March 29, 2011 | vol. 108 | no. 13 | 5141–5472

PNAS

Proceedings of the National Academy of Sciences of the United States of America www.pnas.org

In This Issue

Maternal diet shapes progeny's health

A growing body of evidence suggests that maternal diet during fetal and postnatal life can influence the long-term risk of developing diseases such as type 2 diabetes in the offspring, possibly through epigenetic control of gene activity. But precisely how maternal diet brings about epigenetic changes in the offspring remains poorly understood. Ionel Sandovici et al. (pp. 5449–5454) analyzed changes in the production of a master gene switch that mediates pancreatic cell development and glucose metabolism in the offspring of rat dams that were fed a low-protein diet or a normal diet during pregnancy and lactation. The authors found that epigenetic changes, such as DNA methylation and histone marks, control the production of the master gene switch in insulin-secreting cell lines. In rats whose mothers were exposed to a low-protein diet, epigenetic changes weakened the interaction between two key regulatory regions in the gene encoding the gene switch, leading to a drop in the levels of the switch in pancreatic cells. The authors further found that aging exacerbated the epigenetic effect in the progeny. Because the gene switch has been implicated in type 2 diabetes, the authors suggest, epigenetic changes triggered by maternal diet could influence the progeny's risk of developing the disease. The findings demonstrate how diet during early life can interact with the genome to affect metabolic health, according to the authors. — P.N.

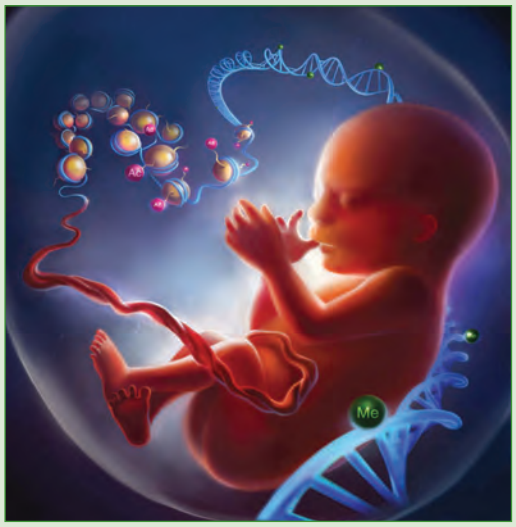
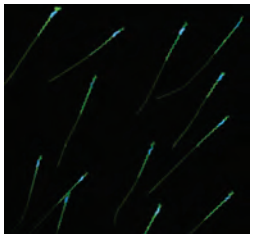


Image courtesy of Wen-Xi Chen and Jian-Hua Chen (University of Cambridge Metabolic Research Laboratories, United Kingdom).

Maternal diet and gene expression.

Sperm size vs. numbers in the female reproductive tract

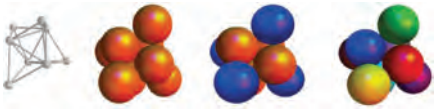
Fruit flies are known for having giant sperm, which, at a thousand times the size of human sperm, stretch to over 2 inches in some species. Although researchers have long assumed a trade-off between sperm size and number, empirical evidence for this discrepancy has proven elusive. Simone Immler et al. (pp. 5325–5330) compare sperm size and sperm number in several species of *Drosophila* fruit flies and passerine birds, and propose that the trade-off depends on sperm competition strategy, which is determined by the volume of the female reproductive tract. The researchers quantify the relationship between sperm size, sperm number, and the animal's total investment in sperm production, defined as the product of sperm size and number. At values that are physiologically relevant for small animals, sperm size scales more rapidly with body size than sperm number, the authors found. In larger animals, however, a competitive advantage is more rapidly gained from having higher numbers of sperm. In the large reproductive tracts of passerine birds, sperm are vulnerable to becoming diluted and lost, so large numbers better guarantee fertilization, the authors explain. In small fruit flies, sperm compete by direct physical contact, and the larger sperm win. The results help resolve a long-standing debate and account for a lack of consensus between previous studies, the authors report. — J.M.



Sperm of a zebra finch, a type of passerine bird.

