LGALS3 Suppresses Colon Cancer Progression by Reprogramming TCA Cycle Metabolism Through the P53 Pathway

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Abstract

Colon cancer is a prevalent gastrointestinal malignancy with rising incidence. Tumor metabolic reprogramming, particularly involving the tricarboxylic acid (TCA) cycle, is a critical hallmark of cancer. While LGALS3 and the tumor suppressor P53 are known regulators of tumor metabolism, the specific mechanism by which LGALS3 mediates metabolic reprogramming via P53 in colon cancer remains unclear. This study aims to investigate the expression changes of LGALS3 under serum deprivation and elucidate its effects on colon cancer cell proliferation, TCA cycle metabolism, and the underlying molecular mechanisms. Subcellular fractionation and Western blotting were used to determine LGALS3 localization and expression changes under serum starvation. Using lentiviral-mediated knockdown and overexpression models in HCT116 (TP53+/+ and TP53-/-) cells, cell proliferation was assessed via CCK-8, colony formation, and EdU assays. Mechanisms were explored using immunofluorescence, protein stability assays with cycloheximide (CHX) and MG132, Seahorse mitochondrial stress tests, and ATP and α-ketoglutarate measurements. The regulatory relationship between LGALS3 and P53 was further validated by co-knockdown of Pirh2. The results show: LGALS3 was primarily localized in the mitochondria and nucleus, with its expression significantly upregulated under serum deprivation. Knockdown of LGALS3 significantly promoted colon cancer cell proliferation, whereas overexpression inhibited it. Mechanistically, LGALS3 co-localized with P53 in the nucleus and reduced P53 protein half-life by upregulating the E3 ubiquitin ligase Pirh2-mediated proteasomal degradation pathway; this effect was reversed by MG132 or Pirh2 co-knockdown. Furthermore, LGALS3 suppressed the cellular oxygen consumption rate, ATP production, and α-ketoglutarate accumulation. It specifically downregulated the expression of TCA cycle enzymes MDH2 and SDHA. Notably, the regulatory effects of LGALS3 on MDH2 and SDHA were completely abolished in TP53-/- cells. In conclusion LGALS3 inhibits colon cancer cell proliferation by destabilizing P53 protein via Pirh2, thereby regulating the TCA cycle and cell cycle through the P53 pathway. These findings provide a promising potential therapeutic target for colon cancer.

Keywords

Tricarboxylic Acid Cycle, Colon Cancer, LGALS3, P53, Mitochondrial Metabolism