THE ROLE OF COPPER IN ANGIOGENESIS

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Background. In disease conditions, the goal of therapeutic targeting of the angiogenic process is to normalize vasculature in target tissues by enhancing angiogenesis, where reduced vascularity and blood flow occur, such as in tissue ischemia and wound repair; or to inhibit angiogenesis, as in the case of excessive and abnormal angiogenesis originating from cancer. Copper (Cu) is a trace element and vital cofactor of more than 60 enzymes implicated in blood clotting, hormone maturation, energy metabolism, oxidative detoxification, mitochondrial respiration, DNA synthesis, cell division, antioxidant processes and angiogenesis. The objective of the study was to elucidate the role of Cu in angiogenesis in order to be used in wound healing and in transplanted graft.
Materials and methods. Literature review from 2016-2026 was performed, using 11 articles, including data from ScienceDirect, PubMed Central, Biomed Central, MedScape, and others.
Results. Cu homeostasis is regulated by *Copper Transporter 1* (CTR1), *Adenosine Triphosphatase* (ATPase) *copper-transporting alpha* (ATP7A) and Cu chaperones. Intracellular Cu can stabilize the biochemical structure of transcription *hypoxia-inducible factor 1α* (HIF-1α) and promote the expression of angiogenic mediators: basic fibroblast growth factor (*FGF-Basic)*, vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α) and angiogenin. As a result these mediators promote proliferation of *endothelial cells* (ECs) and migration of *vascular smooth muscle cells* (VSMCs). Also Cu as an coenzyme modulates angiogenin's affinity towards ECs and VSMCs and modulates *amine oxidase Cu-containing 3* (AOC3) which involve IL-1β-driven M2 macrophage infiltration. Furthermore, Cu ions mediate the activity of endothelial nitric oxide synthase and increase the production of the vasodilator nitric oxide, thereby promoting angiogenesis. Also, Cu has been extensively studied for its antibacterial activities through *mismetalation* (a process in which a metal-binding site in a protein is occupied by the wrong metal ion). Proteins containing iron, manganese, cobalt, nickel, and zinc as cofactors are all potential targets of mismetalation by Cu. Moreover, Cu is a cofactor of *Superoxide dismutase 1* (SOD1) exerting anti-inflammatory activities.
Conclusions: In conclusion angiogenic, antibacterial and anti-inflammatory Cu properties demonstrate that Cu derived compounds may be used in wound healing and stimulating angiogenesis in transplanted graft.
Keywords: Copper, angiogenesis, ECs, VSMCs.