Designing self-assembling molecular structures

Virus shells and microtubules are well-known examples of complex biological structures that can spontaneously self-assemble from simple components. The reason for this seemingly magical construction is that each building block has evolved specific interactions with the component it will connect to. Sahand Hormoz and Michael Brenner (pp. 5193–5198) expand on current engineering approaches to creating self-assembling structures, which include tweaking the surface properties of the building blocks such as the charge and polarization, and instead attempt to coat the surface of the components with sticky elements like DNA. The authors have developed a set of rules for designing short-range interactions that favor the assembly of specific components. Their approach incorporates a "Goldilocks"

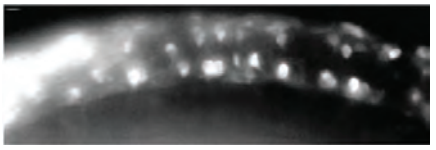


Possible designs for the self-assembly of a tetrahedral cluster.

principle, in that the bond strength of these interactions must be just right so that the structures are not too weak and fall apart, but not so strong that incorrect assemblies cannot be fixed. The authors illustrate their approach by using eight colloidal spheres that have been covered with DNA strands that bind specifically to another sphere, and showing that these spheres will self-assemble into a particular polytetrahedral structure. — B.J.T.

Technology illuminates zebrafish neural circuits

The transparency of zebrafish provides researchers with an excellent opportunity to observe the coordinated activation of neural circuits that drive vertebrate behaviors. Akira Muto et al. (pp. 5425–5430) developed a technique that allows researchers to visualize how motor circuits in the zebrafish spinal cord are activated as early as 17 hours after fertilization, when the embryos first begin to display spontaneous

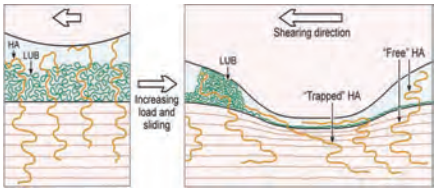


GCaMP signals in a transgenic zebrafish embryo.

muscle contractions. Their technique relies on a "calcium indicator" protein known as GCaMP, which fluoresces brightly upon binding to the calcium ions that flow into the cell during the generation of action potentials. To develop the technique, the authors introduced a series of mutations into the previously engineered GCaMP gene so that the corresponding protein, known as GCaMP-HS, would fluoresce more brightly and react more sensitively to calcium. The authors then created transgenic zebrafish in which expression of the GCaMP-HS gene was under the control of a transcriptional activator known as Gal4FF. The authors used their technique to observe the synchronized activation of ipsilateral motor neurons on the vertebrate's right and left trunk during the organism's first muscle movements. The GCaMP technology, combined with the expression system, may provide a powerful tool to study functional neural circuits in zebrafish, according to the authors. — B.A.

How joint lubrication and durability combine

Human joints can take a beating and still glide fluidly past one another, thanks in part to articular cartilage, the type of cartilage that covers bone. Joint lubrication is thought to stem from hyaluronic acid (HA) and lubricin proteins, two of the primary components of synovial fluid within the knee. However, George Greene et al. (pp. 5255–5259) explore the increasingly popular notion that the performance of articular cartilage results from multiple modes of adaptive lubrication. The authors collected cartilage tissue from pig knees and tested the friction and wear of the material in response to loading and sliding using a machine that measures surface forces. Consistent with some previous reports, the researchers found that as loads on the joint increased, surface friction forces increased and then stabilized. In additional tests, wear increased after enzymes digested HA on the



HA trapping mechanism under low (*Left*) and high (*Right*) loads.

surface, which suggested to the authors that HA may primarily provide wear resistance rather than lubrication. The authors propose a model in which free-moving HA becomes physically trapped at the cartilage interface during compression, and forms a complex with lubricin to reduce wear damage. The results challenge widely held beliefs that low friction implies better durability and that friction and wear are separate processes, according to the authors. — J.M.

Modern humans may have originated in southern Africa

Although African populations are known to be the world's most genetically diverse, limited genetic samples and sparse archaeological remains have skewed a fine-scale understanding of the continent's population history, evolution, disease susceptibility, and resistance to infection. Brenna Henn et al. (pp. 5154–5162) examined 580,000 SNPs from hunter-gatherer populations including Tanzania's Hadza and Sandawe groups, and the ≠Khomani Bushmen of southern Africa. The authors propose that the click-speaking Bushmen residing in the Kalahari Desert region of Botswana, Namibia, and northern South Africa harbor among the highest levels of genetic diversity in the world. According to the authors, this level of diversity indicates that modern humans originated in southern Africa and not eastern Africa as previously thought. The authors then examined the SNPs in 90 click-speaking individuals from the Hadza, Sandawe, ≠Khomani, and three additional hunter-gatherer groups to probe their ancestry and determine whether they are remnants of the original hunter-gatherer populations from which all other African populations diverged, or if they represent more recent communities of farmer-herders that reverted to a hunting and gathering lifestyle. Comparison with 21 farmer-herder African populations suggests, according to the authors, that these hunter-gatherers represent deeply diverged populations that possess a level of genetic diversity not seen in other African populations. — B.P.T.

Kalahari Desert region of South Africa.