EDITORIAL

Sociogenomic Approach to Wound Care: A New Patient-Centered Paradigm

Chandan K. Sen* and Sashwati Roy

The Indiana University Health Comprehensive Wound Center, Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana.

Chandan K. Sen, PhD

Submitted for publication September 13, 2019. Accepted in revised form September 13, 2019.

*Correspondence: Indiana Center for Regenerative Medicine, Indiana University School of Medicine, 975 W Walnut Street, Indianapolis, IN 46202 (e-mail: cksen@iu.edu).

Psychoneuroendocrinology studies provided first insight into social determinants of wound healing. Social stressors impede wound healing. In 2005, we first reported that the transcriptome of wound-site neutrophil is highly responsive to psychological stress in young men. Bioinformatics processing of transcriptome-wide data from neutrophils provided first insight into social transduction pathways relevant to wound healing. In 2010, Idaghdour *et al.* presented striking evidence demonstrating that genetic factors are responsible for only 5% of the variation in genomic expression. In contrast, the living environment of the individual, urban or rural, was responsible for as much as 50% of such variation. Genetic and environmental factors acted in a largely additive manner. This observation may be credited as the foundation stone of human social genomics. The environment of a patient, including social factors, influences gene expression relevant to wound healing. The nonhealing wound itself and its worsening outcome, including pain, are likely to cause stress. Conversely, positive social interactions may circumvent barriers to wound healing. Thus, interventions directed at the social environment of a wound care patient are likely to help manage wound chronicity. The genomic and related Big Data technology platforms have vastly improved during the past 5 years during which these technologies have also become widely accessible and affordable. Thus, this is the right time to revisit the choice of technologies for the study of social genomics of wound healing. Against the backdrop of our current understanding of the mechanisms of wound healing, such precision approach is likely to transform wound care and its outcomes making it patient-centered and, therefore, more effective.

Keywords: social genomics, patient-centered care, wound care paradigm

Thirteen women psychologically stressed because of caring for demented relatives were experimentally wounded to obtain first insight from a well-controlled study demonstrating that caregiver stress impedes wound healing.[1] Peripheral-blood leukocytes were impaired in their ability to mount a response that induces the interleukin-1β gene in response to lipopolysaccharide stimulation compared with cells from those who were not subject to caregiver stress. Not just inducible interleukin-1β gene alone, follow-up studies in our laboratory demonstrated that in psychologically stressed young men, of the 22,283 transcripts surveyed in wound-site neutrophils, 328 genes were downregulated and 264 genes were upregulated in all subjects studied.[2] Functional analyses of the transcriptome data revealed that stress tilted the balance of the transcriptome toward genes encoding proteins responsible for cell cycle

DOI: 10.1089/wound.2019.1101

arrest, death, and inflammation. The observation that psychosocial stress impairs wound healing have robust support from a number of independent experimental settings, including hostile marital interactions,[3] examination stress,[2] wound-related pain,[4] anger,[5] and social isolation.[6] Wound can be painful. Anxiety and depression can make pain worse. Pain can slow healing. Furthermore, psychological stress can adversely influence healing outcomes by promoting the adoption of health-damaging behaviors.[7] For example, self-cutting behavior is common among inmates.[8] The influence of social factors on wound healing has a broad base. Worse clinical and functional outcomes for minority children compared with white children have been reported for injury in children. In such cases, African American race is recognized as an independent predictor of mortality. These disparities persist even when injury severity and socioeconomic status are controlled in the experiment design.[9] Consistently, in adults, socioeconomic factors, including poorer household income, are strongly associated with an increased risk of postoperative surgical site infections after lower extremity revascularization.[10] The study of healing rates in a 27 year data set of natural injuries and illnesses in wild baboon males concluded that social status predicts wound healing. Alpha male baboons, with high glucocorticoids and highest testosterone and reproductive effort, healed significantly faster than other males.[11] The case for social factors influencing healing outcomes is compelling. The stage is thus set for looking at environmental modulation, including social influence, on gene expression relevant to wound healing.

