Sex cells have a sweet tooth, and they pass it on to the brain

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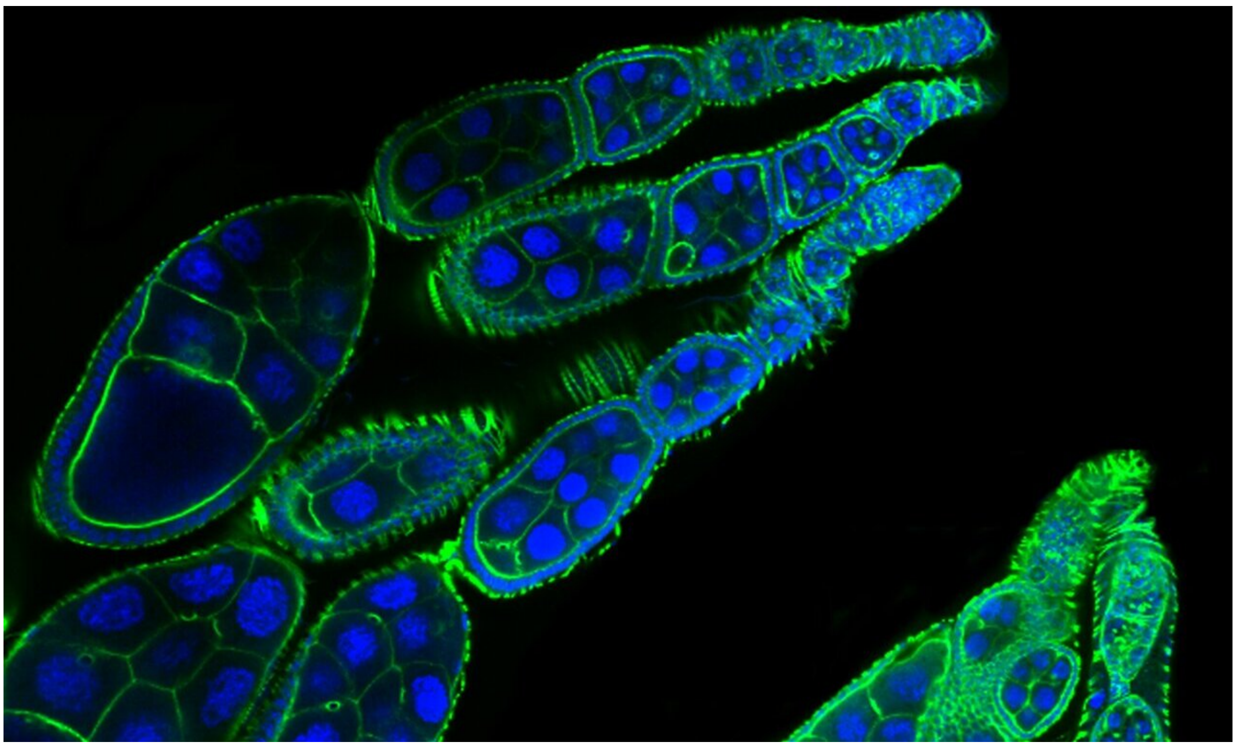

Inside the ovary of the fruit fly, sex cells divide, multiply and grow to become mature eggs. Novel discovery shows that this normal physiological process causes female fruit flies to develop a preference for sugar. Credit: Zita Santos & Carlos Ribeiro

Our job seems easy when compared with that of our cells. While they are hard at work, breaking some molecules and building others, we mainly have to do one thing—feed them. But what exactly should we feed them? This is not an easy problem to solve considering the constant competition happening inside. Whereas some cell types, like fat cells, crave lipids, others may prefer protein or sugars. How does the brain factor in all competing demands and spit out a decision when faced with difficult choices like steak or ice cream?

Now, in a study performed in fruit flies, a team of scientists at the Champalimaud Center for the Unknown in Portugal, have made a surprising discovery. Their results, published August 31 in *Nature Metabolism*, reveal that changes in the nutritional requirements of sex cells make female flies crave sugar. Until now, this phenomenon was mainly described in pathological conditions, namely cancer. Its discovery in the normal physiological process of egg formation provides important insight into the link between fertility and nutrition.

