Cancer and Wound Healing: a Story of Alternative Splicing

Marco Demaria
Buck Institute for Research on Aging, 8001 Redwood Blvd, Novato, CA 94945, USA
Email: mdemaria@buckinstitute.org

Abstract
Cancer and wound healing are promoted by similar cellular and molecular mechanisms. One explanation to the difference between the two processes resides in the duration of induction of several inflammatory and growth factors. Recently, a paper from Jensen et al. added a new hypothesis to explain the loss of tissue homeostasis and gain of aberrant functions.

Keywords: alternative splicing, cancer, growth factors, inflammation, SRSF6, tenascin C, tissue homeostasis, wound healing

In 1986 Dvorak described tumors as wounds that don't heal [1]. His hypothesis was based on the similarities between the tumor stroma and the wound site, and on one big difference: the duration of cytokines and growth factors secretion. Wound healing is a self-limiting process, whereas each step is well defined by the secretion of specific factors for specific amounts of time [2]. Cancer is often characterized by the chronic induction of several factors, by either the cancer cells or the surrounding tissue. This cancer-associated chronic inflammation was first observed by Rudolph Virchow in 1863, and now is considered an essential hallmark for tumourigenesis [3].

We know from several studies in animal models that altering the levels of secreted factors affects optimal wound healing, but may represent a rather specific and non-toxic anti-cancer intervention, such as in the case of IL-6 and FGF [4,[5,[6,[7].

A more specific example of this dichotomy is VEGF, an essential pro-angiogenesis factor, induced during wound healing and in cancerous lesions. Several animal models show that low levels of VEGF lead to impaired tissue repair, and that exogenous expression of the recombinant protein is able to recue this defect [8]. On the other side, bevacizumab, a monoclonal antibody against VEGF, has been approved by the FDA in 2004 for the treatment of different metastatic cancers [9].

It is clear that wounded skin and cancer show striking similarities in terms of gene expression profiling, signaling cascades, and protein secretion, suggesting that the mechanisms involved might be of similar nature but of different magnitude [10].

Interestingly, Jensen et al. recently showed that a basic molecular mechanism, i.e. alternative splicing, may be at the base of the difference between homeostatic and aberrant responses to injury [11].

Alternative splicing (AS) allows most mammalian cells to express multiple mRNA isoforms starting from the same gene, thus contributing to the enormous complexity of the proteome.

Jensen et al. demonstrated that the serine/arginine-rich (SR) protein SRSF6 [12], which belongs to the family of RNA-binding splicing-factor proteins, may be an important regulator of wound healing and tissue homeostasis in skin, and that its perturbation can promote tumourigenesis.

Transgenic mice that over-express the human SRSF6 showed aberrant proliferation and hyperplasia in the skin. Epithelial cells over-

expressing SRSF6 induced a wound-healing gene expression signature, characterized by several inflammatory factors and differentiation markers.

Interestingly, SRSF6 was induced during normal wounding, suggesting that perturbing its expression may be critical for misregulating tissue repair. They also have some preliminary data that the skin hyperplasia is due to depletion of a specific subtype of stem cells (Lgr6+) that populate the upper-hair-follicle.

The authors showed that sustained SRSF6 expression leads to specific AS signatures, and they identified some alternative spliced variants for some important proto-oncogenes, such as pyruvate kinase M (PKM) and tenascin C (TNC) [13]. They then focused on TNC, demonstrating that the generation of the long spliced variant was SRSF6-dependent. Importantly, the analysis of human basal-cell carcinomas, squamous-cells carcinomas, and malignant melanomas revealed a strong correlation between high levels of SRSF6, the long form of TNC, and the severity of the malignancy.

These data candidate SRSF6 as a new important player for the transition from a wound healing signature to a malignant phenotype, but also arises several questions: 1) what is the role of SRSF6 during normal wound healing?; 2) how is SRSF6 regulated?; 3) what causes the over-expression of SRSF6 in cancer? Direct mutations or upstream signaling?; 4) is TNC a possible candidate for cancer treatments? 5) is TNC involved during normal wound healing?

References

[1] H.F. Dvorak. N Engl J Med. 315 (1986) 1650-1659.
[2] G.C. Gurtner, S. Werner, Y. Barrandon & M.T. Longaker. Nature. 453 (2008) 314-321.
[3] H. David. Pathol Res Pract. 183 (1988) 356-364.
[4] R.M. Gallucci, P.P. Simeonova, J.M. Matheson, C. Kommineni, J.L. Guriel, T. Sugawara & M.I. Luster. FASEB J. 14 (2000) 2525-2531.
[5] Y. Guo, F. Xu, T. Lu, Z. Duan & Z. Zhang. Cancer Treat Rev. 38 (2012) 904-910.
[6] S. Ortega, M. Ittmann, S.H. Tsang, M. Ehrlich & C. Basilico. Proc Natl Acad Sci U S A. 95 (1998) 5672-5677.
[7] A.N. Brooks, E. Kilgour & P.D. Smith. Clin Cancer Res. 18 (2012) 1855-1862.
[8] H. Brem, A. Kodra, M.S. Golinko, H. Entero, O. Stojadinovic, V.M. Wang, C.M. Sheahan, A.D. Weinberg, S.L. Woo, H.P. Ehrlich & M. Tomic-Canic. J Invest Dermatol. 129 (2009) 2275-2287.
[9] R. Bicknell. Ann Oncol. 17 Suppl 10 (2006) x76-78.
[10] H.Y. Chang, D.S. Nuyten, J.B. Sneddon, T. Hastie, R. Tibshirani, T. Sorlie, H. Dai, Y.D. He, L.J. van't Veer, H. Bartelink, M. van de Rijn, P.O. Brown*, et al.* Proc Natl Acad Sci U S A. 102 (2005) 3738-3743.
[11] M.A. Jensen, J.E. Wilkinson & A.R. Krainer. Nat Struct Mol Biol. (2014)
[12] A.R. Krainer, G.C. Conway & D. Kozak. Cell. 62 (1990) 35-42.
[13] K.S. Midwood & G. Orend. J Cell Commun Signal. 3 (2009) 287-310.