Researchers reveal metabolic root of Zika virus-induced microcephaly, and a possible treatment

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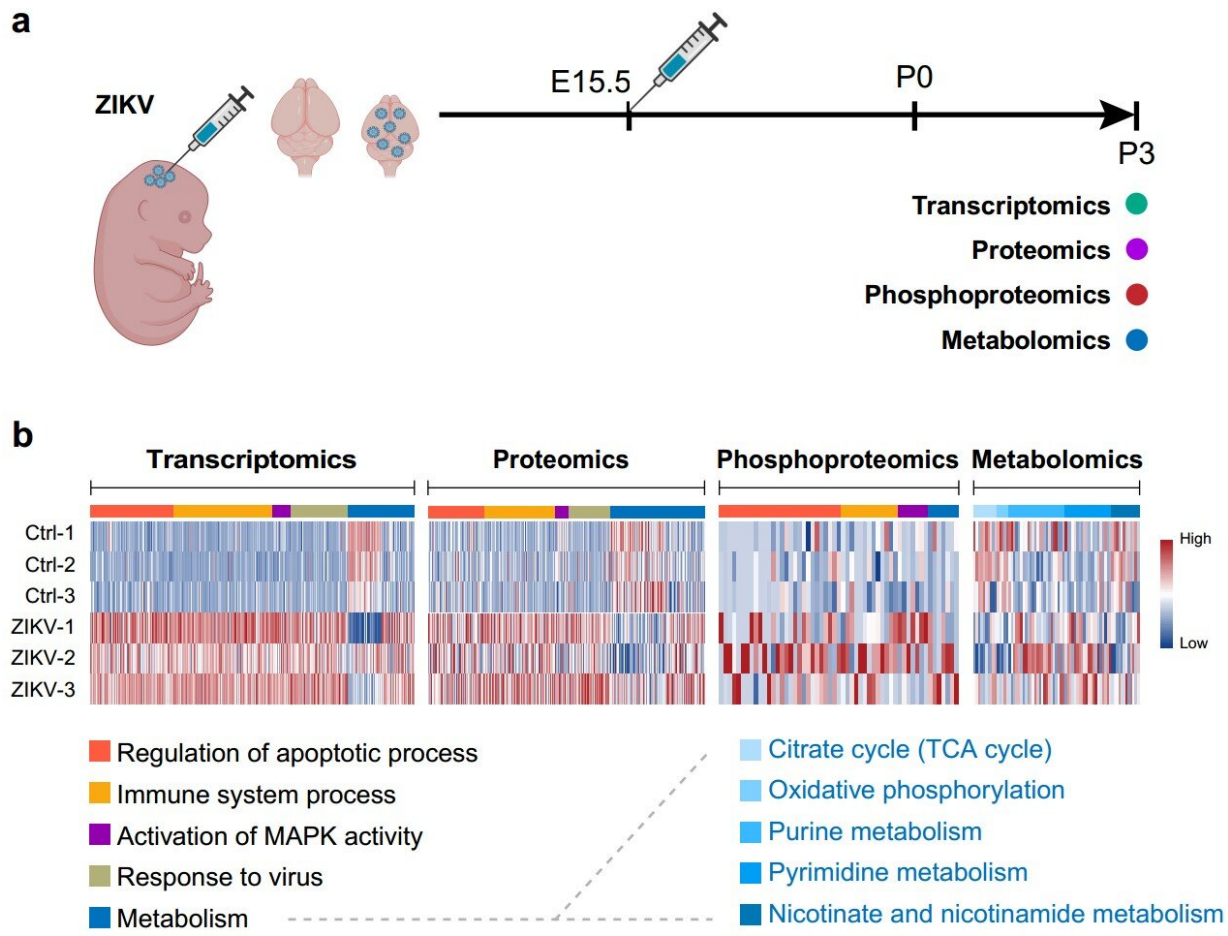

Schematic overview and multi-omics summary of the study. Credit: Huanhuan Pang et al.

Chinese scientists have recently found that supplementation of nicotinamide adenine dinucleotide (NAD^+) or its precursors can inhibit Zika virus (ZIKV)-induced neuronal death. This discovery suggests a potential therapeutic strategy for newborns suffering from ZIKV-infection.

Prof. XU Zhiheng's group from the Institute of Genetics and Developmental Biology (IGDB) of the Chinese Academy of Sciences, in collaboration with Prof. HU Zeping's and Prof. LAN Xun's groups from Tsinghua University and Prof. SONG Lei's group from the National Center for Protein Sciences, used multi-omics approaches to investigate changes in biological processes in ZIKV-infected mouse brains.

Their research, entitled "Aberrant NAD^+ metabolism underlies Zika virus-induced microcephaly," was published on-line in *Nature Metabolism* on August 12.

ZIKV is a mosquito-transmitted flavivirus that has caused tremendous global public health challenges in recent years. Although most ZIKV-infected patients exhibit no or mild symptoms, ZIKV infection during pregnancy can cause microcephaly in newborns.

In 2016, Prof. XU's group confirmed that ZIKV mainly infects neural precursor cells. Such infection leads to cell-cycle arrest and inhibition of differentiation as well as neuronal death. This research provided the first evidence for a direct link between ZIKV infection and microcephaly.

In the current study, the researchers found a profound dysregulation of NAD^+ metabolism in ZIKV-infected brains. Based on their observation that the level of NAD^+ dramatically declined in ZIKV-infected brains, the researchers assumed that boosting the level of NAD^+ might provide protective effects in ZIKV-infected brains.

To confirm this, they treated mouse pups with NAD^+ or its precursors via lambda-point brain injection or intraperitoneal injection once a day after ZIKV infection. They found that boosting NAD^+ with NAD^+ or nicotinamide riboside supplementation can effectively inhibit neuronal death and the excessive activation of microglia, prevent the reduction of cortical thickness and brain weight, and improve the survival of ZIKV-infected pups.

This study is the first to show that Zika virus infection affects NAD^+ metabolism in the brain and that boosting NAD^+ levels can provide significant beneficial effects.

It also offers high-quality biological data that may support future investigations of ZIKV-induced microcephaly and the development of therapeutic strategies. Furthermore, it highlights the value of a multi-omics approach to the study of disease.

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More information: Huanhuan Pang et al, Aberrant NAD+ metabolism underlies Zika virus–induced microcephaly, *Nature Metabolism* (2021). DOI: 10.1038/s42255-021-00437-0

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