Could cholesterol explain why childhood obesity leads to early puberty?

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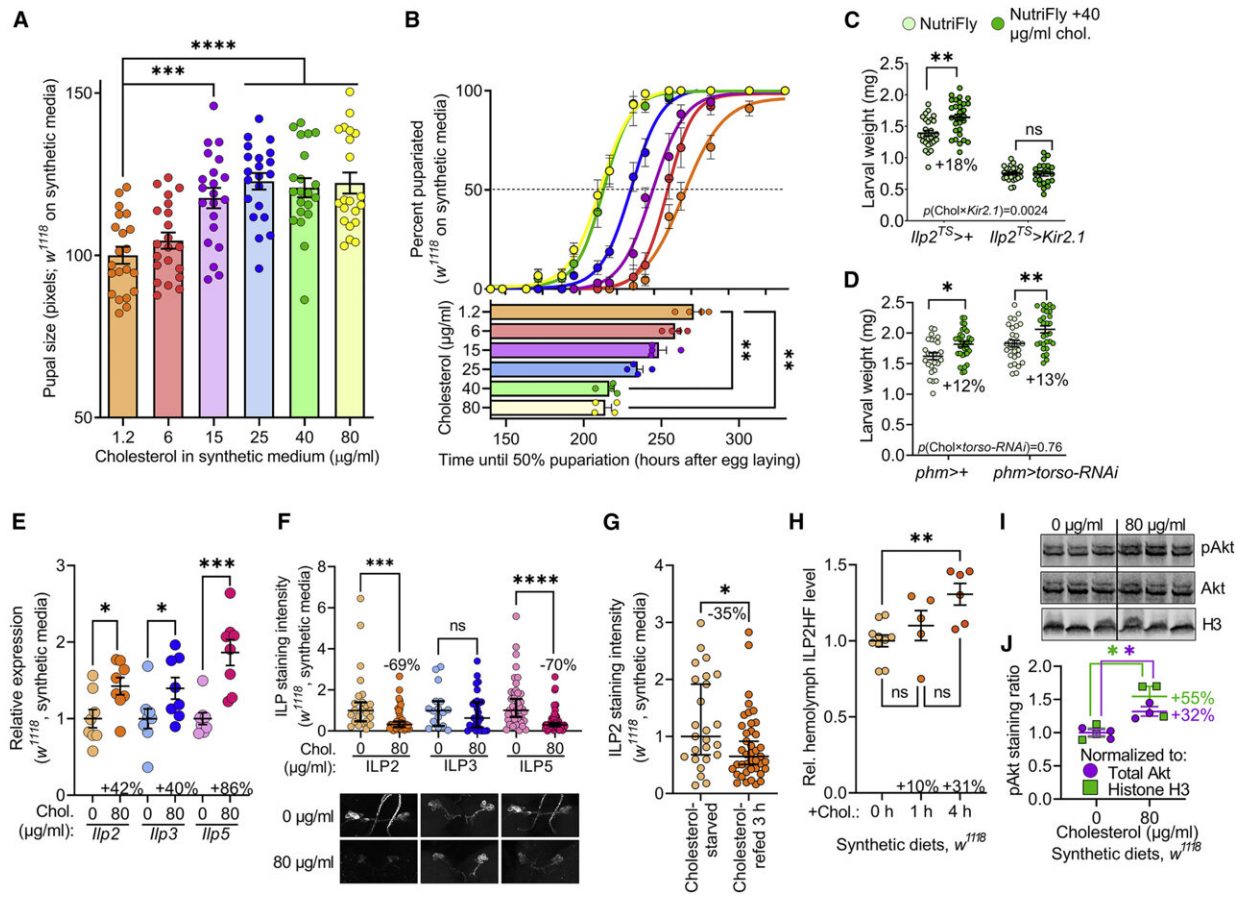

Dietary cholesterol systemically promotes growth through insulin signaling(A) Larval growth on synthetic medium, reflected in pupal size, increases with increasing dietary cholesterol concentration.(B) Development to the pupal stage on synthetic medium is accelerated with increasing dietary cholesterol concentration. Top: fraction pupariated over time; bottom: time until 50% pupariation; each data point represents a vial of flies.(C) Cholesterol's growth-promoting effect requires insulin signaling. Dietary supplementation of lower-