The environment of a patient, including social factors, influences gene expression relevant to wound healing. Such altered expression of gene manifest function that, on the one hand, may directly influence the trajectory of wound healing. On the other hand, such altered expression of genes in different tissue compartment of the body may directly or indirectly change the social response of the person to the environment, thus indirectly influencing pathways relevant to wound healing. The nonhealing wound itself and its worsening outcome, including pain, are likely to cause stress. Other relevant factors such as social isolation, mood disorders, demoralization, community stress, reduced independence, limited ability to perform activities of daily living, low self-esteem, and poor body image are likely to drive genomic changes impeding wound healing through social signal transduction.[12,13] Conversely, positive social interactions circumvent barriers to wound healing. Positive social interactions influence the activity of the hypothalamic-pituitary-adrenal (HPA) axis to restore wound healing. Positive social interactions is known to antagonize the effects of stress on wound healing through a mechanism that involves oxytocin-induced suppression of the HPA axis.[14] Thus, interventions directed at the social environment of a wound care patient are likely to help manage wound chronicity. Such interventions are likely to impact gene expression *via* epigenetic pathways. These pathways produce heritable changes in gene expression that do not involve any change in the sequence of DNA. DNA methylation and histone modifications represent two major mechanisms that have profound effects on controlling gene expression. Promoter methylation of noncoding genes contributes to diabetic vasculopathy.[15] Small noncoding genes, miRNA, themselves are also epigenetic modulators of gene expression. In 2007, the first study addressing the significance of miRNAs in wound healing was published.[16] During the course of past decade considerable studies from our as well as other laboratories underscore the significance of miRNAs on wound healing outcomes.[17,18] Early life stress, such as childhood abuse and neglect, can cause epigenomic changes, which in turn may be responsible for development of psychiatric and behavioral disorders later in adult life.[19] When pregnant with the mother, smoking by grandmother increased disease risk in the grandchild independent of the mother's smoking status.[20] Thus, in wound care, sociogenomic factors may impact wound healing outcomes across generations.

Infection is a major complicating factor in wound care. More than one-half of all diabetic ulcers are clinically infected.[21] Considering that standard clinical tests are not likely to detect biofilm infection in all of its forms, that fraction is an underestimation. Infection of the foot is known to precede 80% of nontraumatic lower limb amputations.[22,23] Psychosocial stress suppresses the immune system, thus compromising the body's ability to fight infection.[24] How such interaction influences wound infection status, biofilm aggregation, and host-microbial interaction remains to be understood. The Center for Disease Control estimates that 65% of all human infections are caused by bacteria with a biofilm phenotype and National Institutes of Health estimates that this number is closer to 80%. Biofilm infection contributes to chronicity of inflammation and so does stress.[25–27] In turn, inflammation is a risk factor for the development of depressed mood and other neuropsychiatric, neurodevelopmental, and neurodegenerative disorders.[28] Biofilm infection impairs granulation tissue

collagen causing compromised wound tissue biomechanics making the wound more susceptible to recurrence.[29] Biofilm infection impairs the ability of the repaired skin to restore its barrier function.[30] Impaired barrier function of the skin is also a hallmark of the aged and diabetic human skin.[31] Thus, at the intersect of aging and wound infection is a vicious interactive process where stress-induced immune suppression and subdued ability to fight infection is likely to compromise skin function such that the risk of wound recurrence is higher in an already vulnerable aged and/or diabetic skin. The older, evolutionarily conserved defense strategy, innate immunity is of extraordinary significance in this context. Macrophage function is highly responsive to social stress as well as is to wound and infection making it a pointed target of study in the context of the social genomics of the wound.[32–35]

In 2010, Idaghdour *et al.* presented striking evidence demonstrating that genetic factors are responsible for only 5% of the variation in genomic expression. In contrast, the living environment of the individual, urban or rural, was responsible for as much as 50% of such variation.[36] The study, and other related evidence, presents a compelling case supporting inclusion of genomic data as an integral component of large social and behavioral data sets. The Health and Retirement Study and the National Longitudinal Study of Adolescent to Adult Health are examples that have shown us the way and its value.[37,38] Social signal transduction is controlled by different and interacting molecular circuits that culminate in gene expression that is different in different subsets of any cell population studied. Thus, in addition to global epigenetic changes, as discussed, one may expect changes in gene expression that are specific to cellular subsets. High-throughput single-cell transcriptomics, not yet commonly applied to social genomics, is a technology platform with considerable potential. Thousands of cells can be profiled simultaneously and analyzed accurately, revealing unique insights into developmental progressions, transcriptional pathways, and the molecular heterogeneity of tissues.[39] An average trait within a population is often not representative of the state of any individual cell. Even within populations that are homogeneous in terms of cell surface markers, hidden cell-to-cell variations have direct and significant consequences on system function.[40]

