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Mutant p53 attenuates oxidative phosphorylation and facilitates cancer stemness through downregulating microRNA-200c-PCK2 axis in basal-like breast cancer

Abstract

MicroRNA-200c (miR-200c) is a tumor suppressor microRNA that plays a critical role in regulating epithelial phenotype and cancer stemness. p53 deficiency downregulates the expression of miR-200c and leads to epithelial-mesenchymal transition (EMT) and stemness phenotype which contributes to the progression of breast cancers. In this study, we demonstrated that CRISPR-mediated knockout of miR-200c induces metabolic features similar to the metabolic rewiring caused by p53 hot-spot mutations, and impairing this metabolic reprogramming interferes with miR-200c deficiency-induced stemness and transformation. Moreover, restoring miR-200c expression compromised EMT, stem cell properties, and the Warburg effect caused by p53 mutations, suggesting mutant p53 induces EMT-associated phenotypes and metabolic reprogramming through downregulating miR-200c. Mechanistically, decreased expression of PCK2 was observed in miR-200c- and p53-deficient mammary epithelial cells, and forced expression of miR-200c restored PCK2 in p53 mutant expressing cells. Declined PCK2 expression not only led to attenuated oxidative phosphorylation (OXPHOS) and increased stemness in normal mammary epithelial cells, but also compromised the enhanced OXPHOS and suppression of cancer stemness exerted by miR-200c in p53 mutation-bearing basal-like breast cancer (BLBC) cells. Clinically, PCK2 expression is negatively associated with EMT markers, and downregulated in basal-like subtype and cases with low miR-200c expression or p53 mutation. Notably, low expression of PCK2 is associated with poor overall survival in breast cancer patients. All these results together suggested p53 and miR-200c could regulate OXPHOS and stem/cancer stemness through PCK2, and loss of the p53-miR-200c-PCK2 axis might provide metabolic advantages to facilitate cancer stemness, leading to the progression of BLBCs.