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# Cellular and molecular mechanisms of impaired angiogenesis and delayed wound healing in type 2 diabetes: Amelioration using siRNA-Pluronic acid-based technology

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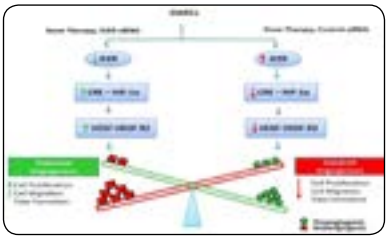
Angiogenesis, *de novo* capillary outgrowth from pre-existing vascular network, is crucial for wound healing and involves endothelial loosening, endothelial cell migration, stalk elongation, anastomosis and stabilization. This process is initiated and sustained until the terminal stage of healing and is orchestrated by a variety of growth factors/cytokines with vascular endothelial growth factor (VEGF) being the predominant regulator. Insufficient angiogenesis and non-functional vasculature are common features of non-healing diabetic wounds. This phenomenon may stem from an imbalance between pro-angiogenic (e.g., VEGF) and anti-angiogenic (e.g., thrombospondins) mediators with a shift in balance occurring in favor of suppressed angiogenesis. Current therapeutic strategies to enhance wound-based angiogenesis, including topical applications of growth factors are inadequate and new treatment is needed especially when viewed in the context of increasing rates of obesity and diabetes during the recent years. To this end, we will describe the "angiogenesis model of wound healing". Moreover, the cellular and molecular cascades that coordinate angiogenesis in healthy and diabetic wounds will be addressed. Finally, rather than providing an encyclopedia survey, we will focus on a recent discovery by our laboratory confirming a new molecular target (e.g., CREM/ICER-HIF-1-VEGF axis) that may have translational potential in providing therapeutic avenues, aimed at advancing the treatment of angiogenesis-dependent disorders including delayed wound healing.



## Recent Publications

1. Bitar, M.S. and F. Al-Mulla, *Upregulation of CREM/ICER suppresses wound endothelial CRE-HIF-1alpha-VEGF-dependent signaling and impairs angiogenesis in type 2 diabetes.* Dis Model Mech, 2015. 8(1): p. 65-Falanga, V., *Wound healing and its impairment in the diabetic foot*. Lancet, 2005. 366(9498): p. 1736-43.
2. Swift, M.E., H.K. Kleinman, and L.A. DiPietro, Impaired *wound repair and delayed angiogenesis in aged mice.* Lab Invest, 1999. 79(12): p. 1479-87.
3. Carmeliet, P. and R.K. Jain, *Molecular mechanisms and clinical applications of angiogenesis.* Nature 2011.473(7347): p. 298-307.
4. Folkman, J., *Angiogenesis: an organizing principle for drug discovery?* Nat Rev Drug Discov, 2007. 6(4): p.273-86.
5. Bitar, M.S., *Insulin and glucocorticoid-dependent suppression of the IGF-I system in diabetic wounds.* Surgery, 2000. 127(6): p. 687-95.

## Biography

Milad S. Bitar earned a B.S at Oklahoma State University and a M.Sc. in biochemistry and a Ph.D. in Pharmacology at University of Maryland. He performed his postdoctoral at the National Institutes of Health in Bethesda, Maryland. Currently, he is a Professor of Pharmacology at Kuwait University, School of Medicine and he is also a Fellow in American Collage of Clinical Pharmacology. He has long experience in the field of oxygen radical biology, with special emphasis regarding the role of Reactive Oxygen Species (ROS) in signalling derangement leading to tumor growth and various diabetic complications including cardiovascular diseases, delayed wound healing and impaired angiogenesis. Most experiments in these areas are conducted on genes, cells and animal models in addition to clinical research in patients with diabetes and cancer. He has a number of patents for new drugs to treat oxidative stress, impaired angiogenesis and delayed wound healing.

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