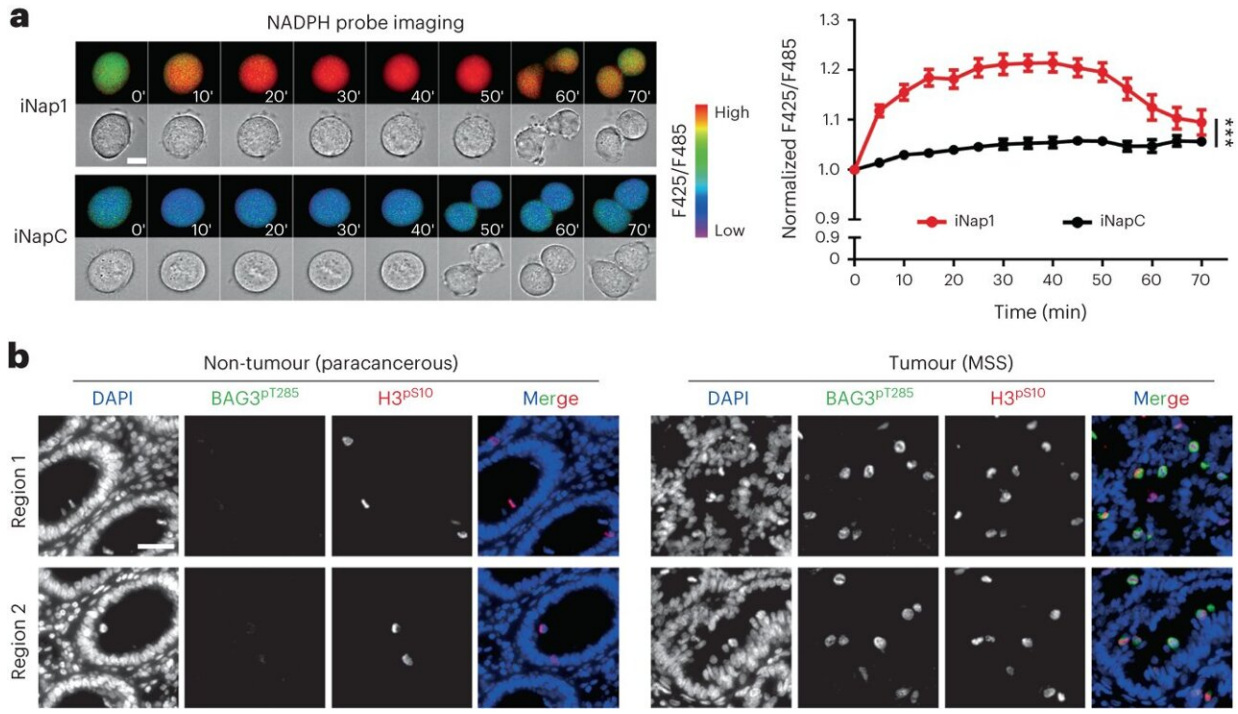
Researchers unravel metabolic regulation in aneuploid tumor cells

July 14 2023, by Liu Jia



NAPDH and BAG3 pT285 levels are increased during mitosis in aneuploid cancer cells. Credit: *Nature Metabolism* (2023). DOI: 10.1038/s42255-023-00848-1

A research team led by Prof. Yang Zhenye from the University of Science and Technology of China (USTC) of Chinese Academy of Sciences (CAS), in collaboration with Guo Jing from the First Affiliated Hospital of USTC, has made progress in the field of metabolic

regulation during the mitotic phase of aneuploid tumor cells. The study was published in *Nature Metabolism*.

Aneuploidy, characterized by an abnormal number of chromosomes in tumor cells, is the most common feature observed in human cancer cells.

More than 85% of tumor genomes are aneuploid, while normal cells are diploid. Finding specific targets for aneuploid tumors is an effective way to precisely kill cancer cells without affecting normal diploid cells. However, the mechanisms by which aneuploid tumor cells cope with the dual pressures of oxidative stress and mitosis during cell division are not yet fully understood.

The researchers employed live-cell probes for metabolites, cellular and animal models, as well as the analysis of clinical sample cohorts, to delve into the dynamic changes and regulatory mechanisms of redox metabolism in aneuploid tumor cells during the mitotic phase.

They discovered the crucial role and significance of the core metabolite nicotinamide adenine dinucleotide phosphate (NADPH) during the mitotic phase of the cell cycle, and demonstrated that this metabolic regulation ensures accurate chromosome segregation and maintenance of genomic integrity in aneuploid tumor cells.

This provided a comprehensive understanding of the upstream regulation of NADPH during mitosis, involving the kinase CDK1/AMPK, which phosphorylates the co-chaperone molecule BAG3-T285, leading to the release and activation of the metabolic enzyme G6PD.

In addition, the researchers identified downstream metabolic and cell cycle signals involved in chromosome segregation regulation. They found that the phosphorylation of BAG3-T285 was significantly higher

in microsatellite-stable (mostly aneuploid) colorectal cancer samples, and was associated with poor prognosis.

This study sheds light on the metabolic regulation of aneuploid tumor cells during the mitotic phase, which deepens the understanding of the mechanisms behind aneuploidy and provides potential targets for the development of novel therapies against aneuploid tumors. It provides new biomarkers and treatment strategies for selectively inhibiting aneuploid tumors by intervening in metabolic pathways.

More information: NADPH increase in mitosis in aneuploid tumour cells protects against genomic aberrations, *Nature Metabolism* (2023). DOI: 10.1038/s42255-023-00848-1

Provided by Chinese Academy of Sciences