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Non-mammalian metabolic models in the spotlight

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Work in non-mammalian model organisms has shed light on many fundamental biological processes. At *Nature Metabolism*, we are interested in studies that make use of the unique advantages of these models to unravel new insights into metabolic biology.

Although most studies published in *Nature Metabolism* involve rodent models or contain human data, over the years we have published a small but growing number of studies that make use of non-mammalian model organisms. Organisms such as the fruit fly *Drosophila melanogaster* or the nematode *Caenorhabditis elegans* possess unique advantages for the study of metabolism, including a short lifespan and generation time, the suitability to perform large in vivo screenings and the availability of a plethora of advanced genetic tools. Thus, we have generated a new web collection to underline their usefulness and emphasize our interest in this research to the community.

Non-mammalian animal models have made integral contributions to our understanding of fundamental biological processes, including metabolic pathways. For instance, research in *Drosophila* has increased our knowledge of lipid metabolism and insulin signalling. In addition, the fruit fly is a useful model to study nutrient sensing and feeding behaviour, as shown in recent articles published in *Nature Metabolism*. As examples, in our current issue, a study by the group of Dr. Rewitz showed that a gut-derived peptide hormone regulates the preference for protein-rich food in female flies after mating. A publication by the group of Dr. Obata elucidated the role of the non-essential amino acid tyrosine in regulating the adaptive response to protein restriction in *Drosophila*. We are also interested in outstanding work carried out in *C. elegans*, which has been used as a powerful tool to study the biology of aging and xenobiotic metabolism. As one example, a study by Dr. Ermolaeva's group takes advantage of the short lifespan of *C. elegans* to show that metformin, which is commonly used to treat type 2 diabetes, reduces lifespan in worms when administered late in life and exacerbates age-related mitochondrial dysfunction in worms and cultured human cells. The zebrafish *Danio rerio*, on the other hand, is a popular model organism to study cardiometabolic and vascular diseases. The work by Dr. Andersson and colleagues takes advantage of the small size and transparent nature of zebrafish in a high-throughput screen to identify regulators of β-cell proliferation.

Despite all these advantages that underline the suitability of non-mammalian model organisms for metabolic research, certain major limitations have to be considered. Most importantly, not all biological and metabolic processes are conserved from flies or worms to humans, which can be a major caveat of disease models and therapeutic interventions, which casts doubt on the translatability of such findings. In addition, although an asset when studying fundamental biological questions, the simplicity of certain signalling pathways in non-mammalian organisms often fails to depict their complexity in higher organisms, such as humans.

With these limitations in mind — and considering our broad readership and our goal to publish impactful, novel metabolic research — what is *Nature Metabolism* looking for in studies involving non-mammalian model organisms?

When considering model organism studies for publication, those with demonstrable relevance to human metabolic biology or pathophysiology are naturally the strongest contenders for peer review. That said, we do not always insist on a demonstration of evolutionary conservation and physiological relevance in mammals, provided the conceptual advance is high, as illustrated for instance in a publication by the group of Dr. Preat, which demonstrates that, under starvation, glial-derived ketone bodies fuel neurons to sustain memory formation in *Drosophila*. Alternatively, we are satisfied if findings are specific to the biology of a particular model organism, provided that they are likely of great importance for shaping future research involving this organism. One such example might be the study by Dr. Yoo and colleagues in which the authors found that the *white* gene — a commonly used genetic marker in *Drosophila* — influences intestinal stem cell homeostasis in flies during aging. However, if a study features a disease model or focuses on signalling pathways that are known to be conserved in humans, we would typically require some demonstration of evolutionary conservation.

Another aspect we consider is whether studies that use non-mammalian model organisms effectively leverage their respective strengths. For instance, the transparent nature of zebrafish embryos offers unique possibilities for imaging, whereas elaborate genetic tools in *Drosophila* or *C. elegans* allow for sophisticated manipulation of biological pathways in a way that would be much more challenging and time-consuming in mammalian models. The use of non-mammalian model organisms also enables high-throughput analyses using a large number of animals, as well as enabling lifespan studies, such as shown in a study by Dr. Vilchez and colleagues on the influence of temperature on reproductive ageing and longevity in *C. elegans*.

In summary, although our editorial standards for studies using non-mammalian animal models are comparatively high, we fully appreciate the value these studies bring to the field of metabolism. We would like *Nature Metabolism* to remain a platform for influential metabolic research conducted in non-mammalian model organisms, and we are looking forward to publishing more exciting examples of this research in the future.

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