AMP biosynthesis key to longevity and metabolic health in vertebrates, study finds

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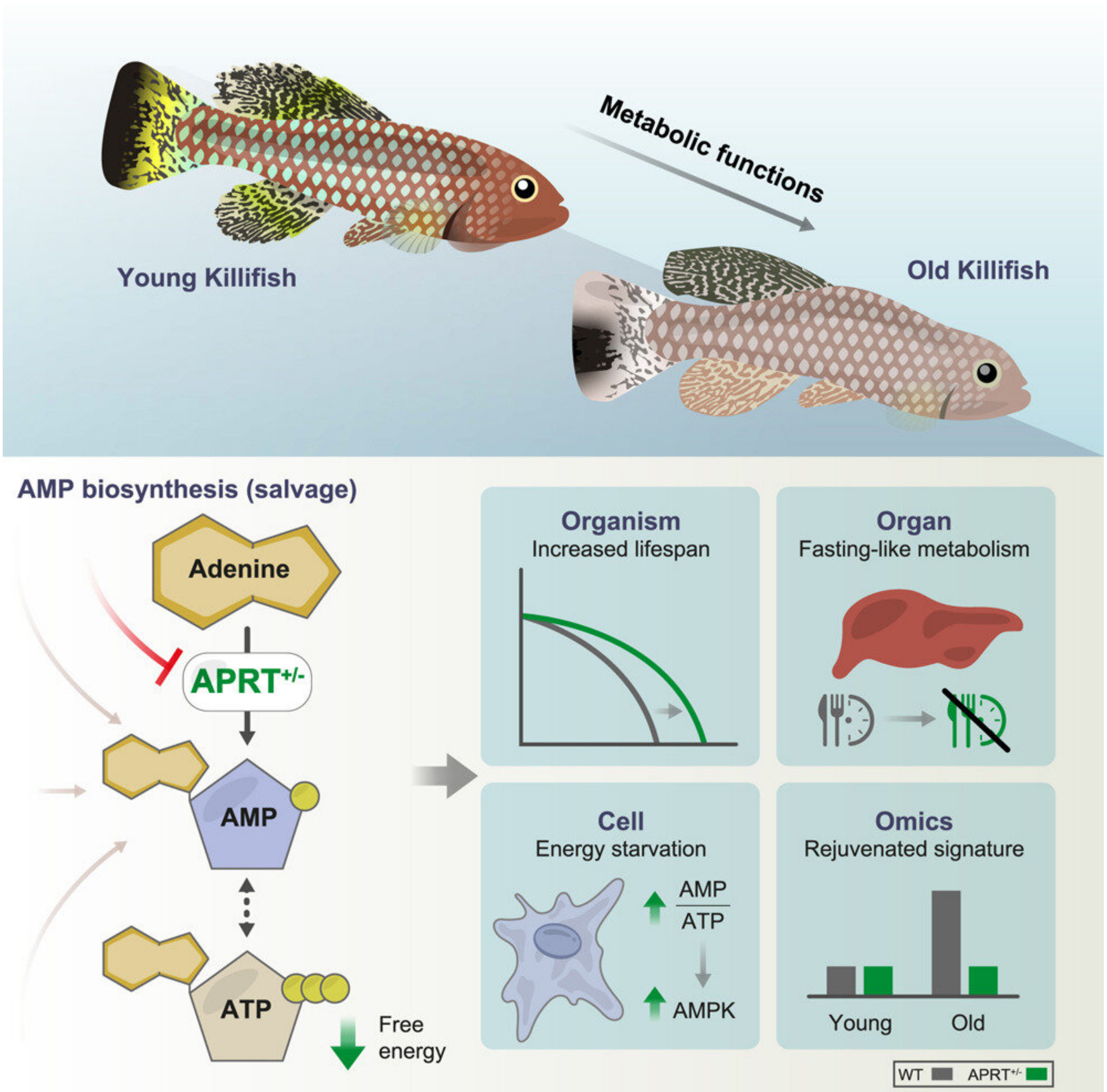

Graphical abstract. Credit: *Developmental Cell* (2023). DOI: 10.1016/j.devcel.2023.05.015

A recent study led by Dr. Itamar Harel from the Silberman Institute at the Hebrew University of Jerusalem has revealed new insights into the role of AMP biosynthesis in the lifespan and metabolic health of vertebrates.

The findings of this study have far-reaching implications, significantly advancing our understanding of the intricate interplay between energy metabolism, aging, and lifespan regulation. Moreover, the study opens up exciting possibilities for developing interventions to combat age-related metabolic diseases and enhance healthy aging. The work is published in the journal *Developmental Cell*.

Aging is commonly associated with disruptions in metabolic homeostasis, which contribute to various health issues. The AMP-activated protein kinase (AMPK) plays a critical role in cellular energy regulation and organismal metabolism. However, previous attempts to genetically manipulate the AMPK complex in mice yielded unfavorable outcomes.

In search of an alternative approach, the research team focused on manipulating the upstream nucleotide pool to modulate energy homeostasis.

Using the turquoise killifish as their model organism, the team targeted and mutated APRT, a key enzyme involved in AMP biosynthesis.

Remarkably, this manipulation resulted in a significant extension of lifespan in heterozygous male killifish. The study further employed an integrated omics approach, revealing rejuvenation of metabolic functions in the aged mutant fish. These included the adoption of a fasting-like metabolic profile and enhanced resistance to a high-fat diet.

At the cellular level, the heterozygous fish exhibited remarkable traits such as enhanced nutrient sensitivity, reduced ATP levels, and activation of AMPK. These findings highlight the potential of perturbing AMP biosynthesis to modulate vertebrate lifespan and promote metabolic health.

Dr. Itamar Harel said, "This is the first long-lived genetic model in killifish, highlighting the potential is this emerging model for aging. Genetic manipulation of AMP biosynthesis in the turquoise killifish reveals remarkable effects on lifespan and metabolic health. Our study unravels the intricate interplay between energy metabolism, aging, and lifespan regulation, offering exciting possibilities for the development of interventions to combat age-related metabolic diseases and enhance healthy aging."

However, the study also unveiled an intriguing observation. The benefits of extended lifespan and rejuvenated metabolic functions were nullified when lifelong intermittent fasting was applied. Furthermore, the longevity phenotypes were sex-specific. This discovery underscores the complex underlying mechanisms and emphasizes the delicate balance required for optimizing health outcomes, which be different in males and females.

The research sheds new light on the potential of targeting APRT as a promising strategy for promoting metabolic health and extending lifespan in vertebrates. Further investigations in this field hold promise for the development of interventions that enhance healthy aging and combat age-related metabolic diseases.

More information: Gwendoline Astre et al, Genetic perturbation of AMP biosynthesis extends lifespan and restores metabolic health in a naturally short-lived vertebrate, *Developmental Cell* (2023). DOI: 10.1016/j.devcel.2023.05.015

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