

Sen, C. K., S. Khanna, M. Venojarvi, P. Trikha, E. C. Ellison, T. K. Hunt, and S. Roy. 2002. Copper-induced vascular endothelial growth factor expression and wound healing. *Am.J.Physiol Heart Circ.Physiol* 282:H1821-H1827.

**Abstract:** Angiogenesis plays a central role in wound healing. Among many known growth factors, vascular endothelial growth factor (VEGF) is believed to be the most prevalent, efficacious, and long-term signal that is known to stimulate angiogenesis in wounds. Whereas a direct role of copper to facilitate angiogenesis has been evident two decades ago, the specific targets of copper action remained unclear. This report presents first evidence showing that inducible VEGF expression is sensitive to copper and that the angiogenic potential of copper may be harnessed to accelerate dermal wound contraction and closure. At physiologically relevant concentrations, copper sulfate induced VEGF expression in primary as well as transformed human keratinocytes. Copper shared some of the pathways utilized by hypoxia to regulate VEGF expression. Topical copper sulfate accelerated closure of excisional murine dermal wound allowed to heal by secondary intention. Copper-sensitive pathways regulate key mediators of wound healing such as angiogenesis and extracellular matrix remodeling. Copper-based therapeutics represents a feasible approach to promote dermal wound healing.