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Impaired Fracture Healing Related to Malnutrition through Arginine-Citrulline-Nitric Oxide Signaling Pathways

Nisrina Ekayani Nasrun, Saki Fujii, Mari Shimatani, Tsuyoshi Shimo

Division of Reconstructive Surgery for Oral and Maxillofacial Region, Department of Human Biology and Pathophysiology, School of Dentistry, Health Sciences University of Hokkaido, Hokkaido 061–0293, Japan

Fracture healing is a complex process that partially overlaps successive stages, from inflammation stages to bone remodeling stage. Among other risk factors, the patient's nutritional status posses a major role in the fracture healing process. (Meesters et al., 2018) A few studies have described the effect of malnutrition on fracture healing. Protein malnutrition has been reported to endanger on quality of fracture callus. Hughes et al. proposed a significant effect on the protein intake of fracture healing in rats. Compared with the low protein intake group, the high protein intake group had increased muscle mass and bone mineral density in the fracture callus observed during the 6–weeks healing period. (Hughes et al., 2006)

Protein malnutrition, especially arginine–citrulline–nitric oxide metabolism, can affect fracture healing through several collagen–forming precursors, and affect biomolecular inflammation and local capillary growth through the nitric oxide synthase cycle. (Meesters et al., 2020 ; Meesters et al., 2018) The arginine–citrulline–nitric oxide, like essential amino acids, has two important roles in the fracture healing process. Firstly, the nitric oxide synthase (NOS) enzyme, which is secreted in the arginine–citrulline–nitric oxide metabolism, takes the role in one of the stages of the fracture healing process. Secondly, the conversion of arginine into ornithine by the arginase–1 enzyme is essential in bone remodeling. Through the formation of polyamines, ornithine is a precursor for collagen synthesis, necessary for osteogenesis (Fig. 1).

It has been reported that non–union or delayed union is related to protein malnutrition especially insufficient arginine, citrulline, and ornithine levels. This is probably caused due to an increasing amount of NOS enzyme in

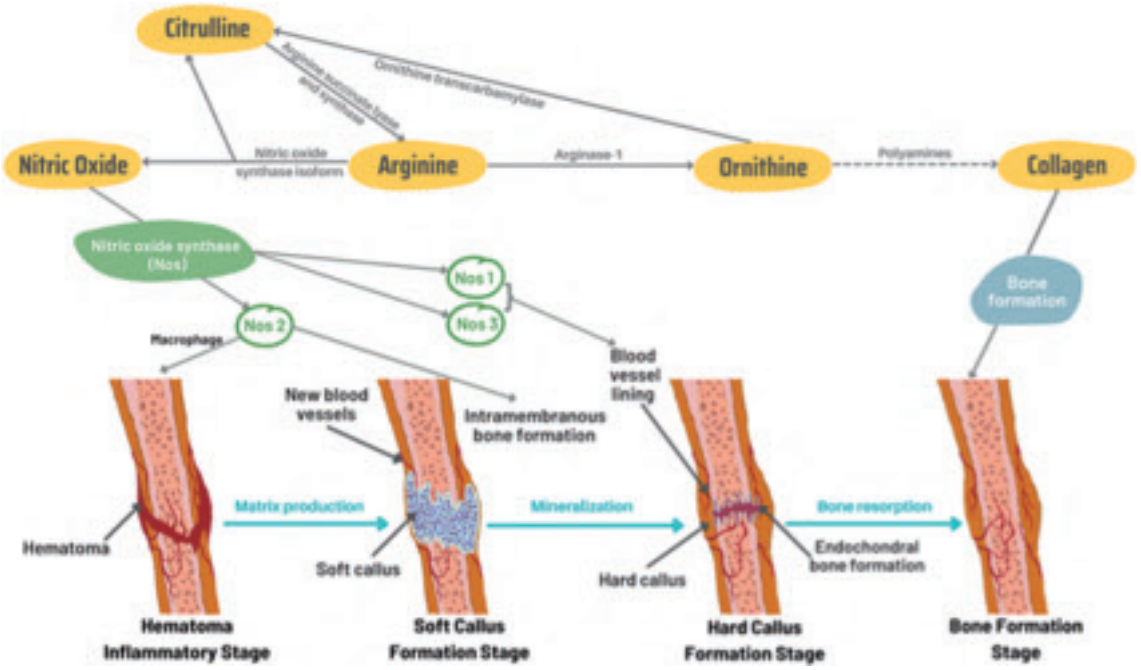

Figure 1. The schematic model of protein regulates fracture healing in arginine-citrulline-nitric oxide signaling pathways.

chondrocytes and bone cells in normal fracture healing. On the contrary, a decline in nitric oxide (NO) number suppressing the callus formation through osteoclast-induced bone resorption. This most likely triggers non-union development. (Wijnands et al., 2012)

Under physiological conditions, the semi-essential amino acid arginine is produced by the conversion of citrulline by the cytoplasmic enzymes arginine succinate lyase and arginine succinate synthase. Arginine can be converted back to citrulline by one of the nitric oxide synthase (NOS) enzymes. In the inflammatory phase of fracture healing, the NOS 1 (inducible form ; iNOS) is active, mainly in the intramembranous area along with the periosteum callus. In the later stages of the healing process, constitutive and calcium-dependent NOS 3 (endothelial form ; eNOS) and NOS 1 (neuronal form ; nNOS) are expressed in the lining of blood vessels and in fibrous and cartilage tissues. During these conversion processes, free radical NO is formed. NO stimulates bone cells to regulate bone remodeling by affecting osteoblasts and osteoclasts, and on the other hand, affects vascular reactivity on the fracture healing process. (Meesters et al., 2020)

It has been shown that arginine-citrulline-nitric oxide metabolism regulates critical signaling pathways in fracture healing through in vitro and animal studies. However, human research is a major and interesting perspective for further investigation. Although the bone healing metabolism between rats and humans is nearly similar, there are small differences in the biomechanical loading.

References

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