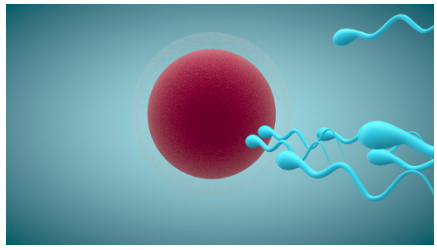
A mechanism for inherited metabolic disorders

From worms to mammals, environmental influences on one generation can be passed on to another through 'epigenetics', a set of mechanisms controlling gene expression without a change to the underlying DNA sequence. In humans, for example, malnutrition can predispose future generations to disease, and in mice, altering the diet of an adult can affect the metabolism of its offspring, all through epigenetic changes to gene expression. However, in most cases the precise molecules regulating this epigenetic inheritance remain unknown.

Recent work published by Qi Chen of the Chinese Academy of Sciences, in collaboration with researchers at the University of Nevada, addresses this gap in knowledge (*Science* **351**, 397–400; 2016). The researchers used mice fed a high-fat diet to explore how diet-induced changes in the father are passed on to his offspring. They microinjected sperm from mice fed either the high-fat diet or a normal diet into oocytes, and transplanted the developing embryos into surrogate mothers. The resulting offspring of mice that had been fed a high-fat diet displayed glucose intolerance and insulin sensitivity, two symptoms associated with diabetes.

Previous data suggest that the RNA profiles of sperm are altered in response to changes in diet, indicating that an RNA molecule might transmit these phenotypes. By sequencing the RNA in the sperm of male mice, the authors identified a group of RNAs, known as tsRNAs, that were expressed most differentially between the two groups of mice. After purifying tsRNAs from sperm, researchers then injected these molecules into embryos. Strikingly, injection of only tsRNAs from mice fed the high-fat diet recapitulated the phenotype of glucose intolerance in resulting progeny, whereas injection of other types of small non-coding RNAs, such as microRNAs, did not. These results demonstrate that tsRNAs are sufficient to transmit metabolic information from parent to offspring.



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Further analysis of these tsRNAs revealed that they are chemically modified such that they are more stable than tsRNAs from mice fed the normal diet; this suggests a possible avenue through which diet-induced information is stored. Moreover, RNA sequencing of embryos that had been injected with the RNA of mice fed the high-fat diet demonstrated decreased expression of genes that regulate key metabolic pathways. With these findings, the authors concluded that tsRNAs represent an epigenetic factor that is differentially modified in response to a high fat diet, mediating the transfer of metabolic disorders to offspring.

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A NOVEL ADJUVANT PROMISES IMPROVED RABIES VACCINE

Rabies is a zoonotic virus transmitted from bites or scratches from infected animals, and it is among the most lethal of infectious diseases. Once clinical symptoms develop, mortality is almost 100%. Although current vaccine treatments are highly effective at preventing the onset of this disease, a few deaths still occur each year from rabies. In these instances, the post-exposure vaccine treatment most likely fails to elicit a sufficiently rapid production of antibodies and also fails to induce the strong cellular immunity needed to eliminate infected cells. Without an early and robust response to the vaccine, the host's central nervous system can be invaded by the virus, which leads to paralysis and ultimately death.

In a recent preclinical study Yi Zhang *et al.* tested the ability of a novel adjuvant, known as PIKA, to increase the efficacy of the rabies vaccine in mice (*Virology* **489**, 165–172; 2016). PIKA is a stabilized chemical analog of double-stranded RNA that acts through Toll-like receptor 3 to enhance the presentation of antigens on antigen-presenting cells. This function, coupled with the release of pro-inflammatory cytokines through other pathways, enables PIKA to help induce non-specific immunity. Zhang *et al.* evaluated the ability of this PIKA rabies vaccine (PIKA-RV) to induce humoral and cellular immunity, finding that mice injected with PIKA-RV generated a titer of neutralizing antibodies that was almost 3-fold higher than that of mice injected with the rabies vaccine alone. They also found that T-cell activation, which is important for removing infected cells from the body, was also significantly higher in mice injected with PIKA-RV.

To test the level of protection conferred by PIKA-RV, beagles and golden hamsters were challenged with wild rabies virus and subsequently immunized with PIKA-RV or the vaccine alone. PIKA-RV protected 70% of beagles from the onset of disease, whereas the vaccine alone protected only 30% of beagles. In golden hamsters, the survival rates showed a similar trend, with 70% of hamsters surviving after immunization with PIKA-RV compared with about 20% survival with the vaccine alone.

Current treatments for rabies are successful in halting the onset of disease in most cases, but improvements in treatment regimens and survival rates are still needed, particularly in high-risk areas. Although these results with animal models await clinical-trial tests in humans, Zhang *et al.* have successfully demonstrated that PIKA-based enhancement of the rabies vaccine provides a potential new treatment for one of the most deadly infectious diseases.

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