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Planarians enter the genomic era

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Researchers at the University of Utah have figured out a way to inhibit the function of the planarian genome to create a wide range of phenotypes. Their study, appearing in the May issue of *Developmental Cell*, is the first of its kind to use large-scale genetics to study the planarian *Schmidtea mediterranea*, which contains a genome thought to contain insight into adult stem cell pluripotency and tissue regeneration.

The study "changes things because it effectively makes an animal that was not accessible to genetic studies accessible," lead author Alejandro Sánchez Alvarado told *The Scientist*.

The planarian is capable of regrowth due to the pluripotency of its neoblasts. Even a fraction of the worm is capable of regenerating into an entirely new organism. However, because the organism does not reproduce sexually, it cannot be studied using traditional genetic techniques.

The team circumvented the problem using bacterial-fed RNA interference (RNAi). The group was looking for "robust, specific, and reproducible" genetic perturbations, and they "took the next step to recapitulate [RNAi] from *C. elegans*," Sánchez Alvarado said. They first generated and optimized an RNAi vector, and then inhibited 1065 genes in the planarian.

Animals were screened for both visible defects, such as amputation defects, light sensitivity, or mobility deficits, and nonvisible defects, such as cellular level phenotypic changes. Researchers then performed a record 54,300 genetic amputations to observe the worms for regeneration defects. They determined that 240 of the 1065 genes screened (22.5%) generated phenotypes following perturbation. These phenotypes included observable deficits in movement, behavior, organ function, and regeneration.

The work "changes the way in which people will approach planarian biology," said Phil Newmark, who studies planarian regeneration at the University of Illinois. Newmark, who worked as a postdoc in Sanchez Alvarado's group, praised the study for "technical improvements in methodology" such as "optimizing the vector at the beginning which was crucial to why the study worked well." According to Newmark, the excitement not only lies in the phenotypes presented here, but in the ones yet to be found. "Given the planarian's ability to maintain its tissue indefinitely, there is a real possibility that some subset of its genes is involved in regulating tissue maintenance, which is not yet well understood," he told *The Scientist*.

Michael Levin, of the Forsyth Institute, Boston, who has worked with the planarian model to study development, is banking on the model for clues into aging, senescence, and pluripotency. "Planaria are practically immortal - their cells undergo senescence - but on the organism level, they are immortal because all aging cells are replaced and so they have no lifespan limit, which is extremely unique," he told *The Scientist*. "It is going to have great ramifications when we figure out how that works."

But just how closely do humans resemble a flatworm? While the worm lacks a respiratory or circulatory system, it still contains features that give the creature strong links to humans' evolutionary past, including three tissue layers, bilateral symmetry, and distinct organs. In addition, although humans are far down the genetic path from the worm, they are still more closely related to it than to other classically used genetic systems. "Many [planarian] genes have counterparts in the human genome, yet

are absent in *C. elegans* and *Drosophila*, allowing planarians to be used as a system to inform the functions of human genes quickly and effectively," noted Sánchez Alvarado.

Further, since the planarian genome is not yet fully mapped, there is no way to know what fraction is represented by the 1065 genes studied here. Sánchez Alvarado suspects the genome contains as many as 15,000 to 20,000 genes and suggested that the phenotypes presented in the paper are just the tip of the iceberg.

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