sterol NutriFly medium with cholesterol (NutriFly versus NutriFly + 40 μg/μl chol) promotes growth in control animals ($Ilp2^{TS}$>+), but if the IPCs are silenced through expression of the inhibitory channel Kir2.1 ($Ilp2^{TS}$>Kir2.1), this growth promotion is blocked (2-way ANOVA p for interaction of genotype and diet, 0.0105). Animals were reared at 18°C on NF medium until 130 h AEL, when half were transferred to NutriFly+40. Animals were then kept at 29°C, and L3 larvae were weighed 24 h later.(D) The growth-promoting effect of added cholesterol does not arise through effects on ecdysone production. Animals were reared on NF medium until 72 h AEL, when half were transferred to NF+40. L3 larvae were weighed at 104 h AEL. Blocking the production of ecdysone by expressing RNAi against the PTTH receptor Torso in the prothoracic gland (phm>torso-RNAi) had no effect on cholesterol-induced growth (2-way ANOVA p for interaction of genotype and diet, 0.974). See also Figure S1A.(E and F) Insulin-gene expression is higher (E), and anti-ILP2 and –ILP5 staining intensity is lower (F), in animals that fed on synthetic medium containing 80 μg/ml cholesterol than in animals that fed on cholesterol-free medium, suggesting increased ILP release on cholesterol-containing medium. Illustrative images are shown below.(G) Feeding on cholesterol-containing synthetic medium after cholesterol starvation on cholesterol-free synthetic medium appears to acutely induce ILP2 release (within 3 h), as indicated by reduced anti-ILP2 stain in the IPCs.(H) Hemolymph ELISA against tagged ILP2 indicates correspondingly increased circulating ILP2 after larvae are transferred from cholesterol-free synthetic diet to cholesterol-replete medium.(I and J) Peripheral insulin-signaling activity is increased by cholesterol refeeding, reflected in anti-phospho-Akt staining normalized to total Akt or to histone H3. Statistics: (A) Welch's ANOVA with Dunnett's T3 multiple comparisons. (B and H) Kruskal-Wallis ANOVA with Dunnett's multiple comparisons. (C and D) Two-way ANOVA with Šídák's multiple comparisons. (E, F, and G) Mann-Whitney pairwise test. (J) unpaired t test. (A–E, H, and J) Mean ± SEM. (F and G) Median with 95% confidence interval. Significance is noted as ns, $p > 0.05$; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$; $^{****}p \leq 0.0001$. See also Figure S1. Credit: *Current Biology* (2022). DOI: 10.1016/j.cub.2022.02.021

Puberty often begins early for children who are obese. While there is

nothing new about this fact, a scientific explanation has been elusive. Now, a team of scientists at the University of Copenhagen offers what may be a partial explanation.

Along with an ever-increasing number of obese children around the world, children are entering puberty earlier and earlier. This is particularly true for girls. According to a survey, the onset of puberty occurs on average three months earlier for girls in every decade since 1977.

Early puberty, also known as precocious puberty, can leave children with psychological and social problems, as well as causing them to be shorter than they would otherwise be. Studies also suggest that early puberty can increase the risk of developing cancer, diabetes, depression and cardiovascular disease later on in life.

While various reasons have been speculated upon, there are no clear scientific explanations for early puberty. Nevertheless, the link between childhood obesity and early puberty has long been apparent. The more body fat a child has, the greater their likelihood of beginning puberty at an earlier age. However, no one has been able to fully explain the connection.

Now, a team of research scientists from the University of Copenhagen has found what may be part of the answer in a so-called "model organism" that is genetically similar to humans—namely, in Drosphila fruit flies.

"Cholesterol is a fat. So, if you're overweight, your body fat harbors more cholesterol. And it turns out that higher cholesterol is a key to earlier maturation in the fruit fly, our model organism. Our results demonstrate that the amount of cholesterol in adipose tissue and in certain support cells in the brain affects the growth of fruit flies and

controls when they reach maturity," explains Professor Kim Rewitz, a lead author of the study, now published in the journal *Current Biology*.

"And because the systems in fruit flies and humans are remarkably similar, we believe that the same may apply to humans—i.e., that cholesterol in adipose tissue may help explain the connection between childhood obesity and early puberty."

Puberty begins when the body reaches a certain weight

Professor Rewitz and the Department of Biology research team tested their hypothesis by putting fruit fly larvae on a fatty diet of cholesterol-packed foods. The development of these larvae was compared with larvae that hadn't received the high cholesterol diet.

"We observed that larvae on the cholesterol diet consistently grew faster and entered puberty sooner. It turned out that the increase of cholesterol stored in the fruit flies' body fat and support cells in the brain increases the release of growth hormones that cause the animals to grow faster. Growth and size is a signal to the body for when to trigger puberty," says Kim Rewitz.

The professor explains that in fruit flies, the signal to undergo maturation is when their weight and amount of body fat reach a certain point during development:

"In one way or another, animals need to know when they're large enough to reach sexual maturity and be able to reproduce. Organisms have a checkpoint in their development that they must pass to enter puberty known as 'critical weight'. This checkpoint is found in fruit flies and most likely in humans too. This means that both fruit fly larvae and

children probably need to reach a certain body size and have a certain amount of fat stored to enter puberty. What we've found is that the amount of cholesterol stored in body fat plays an important role in this process. We see that fruit flies have a mechanism that senses how much cholesterol is stored in their body fat and support cells in the brain. At a certain point, the system then sends a signal to the brain centers that triggers maturation by producing steroid hormones. In humans, these correspond to testosterone and estrogen," says Kim Rewitz.

However, it also means that if the amount of stored cholesterol increases, the organism can actually fail to estimate its overall size accurately, so that it hits the critical weight checkpoint earlier than it normally would:

"Because overweight children have more body fat, they will probably also have stored more cholesterol at an earlier point in their development. So, if our assumption that the same mechanism exists in humans holds true, it could help to explain early puberty in obese children," says the researcher.

Cholesterol may influence cancer as well

Professor Rewitz hopes that other researchers will follow up on this study with models in mammals and eventually humans.

"Early puberty is a growing problem around the world. Now that we might have an important part of the explanation for how obesity and early puberty are connected, we may be able to better establish the great significance that obesity has for childhood development. Thereafter, we can see whether new ways can be found to address the problem. For the time being, lifestyle changes are probably the best solution," says Kim Rewitz.

Professor Rewitz and his research colleagues have now started to look

deeper into the significance of the cholesterol mechanism for cancer development. Their research also shows that, via the same mechanism, cholesterol can activate cell growth that leads to cancer.

More information: Michael J. Texada et al, Insulin signaling couples growth and early maturation to cholesterol intake in Drosophila, *Current Biology* (2022). DOI: 10.1016/j.cub.2022.02.021

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