal growth factor
 KCs = keratinocytes
 mACh-R = muscarinic acetylcholine receptor
 MS = multiple sclerosis
 nACh-R = nicotinic acetylcholine receptor
 NO = nitric oxide
 Pso = psoriasis
 TNF α = tumor necrosis factor alpha
 VEGF = vascular endothelial growth factor