

# Comment on: Biscetti et al. (2010) High-Mobility Group Box-1 Protein Promotes Angiogenesis After Peripheral Ischemia in Diabetic Mice Through a VEGF-Dependent Mechanism. *Diabetes*;59:1496–1505

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In a recent *Diabetes* article, Biscetti et al. (1) report that high-mobility group box-1 (HMGB1) protein levels are reduced in the skeletal muscle of diabetic mice and that exogenous HMGB1 administration, following the induction of hindlimb ischemia, promotes angiogenesis through a VEGF-dependent mechanism.

With regard to the angiogenic effect of HMGB1, we have previously demonstrated that both HMGB1 administration and endogenous HMGB1 blockade, in a mouse model of hindlimb ischemia, modulated neovascularization and myoblast function (2). Specifically, we found that HMGB1 delivery to ischemic hindlimbs promoted tissue perfusion, enhanced arteriole density, and increased myofiber numbers. To our knowledge, that was the first demonstration of HMGB1 in vivo pro-angiogenic action. Further, in another study, we showed that, in the presence of diabetes, HMGB1 levels were reduced in the skin. Under these conditions, HMGB1 administration to diabetic skin wounds promoted angiogenesis and enhanced healing (3). In their study, Biscetti et al. also show that some HMGB1-mediated effects are attributable to VEGF release from cells resident in the ischemic tissues. In agreement with this result, we had previously found enhanced VEGF and

placenta growth factor release from HMGB1-treated cardiac fibroblasts (4).

Thus, the conclusions reached by Biscetti et al. on HMGB1's ability to induce angiogenesis in diabetic mice following hindlimb ischemia is in full agreement with our previous studies (2–4).

In addition to confirming our previous observations, the study by Biscetti et al. extends them by showing that the inhibition of VEGF activity in ischemic diabetic hindlimbs results in a significant reduction of HMGB1-induced blood flow recovery.

## ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

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