What may be viewed as a subset of the established field of behavioral genetics, social genomics, or sociogenomics is inherently inductive as opposed to deductive by approach. To that end, long-term longitudinal studies in established cohorts of chronic wound patients are likely to provide key insight necessary to develop this emergent field. In contrast, hypotheses based on current literature may be tested in early observational studies on patients with wounds. Sets of data from both of these line of inquiries originating from independent studies will lay the foundation to an effort that has much to give in improving our current paradigm of wound care.

ACKNOWLEDGMENTS AND FUNDING SOURCES

Wound healing research in the author's laboratory supported by the following NIH awards: GM 108014, NR 015676, DK 119099, and DK 114718.

AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist.

ABOUT THE AUTHORS

Professor Chandan Sen is the Editor of *Advances in Wound Care*.

REFERENCES

1. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet 1995;346:1194–1196.
2. Roy S, Khanna S, Yeh PE, et al. Wound site neutrophil transcriptome in response to psychological stress in young men. Gene Expr 2005;12:273–287.
3. Gouin JP, Carter CS, Pournajafi-Nazarloo H, et al. Marital behavior, oxytocin, vasopressin, and wound healing. Psychoneuroendocrinology 2010;35:1082–1090.
4. McGuire L, Heffner K, Glaser R, et al. Pain and wound healing in surgical patients. Ann Behav Med 2006;31:165–172.
5. Gouin JP, Kiecolt-Glaser JK, Malarkey WB, Glaser R. The influence of anger expression on wound healing. Brain Behav Immun 2008;22:699–708.
6. Takahashi A, Flanigan ME, McEwen BS, Russo SJ. Aggression, social stress, and the immune system in humans and animal models. Front Behav Neurosci 2018;12:56.
7. Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. Immunol Allergy Clin North Am 2011;31:81–93.
8. Matsumoto T, Yamaguchi A, Asami T, Okada T, Yoshikawa K, Hirayasu Y. Characteristics of self-cutters among male inmates: association with bulimia and dissociation. Psychiatry Clin Neurosci 2005;59:319–326.

