ONCOGENE-DEPENDENT MITOCHONDRIAL DYNAMICS AND ITS THERAPEUTIC MODULATION IN COLORECTAL CANCER CELL LINES

Darina Mukhamejanova[1]& Ainur Sibagatova[2], Zhanel Turganbek[2], Alexey Petukhov[2], Marina Yelsyukova[2], Bayansulu Ilyassova[1], Kristina Raish[1], Dos D Sarbassov[1,3], Agata N Burska[2,3]*

[1]SSH, Biology Department, Nazarbayev University, Astana 010000, Kazakhstan
[2]NUSOM, Department of Biomedical Sciences, Nazarbayev University, Astana 010000, Kazakhstan
[3]CLS, National Laboratory of Astana, Nazarbayev University, Astana 010000, Kazakhstan

**Corresponding author (s): agata.burska@nu.edu.kz*

Background: Colorectal cancer (CRC) is frequently driven by mutually exclusive *KRAS* or *BRAF* mutations, which activate MAPK signalling and promote distinct metabolic programs and clinical phenotypes. Both oncogenes influence mitochondrial biology, yet their specific impact on mitochondrial dynamics and therapeutic vulnerabilities remains underexplored. Pharmacological modulation of mitochondrial morphology using fusion-promoting modulator M1 and fission inhibitor Mdivi-1 offers a novel approach to disrupt cancer cell metabolism and overcome therapy resistance.

Materials and methods: We compared mitochondrial morphology and function in KRAS-mutant CRC cell lines (SW620, HCT116), BRAF-mutant lines (HT29, RKO), and normal colon epithelial cells (CCD841CoN). Confocal microscopy, flow cytometry, Western blot, and RT-qPCR were used to assess mitochondrial morphology, membrane potential, superoxide levels, and expression of fission/fusion regulators (MFN1/2, DRP1, MFF). Proliferation and migration were measured via real-time impedance and wound healing assays. Pharmacological modulation was performed using the mitochondrial fusion promoter M1 and fission inhibitor Mdivi-1, alone or in combination.

Results: KRAS-mutant cells displayed moderately fused mitochondrial networks with reduced fission protein levels. In contrast, BRAF-mutant cells—particularly RKO—exhibited fragmented, hyperdynamic mitochondria with elevated expression of both fission and fusion markers. These structural differences correlated with functional outcomes: BRAF-mutant cells proliferated and migrated more aggressively than KRAS-mutant or wild-type cells. Pharmacological modulation confirmed mutation-specific vulnerabilities. M1 promoted mitochondrial fusion, particularly in KRAS-mutant cells, enhancing proliferation. Mdivi-1 induced mitochondrial stress, reduced proliferation, and increased apoptotic markers across both mutation types. Combined M1+Mdivi-1 treatment exerted additive effects, disrupting mitochondrial remodelling and reducing proliferation rates.

Conclusion: Mitochondrial dynamics differs between KRAS- and BRAF-mutant CRC cells, aligning with distinct growth and migration phenotypes. Pharmacological targeting of mitochondrial morphology using M1 and Mdivi-1 uncovers oncogene-specific vulnerabilities and supports mitochondrial dynamics as a therapeutic target in CRC.

Acknowledgement:

This work was supported by funding from the Ministry of Science and Higher Education of the Republic of Kazakhstan AP23487802.

Key words: colorectal cancer cell lines, mitochondrial dynamics, fusion, fission, proliferation.