Nitric oxide and its role in health and diabetes.

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Part 6. Nitric Oxide's effects on Proliferation/differentiation:

fibroblasts, blood vessels (angiogenesis), and skin.

Nitric Oxide (NO) and its interrelationship with essential growth factors is critically involved in the entire continuum of events associated with wound repair, including cell division, maturation, neovascularization, and collagen synthesis including proper cross-linking of collagen fibers.

NO is a powerful stimulator of cell division. This is called proliferation, one cell into two, two into four, four into eight, and so on. For wounds to heal, new tissue is formed through induced division of existing cells. Several of the 10 to 20 known growth factors are necessary to induce cell division required in tissue repair. Of these, epidermal growth factor and/or keratinocyte growth factor, which are important for re-epithelialization and wound closure, cannot perform their biological function without their common chemical mediator, NO. Additionally, NO is important in duplicating some of the components of the cell so that each new cell is identical to its parent.

Proliferating cells must then differentiate into mature cells capable of responding to external signals. NO also stimulates the process of differentiation, in part, by regulating the formation of other proteins within the cell. One critical protein is the cytoskeleton, a complex network of proteins that form the internal structure of the cell. These cytoskeletal proteins exert many functions, one of which is the insertion of receptors into the cell membrane. One end of some of these proteins is exposed to the external environment (the interstitial fluid) and the other end of the protein communicates with the cell interior (the cytoplasm). In the absence of NO, cytoskeletal protein development does not occur. Thus, without NO, a cell cannot form proteins that recognize, process and transmit information from outside of the cell to the cell interior.

Stated another way, without cell division and receptor formation, mediated in part by NO, wound healing will not occur.

Formation of new blood vessels, called angiogenesis, is essential for wound healing otherwise newly formed tissue will eventually deteriorate again due to lack of oxygen and nutrients. Growth factors, including vascular endothelial growth factor (VEGF) determine the extent of revascularization of damaged tissues. All growth factors bind to receptors on the cell surface and generate NO-mediated cGMP. Therefore, NO is a powerful and necessary mediator of angiogenesis.

JV Boykin first suggested that NO-mediated wound vascularization was an important mechanism for impressive wound healing obtained through the use of hyperbaric oxygen (HBO) therapy. Importantly, Boykin recognized that the enhanced wound healing could not be explained by HBO's effect on hyperoxia alone and he suggested that the additional oxygen helped to stimulate NOS activity and NO formation. We urge investigators to explore the extent to which HBO, and other maneuvers, activates ecNOS so that effective treatment strategies might be developed to enhance the activity of growth factor based products that may be dependent upon restoring normal NO for maximum efficacy.

Fibroblasts are cells that also respond to growth factors. NO increases the number of fibroblasts (fibroblastic proliferation) and thereby enhances collagen formation for the healing wound. Fibroblast growth factor exists in several isoforms but each causes local increases in NO production by fibroblasts. Furthermore, L-arginine availability ensures that the collagen that is formed is structurally similar to native collagen, i.e., that which was present prior to the injury to the skin. L-arginine is absolutely necessary for the proper cross-linking of collagen fibers to one to another, via proline, one of metabolites of L-arginine metabolism. Without L-arginine and thus NO and proline, collagen cross-linking is disrupted and the collagen that is formed is structurally abnormal. Scars or poor tendon/ligament integrity are principally manifestations of inadequate amounts of both L-arginine and NO early in the healing process brought about by fibroblasts.

In summary, NO is critical in many of the cellular processes involved with wound healing. NO is a powerful stimulator of cell division (proliferation) and maturation, particularly formation of appropriate cell receptors (differentiation). NO is a powerful and necessary mediator of neovascularization, i.e., the formation of new and eventually mature blood vessels (angiogenesis) and lymph ducts to nourish the healing tissues. NO increases the number of fibroblasts (fibroblastic proliferation) and thereby enhances collagen formation for the healing wound. Lastly, L-arginine and NO are necessary for the proper cross-linking of collagen fibers to one another, via proline, to minimize scarring and maximize the tensile strength of healed tissue. Nerves must also "regrow" in healing tissues.

In the next article, we will discuss the role of NO in pain suppression and maintenance of nerve function, both of which are particularly important to the patient with diabetes.

Dr. Tom Burke received his PhD in Physiology from University of Houston, Post Doctoral Training at Duke Medical School, He was an Associate Professor of Medicine and Physiology at the University of Colorado Medical School. He has authored more than 70 published scientific clinical articles and has been a visiting scientist at the Mayo Clinic, Yale University, University of Alabama, and University of Florida. He is a recognized international lecturer on cell injury and nephrology

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