9. Brown RL. Epidemiology of injury and the impact of health disparities. Curr Opin Pediatr 2010;22:321–325.
10. Bakshi SC, Fobare A, Benarroch-Gampel J, Teodorescu V, Rajani RR. Lower socioeconomic status is associated with groin wound complications following revascularization for peripheral artery disease. Ann Vasc Surg 2019 [Epub ahead of print]; DOI: 10.1016/j.avsg.2019.05.010.
11. Archie EA, Altmann J, Alberts SC. Social status predicts wound healing in wild baboons. Proc Natl Acad Sci U S A 2012;109:9017–9022.
12. Quinn ME, Stanton CH, Slavich GM, Joormann J. Executive control, cytokine reactivity to social stress, and depressive symptoms: testing the social signal transduction theory of depression. Stress 2019. [Epub ahead of print]; DOI: 10.1080/10253890.2019.1641079.
13. Cole SW. Human social genomics. PLoS Genet 2014;10:e1004601.
14. Detillion CE, Craft TK, Glasper ER, Prendergast BJ, DeVries AC. Social facilitation of wound healing. Psychoneuroendocrinology 2004;29:1004–1011.
15. Singh K, Pal D, Sinha M, et al. Epigenetic modification of microRNA-200b contributes to diabetic vasculopathy. Mol Ther 2017;25:2689–2704.
16. Shilo S, Roy S, Khanna S, Sen CK. MicroRNA in cutaneous wound healing: a new paradigm. DNA Cell Biol 2007;26:227–237.
17. Sen CK, Ghatak S. miRNA control of tissue repair and regeneration. Am J Pathol 2015;185:2629–2640.
18. Banerjee J, Sen CK. MicroRNAs in skin and wound healing. Methods Mol Biol 2013;936:343–356.
19. Provencal N, Binder EB. The effects of early life stress on the epigenome: from the womb to adulthood and even before. Exp Neurol 2015;268:10–20.
20. Magnus MC, Haberg SE, Karlstad O, Nafstad P, London SJ, Nystad W. Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian Mother and Child Cohort Study. Thorax 2015;70:237–243.
21. Prompers L, Huijberts M, Schaper N, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia 2008;51:1826–1834.
22. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293:217–228.
23. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017;376:2367–2375.
24. Hunter HJ, Momen SE, Kleyn CE. The impact of psychosocial stress on healthy skin. Clin Exp Dermatol 2015;40:540–546.
25. Klein P, Sojka M, Kucera J, et al. A porcine model of skin wound infected with a polybacterial biofilm. Biofouling 2018;34:226–236.
26. Kuhlman KR, Robles TF, Haydon MD, Dooley L, Boyle CC, Bower JE. Early life stress sensitizes individuals to the psychological correlates of mild fluctuations in inflammation. Dev Psychobiol 2019 [Epub ahead of print]; DOI: 10.1002/dev.21908.
27. Kinnally EL, Martinez SJ, Chun K, Capitanio JP, Ceniceros LC. Early social stress promotes inflammation and disease risk in rhesus monkeys. Sci Rep 2019;9:7609.
28. Slavich GM, Sacher J. Stress, sex hormones, inflammation, and major depressive disorder: extending social signal transduction theory of depression to account for sex differences in mood disorders. Psychopharmacology (Berl) 2019 [Epub ahead of print]; DOI: 10.1007/s00213-019-05326-9.
29. Roy S, Santra S, Das A, et al. *Staphylococcus aureus* biofilm infection compromises wound healing by causing deficiencies in granulation tissue collagen. Ann Surg 2019 [Epub ahead of print]; DOI: 10.1097/SLA.0000000000003053.
30. Roy S, Elgharably H, Sinha M, et al. Mixed-species biofilm compromises wound healing by disrupting epidermal barrier function. J Pathol 2014;233:331–343.
31. Choi EH. Aging of the skin barrier. Clin Dermatol 2019;37:336–345.
32. Zheng X, Hu M, Zang X, et al. Kynurenic acid/GPR35 axis restricts NLRP3 inflammasome activation and exacerbates colitis in mice with social stress. Brain Behav Immun 2019;79:244–255.
33. Stark JL, Avitsur R, Padgett DA, Campbell KA, Beck FM, Sheridan JF. Social stress induces glucocorticoid resistance in macrophages. Am J Physiol Regul Integr Comp Physiol 2001;280:R1799–R1805.
34. Das A, Sinha M, Datta S, et al. Monocyte and macrophage plasticity in tissue repair and regeneration. Am J Pathol 2015;185:2596–2606.
35. Hanke ML, Heim CE, Angle A, Sanderson SD, Kielian T. Targeting macrophage activation for the prevention and treatment of *Staphylococcus aureus* biofilm infections. J Immunol 2013;190:2159–2168.
36. Idaghdour Y, Czika W, Shianna KV, et al. Geographical genomics of human leukocyte gene expression variation in southern Morocco. Nat Genet 2010;42:62–67.
37. Sathyan S, Wang T, Ayers E, Verghese J. Genetic basis of motoric cognitive risk syndrome in the Health and Retirement Study. Neurology 2019;92:e1427–e1434.
38. Domingue BW, Belsky DW, Fletcher JM, Conley D, Boardman JD, Harris KM. The social genome of friends and schoolmates in the National Longitudinal Study of Adolescent to Adult Health. Proc Natl Acad Sci U S A 2018;115:702–707.
39. Denyer T, Ma X, Klesen S, Scacchi E, Nieselt K, Timmermans MCP. Spatiotemporal developmental trajectories in the Arabidopsis root revealed using high-throughput single-cell RNA sequencing. Dev Cell 2019;48:840–852. e845.
40. Strzelecka PM, Ranzoni AM, Cvejic A. Dissecting human disease with single-cell omics: application in model systems and in the clinic. Dis Model Mech 2018;11:dmm036525.

Abbreviations and Acronyms

HPA = hypothalamic-pituitary-adrenal