Cells with a sweet tooth

How can a small group of cells influence the behavior of an entire organism? "A hint to the answer comes from oncology. When a cell becomes cancerous, it turns on cellular machinery that preferentially consumes sugar and turns it into building blocks necessary for cell multiplication. This process, where the cell changes its 'dietary preference' and function, is called metabolic reprogramming, and it is key for tumor growth," says Carlos Ribeiro, a principal investigator at Champalimaud and a senior author of the study.

"This phenomenon was also recorded in non-pathological processes, mainly related to development. However, it was not known whether the cells' metabolic transformation could hijack the feeding decisions of the organism," adds Ribeiro. "This is what we set out to explore."

Ribeiro, together with Zita Santos, the other senior author of the study, chose to focus on the reproductive system of the fruit fly, specifically on the process of egg generation. "An egg begins with a single sex cell, which divides, multiplies and grows. The descendants of this original cell transform into the different cell types that together make up the complete egg," Santos explains.

When the team examined the cells throughout the egg's assembly process, they discovered that just like cancer cells, they were undergoing metabolic reprogramming. But not only that, they were activating the exact same cellular mechanism cancer cells use to promote cell proliferation by increasing their sugar consumption. In other words, they developed a sweet tooth.

"We were fascinated by these results," says Santos. "They explain previous reports showing that the female's sex cells absorb a high proportion of sugars eaten by the animal. And they also fit well with the role of the egg, which needs to synthesize nutrients for a developing embryo."

Driving food choice from below the belt

These encouraging results drove the team to test whether the metabolic reprogramming of the sex cells in the ovary influences the animal's food choice. When they compared the dietary preferences of normal female flies with flies that are unable to produce eggs, they observed a robust difference. "The group of sterile flies had a significantly lower appetite for sugar."

Moreover, when the team manipulated the cells' ability to metabolize sugar, both the production of eggs and the animals' sugar appetite were affected. "This demonstrates that it's not the cells themselves that generate the change in behavior, but their metabolic program. It is this specific program that drives the flies to obtain the fuel they need for egg production."

How do the cellular changes in the ovary reach the brain and change the flies' behavior? To answer this question, the team investigated the expression of fit. This small molecule is produced in the fat tissue that surrounds the fly's brain. The more Fit a fly has in her system, the less she cares for sweets.

Again, the team discovered a clear difference between normal and sterile females. Fit levels were significantly higher in the infertile group. "This is a strong indication that the effect of the sex cells on the brain is mediated by Fit. We still don't know how the communication between the ovary and the brain's fat tissue happens, but we are looking into it," Santos adds.

Diet and Fertility

Together, the team's findings outline a novel mechanism by which the metabolism of a small group of cells in the ovary controls the feeding behavior of the animal. Could these results be relevant for the field of fertility?

Santos and Ribeiro have recently received a pilot award by the Global Consortium for Reproductive Longevity and Equality to investigate the answer to this question. At the basis of their approach lies an original idea: reversing the process.

"It's a kind of a chicken and egg concept," says Santos. "What comes first: metabolic reprogramming, or changes in food preference? We discovered that the metabolic reprogramming of the cells causes the female to consume more sugar, which she needs to generate eggs. We wonder what happens during aging. Could changes in metabolism explain fertility decline? And if so, would we be able to influence the fly's fertility as she ages by manipulating her diet?"

As Santos explains, female flies, similarly to women, experience age-related infertility. She hypothesizes that changes in the ovarian metabolic programs drive reproductive decline and that this phenomenon can be reduced or even reversed using targeted dietary interventions.

"We will explore this hypothesis in the fruit fly by using a combination of single-cell RNA sequencing and metabolomics. In parallel, we will characterize the cellular outcomes of ovarian decline and monitor the feeding behavior of these animals. This will allow us to devise dietary strategies to reverse the identified alterations and increase reproduction in older female flies. We believe that this is a powerful path to identify potentially reversible processes underlying reproductive age-related decline. Also, since this is a mechanism that is shared by cancer cells, our findings may also be relevant for treating cancer," Ribeiro Concludes.

More information: Cellular metabolic reprogramming controls sugar appetite in Drosophila, *Nature Metabolism* (2020). DOI: 10.1038/s42255-020-0266-x, www.nature.com/articles/s42255-020-0266-x

Provided by Champalimaud Centre for the Unknown