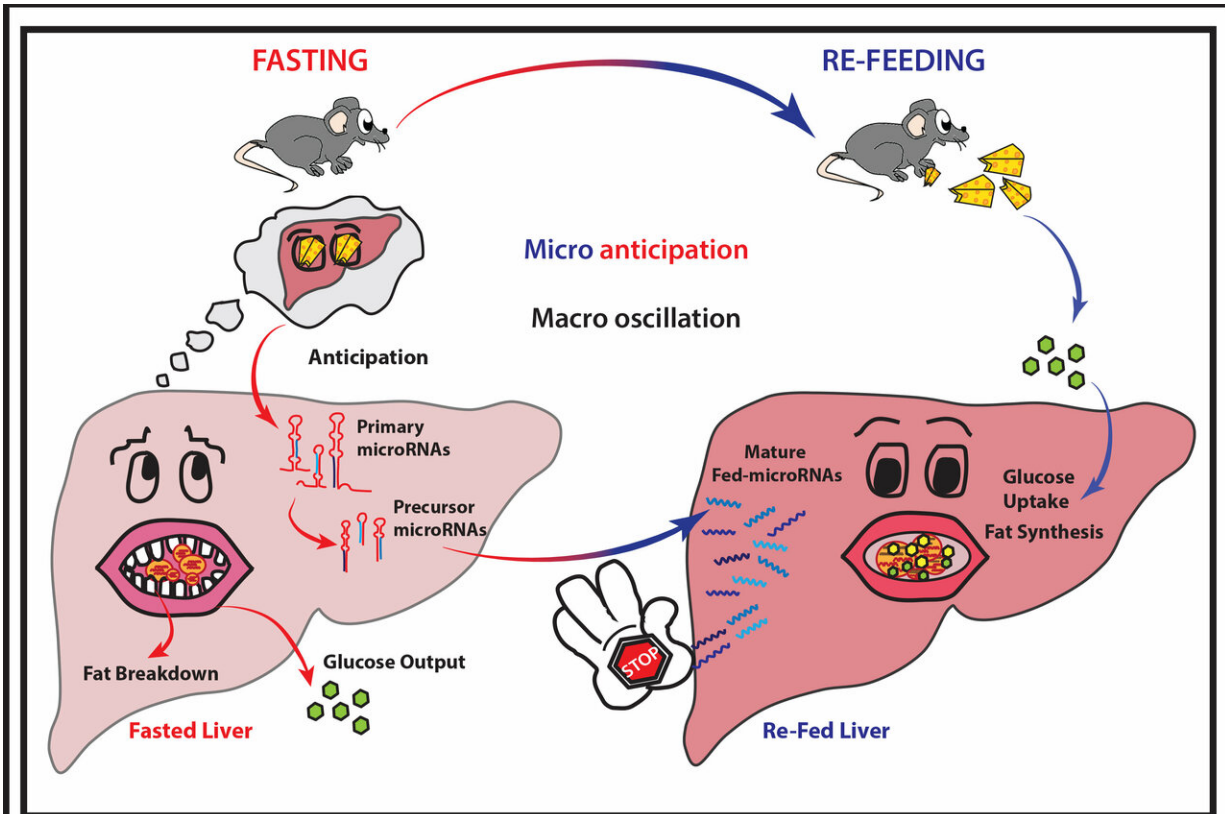


Micro-control of liver metabolism

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Micro-anticipation that enables macro-oscillations: Feed-fast oscillations, in all organisms, entails differential utilization of fat and carbohydrates as energy source. Liver breaks down fat to produce glucose to sustain energetic needs during fasting, which needs to be stopped upon re-feeding, rapidly. Abnormal glucose production is known to be associated with metabolic diseases. Researchers have discovered that liver microRNAs, synthesized as precursors in anticipation, inhibit the starvation pathways upon re-feeding to control glucose and fat metabolism. An absence of these microRNAs leads to liver dysfunctions and diabetic-like condition.

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feeding to control glucose and fat metabolism. An absence of these microRNAs leads to liver dysfunctions and diabetic-like condition. Credit: TIFR scientists: Babukrishna Maniyadath, Tandrika Chattopadhyay and Ullas Kolthur-Seetharam

Researchers at TIFR have discovered molecular anticipation of feeding in the liver that is essential to ensure that the body, after fasting, adapts to use incoming nutrients upon re-feeding. Their findings, published in the international journal *Cell Reports*, show that very small RNA molecules called microRNAs control major metabolic pathways by inhibiting synthesis of proteins, and thus contribute to maintenance of blood glucose levels.

The liver is one of the central metabolic organs that plays a pivotal role in maintaining organismal health and lifespan. All [living organisms](#) go through feed-fast cycles in which the body breaks down fats during [fasting](#) to meet energy demands and uses glucose or carbohydrates following food consumption. Inflexibility to oscillate between these processes comes from the failure of organs (or organisms) to switch metabolic pathways.

Both over- or under-utilization of either fat or glucose is known to affect health of all life forms. In highly evolved species, the liver acts as the primary organ to regulate both fat and [glucose metabolism](#) and ensure that there is neither over- nor under-utilization of these energy sources. Liver dysfunctions are known to be associated with obesity and diabetes. Abnormal liver metabolism is one of the primary drivers of fatty liver disease, which is highly prevalent, more so among Indians. Thus, [molecular mechanisms](#) within liver cells that bring about a [global change](#) in gene expression from a fasted to a re-fed state become critical. There has been a recent surge in the efforts by scientists all over the world to discover molecular factors that respond to food intake (including time of

the day feeding) and circadian rhythm (light-dark cycles), specifically in the liver, and that affect whole body metabolism.

The key aspect of the research carried out at TIFR is the identification of "fed-microRNAs," levels of which increase in the liver following feeding, stopping the production of proteins required during fasting. Although microRNAs have been known to be important for liver functions, the recent discovery shows that a specific group of these small RNAs act together to curb the fasting response upon re-feeding. A highlight of the study is the discovery that the precursors of these fed-microRNAs already exist when the mice are fasting, creating an anticipatory mechanism. Importantly, perturbing these fed-microRNAs results in molecular and physiological changes with associated increase in blood glucose levels, reminiscent of a pre-diabetic state. This study paves the way to use these small RNA molecules as potential therapeutic targets to control [glucose](#) or fat metabolism and as a plausible intervention to metabolic [liver](#) diseases.

More information: Babukrishna Maniyadath et al, Loss of Hepatic Oscillatory Fed microRNAs Abrogates Refed Transition and Causes Liver Dysfunctions, *Cell Reports* (2019). [DOI: 10.1016/j.celrep.2019.01.087](#)

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