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Two-in-One Nanoparticle Formulation to Deliver a Tyrosine Kinase Inhibitor and microRNA for Targeting Metabolic Reprogramming and Mitochondrial Dysfunction in Gastric Cancer

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Citation: Lo, Y.-L.; Wang, T.-Y.; Chen, C.-J.; Chang, Y.-H.; Lin, A.M.-Y. Two-in-One Nanoparticle Formulation to Deliver a Tyrosine Kinase Inhibitor and microRNA for Targeting Metabolic Reprogramming and Mitochondrial Dysfunction in Gastric Cancer. *Pharmaceutics* **2022**, *14*, x. https://doi.org/10.3390/xxxxx

Academic Editors: Keun Sik Kim and Min Woo Kim

Received: 12 August 2022
Accepted: 19 August 2022
Published: 23 August 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Dysregulational EGFR, KRAS, and mTOR pathways cause metabolic reprogramming, leading to progression of gastric cancer. Afatinib (Afa) is a broad-spectrum tyrosine kinase inhibitor that reduces cancer growth by blocking the EGFR family. MicroRNA 125 (miR-125) reportedly diminishes EGFRs, glycolysis, and anti-apoptosis. Here, a one-shot formulation of miR-125 and Afa was presented for the first time. The formulation comprised solid lipid nanoparticles modified with mitochondrial targeting peptide and EGFR-directed ligand to suppress pan-ErbB-facilitated epithelial–mesenchymal transition and mTOR-mediated metabolism discoordination of glycolysis–glutaminolysis–lipids. Results showed that this cotreatment modulated numerous critical proteins, such as EGFR/HER2/HER3, Kras/ERK/Vimentin, and mTOR/HIF1-α/HK2/LDHA pathways of gastric adenocarcinoma AGS cells. The combinatorial therapy suppressed glutaminolysis, glycolysis, mitochondrial oxidative phosphorylation, and fatty acid synthesis. The cotreatment also notably decreased the levels of lactate, acetyl-CoA, and ATP. The active involvement of mitophagy supported the direction of promoting the apoptosis of AGS cells, which subsequently caused the breakdown of tumor-cell homeostasis and death. In vivo findings in AGS-bearing mice confirmed the superiority of the anti-tumor efficacy and safety of this combination nanomedicine over other formulations. This one-shot formulation disturbed the metabolic reprogramming; alleviated the "Warburg effect" of tumors; interrupted the supply of fatty acid, cholesterol, and triglyceride; and exacerbated the energy depletion in the tumor microenvironment, thereby inhibiting tumor proliferation and aggressiveness. Collectively, the results showed that the two-in-one nanoparticle formulation of miR-125 and Afa was a breakthrough in simplifying drug preparation and administration, as well as effectively inhibiting tumor progression through the versatile targeting of pan-ErbB- and mTOR-mediated mitochondrial dysfunction and dysregulated metabolism.

Keywords: nanoparticle; tyrosine kinase inhibitor; microRNA; mitochondrial targeting; tumor metabolism reprogramming; mitochondrial dysfunction