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Authors
Murase, Yurika
Hattori, Takako
Aoyama, Eriko
et al.

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Role of CCN2 in Amino Acid Metabolism of Chondrocytes

Yurika Murase[1,2], Takako Hattori[1], Eriko Aoyama[3], Takashi Nishida[1], Aya Maeda-Uematsu[1], Harumi Kawaki[1], Karen M Lyons[4], Akira Sasaki[2], Masaharu Takigawa[1,3], Satoshi Kubota[1,3]
Affiliations expand

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Abstract

CCN2/connective tissue growth factor (CTGF) is a multi-functional molecule that promotes harmonized development and regeneration of cartilage through its matricellular interaction with a variety of extracellular biomolecules. Thus, deficiency in CCN2 supply profoundly affects a variety of cellular activities including basic metabolism. A previous study showed that the expression of a number of ribosomal protein genes was markedly enhanced in Ccn2-null chondrocytes. Therefore, in this study, we analyzed the impact of CCN2 on amino acid and protein metabolism in chondrocytes. Comparative metabolome analysis of the amino acids in Ccn2-null and wild-type mouse chondrocytes revealed stable decreases in the cellular levels of all of the essential amino acids. Unexpectedly, uptake of such amino acids was rather enhanced in Ccn2-null chondrocytes, and the addition of exogenous CCN2 to human chondrocytic cells resulted in decreased amino acid uptake. However, as expected, amino acid consumption by protein synthesis was also accelerated in Ccn2-null chondrocytes. Furthermore, we newly found that expression of two genes encoding two glycolytic enzymes, as well as the previously reported Eno1 gene, was repressed in those cells. Considering the impaired glycolysis and retained mitochondrial membrane potential in Ccn2-null chondrocytes, these findings suggest that Ccn2 deficiency induces amino acid shortage in chondrocytes by accelerated amino acid consumption through protein synthesis and acquisition of aerobic energy. Interestingly, CCN2 was found to capture such free amino acids in vitro. Under physiological conditions, CCN2 may be regulating the levels of free amino acids in the extracellular matrix of cartilage.

Keywords: CARTILAGE; CCN2; CHONDROCYTES; CTGF; METABOLISM.