COMMENTS AND RESPONSES

Neurovascular Factors in Wound Healing in the Foot Skin of Type 2 Diabetic Subjects

Response to Krishnan et al.

We read with interest the article by Krishnan et al. (1) reporting the healing of acute wounds in type 2 diabetic patients versus control subjects. The authors also reported the expression of vascular endothelial growth factor (VEGF)-A, VEGF-R2, and hypoxia-inducible factor (HIF)-1α in intact skin biopsies from these groups of subjects.

We agree about the pivotal role played by HIF-1α in wound healing (2,3), which is in perfect agreement with our observation regarding lower expression of HIF-1α in chronic diabetic wounds (4)—not referred, however, by the authors. The authors' observation about a lack of difference in HIF-1α expression in unwounded skin between diabetic and control subjects is not surprising. The main stimulus for HIF-1α is hypoxia, and, as far as the tissues are not challenged, they will exhibit a basal, low level of HIF-1α. Our comment about HIF-1α levels can even be extended to the other immunohistological data presented by the authors that were collected solely on biopsies from intact skin. As an example, the basal levels of VEGF are increased in unwounded skin of *db/db* mice (5) but react with a significant delay in the wound healing process. It is therefore better to not extrapolate the steady-state levels of different factors found in intact skin biopsies to their potential role and regulation during the wound healing process in which the main pathogenic mechanism could rely just on the inappropriate reaction to concerted stimuli.

SERGIU-BOGDAN CATRINA, MD, PHD
KERSTIN BRISMAR, MD, PHD

From the Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden.

Address correspondence to Sergiu-Bogdan Catrina, MD, PhD, Molecular Medicine and Surgery, Karolinska Hospital, Rolf Luft Center, Stockholm S-17176, Sweden. E-mail: sergiu-bogdan.catrina@ki.se.

DOI: 10.2337/dc07-1974

© 2008 by the American Diabetes Association.

References

1. Krishnan STM, Quattrini C, Jeziorska M, Malik RA, Rayman G: Neurovascular factors in wound healing in the foot skin of type 2 diabetic subjects. *Diabetes Care* 30: 3058–3062, 2007
2. Elson DA, Ryan HE, Snow JW, Johnson R, Arbeit JM: Coordinate up-regulation of hypoxia inducible factor (HIF)-1alpha and HIF-1 target genes during multi-stage epidermal carcinogenesis and wound healing. *Cancer Res* 60:6189–6195, 2000
3. Li W, Li Y, Guan S, Fan J, Cheng CF, Bright AM, Chinn C, Chen M, Woodley DT: Extracellular heat shock protein-90alpha: linking hypoxia to skin cell motility and wound healing. *EMBO J* 26: 1221–1233, 2007
4. Catrina SB, Okamoto K, Pereira T, Brismar K, Poellinger L: Hyperglycemia regulates hypoxia-inducible factor-1α protein stability and function. *Diabetes* 53:3226–3232, 2004
5. Frank S, Hubner G, Breier G, Longaker MT, Greenhalgh DG, Werner S: Regulation of vascular endothelial growth factor expression in cultured keratinocytes: implications for normal and impaired wound healing. *J Biol Chem* 270:12607–12613, 1995