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PINK1 insufficiency can be exploited as a specific target for drug combinations inducing mitochondrial pathology-mediated cell death in gastric adenocarcinoma

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ABSTRACT

There exist very limited non-hazardous therapeutic strategies except for surgical resection and lymphadenectomy against gastric cancer (GC) despite being the third leading cause of cancer deaths worldwide. This study proposes an innovative treatment approach against GC using a drug combination strategy that manipulates mitochondrial dynamics in conjunction with the induction of mitochondrial pathology-mediated cell death. Comparative analysis was done with gastric adenocarcinoma and normal cells by qPCR, western blot, microscopic immunocytochemistry, and live cell imaging. In this study, impairment of dynamin-related protein 1 (Drp1)-mediated mitochondrial fission by Mdivi-1 created an imbalance in mitochondrial structural dynamics in indomethacin-treated AGS cells in which mitophagy-regulator protein PINK1 is downregulated. These drug combinations with the individual sub-lethal doses ultimately led to the activation of cell death machinery upregulating pro-apoptotic proteins like Bax, Puma, and Noxa. Interestingly, this combinatorial therapy did not affect normal gastric epithelial cells significantly and also no significant upregulation of death markers was observed. Moreover, the drug combination strategy also retarded cell migration and reduced stemness in GC cells. In summary, this study offers a pioneering specific therapeutic strategy for GC treatment, sparing normal cells providing opportunities for minimal drug-mediated toxicity utilizing mitochondria as a viable and specific target for anti-cancer therapy in gastric cancer.

1. Introduction

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer lethality globally [1]. Presently, the therapeutic options comprise perioperative or adjuvant chemotherapy, surgery for endoscopic resection, radiotherapy, and immunotherapy [2] and drugs include fluoropyrimidine, trastuzumab (HER2-positive patients first line), ramucirumab (anti-angiogenic second line), and nivolumab or pembrolizumab (anti-PD-1 third line) [1]. However, increasing resistance, high toxicity, restricted therapeutic options, high cost of advanced drugs, and late diagnosis lead to poor prognoses with metastasis, and recurrence [3,4]. The present study suggests a novel drug combination strategy involving the alteration of mitochondrial dynamics in combination with the induction of mitochondrial pathology as a noncanonical chemotherapeutic approach in the highly aggressive and resistant gastric adenocarcinoma cells.

Going beyond the convention of Warburg, mitochondria play multifunctional roles in various malignancies [5,6]. Mitochondrial signaling of tumor-associated cells modulates cell cycle, gene expression, metabolism, redox homeostasis, immune response, cell growth, and viability [5,7] and is also associated with diverse pathologies [8]. Mitochondria is structurally dynamic going through cycles of fission and fusion which play a vital role in mtDNA dispersal, cristae reformation, bio-energetic distribution, maintenance of mitochondrial turnover, etc. [9]. Mitochondrial fusion is principally regulated by GTPases, mitofusin 1, 2 (Mfn1, Mfn2), and optic atrophy 1 (Opa1), while mitochondrial fission is primarily regulated by GTPase Drp1 [10]. Drp1 expression and activity have been linked with enhanced glycolytic metabolism in lung

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ORIGINAL PAPER

A Comprehensive Pan-Cancer Analysis of Cytochrome C Oxidase Assembly Factor 1 (COA1) Reveals Instrumental Role of Mitochondrial Protein Assembly in Cancer that Modulates Disease Progression and Prognostic Outcome

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Abstract

Cytochrome c oxidase assembly factor 1 (COA1), a mitochondrial respiratory chain complex assembly factor protein of inner mitochondrial membrane (IMM), is involved in translating many mitochondrial components and assembling nuclear-encoded components within mitochondria. Given the lack of extensive research on COA1 in cancer, this study undertakes a comprehensive pan-cancer analysis of COA1, which is overexpressed across various cancer types, shedding light on its multifaceted role in tumorigenesis, prognosis, and tumor microenvironment (TME) modulation. Leveraging bioinformatics tools and public databases, we elucidated its potential as a diagnostic cancer biomarker as well as target for novel anti-cancer therapeutics. Gene expression analysis using "TIMER2.0", "UALCAN" and "GEPIA2" platforms, supported by protein expression data, revealed a significant correlation between COA1 upregulation and poor prognosis in Kaplan-Meir analysis, underscoring its clinical relevance. Additionally, genetic mutation analysis of COA1 with the help of "cBioPortal" warrants further exploration into its functional significance. Moreover, our investigation of the tumor microenvironment unveiled interplay of COA1 with fibroblast and T cell infiltration implicating role of COA1 in tumor immune microenvironment. Furthermore, COA1-related gene enrichment study in "GeneMANIA" and pathway cross-talk analysis with Gene Ontology (GO) gene sets established comprehensive clarifications about the molecular pathways and protein networks associated with COA1 deregulation. Overall, this study lays a sturdy foundation to support future research endeavors targeting COA1, unraveling the molecular mechanisms underlying COA1 deregulation, and exploring its therapeutic potential in cancer.

Keywords COA1 · Cancer · Prognosis · Tumor micro-environment · Survivability rate

Introduction

Throughout the course of the last few years, there has been a surge in the scientific field of cancer research helping mankind get a more profound awareness of the pathophysiological aspects of the disease. Notable accomplishments have been made within the domain of target-based cancer immunotherapeutic drug development and many have been approved for clinical use. Tumor immunology and its alterations in the tumor microenvironment (TME) is a complex and sophisticated approach involving varied oncogenes and environmental risk factors. A single gene could be activated in multiple manners across different tumors, hence, studying it in a particular type of tumor is not sufficient to fully interpret its functions. Therefore, the need for a multi-omics study of the oncogenic proteins in a pan-cancer facet becomes essential. The free databases with

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