Eliminating damaged germline cells preserves germline integrity

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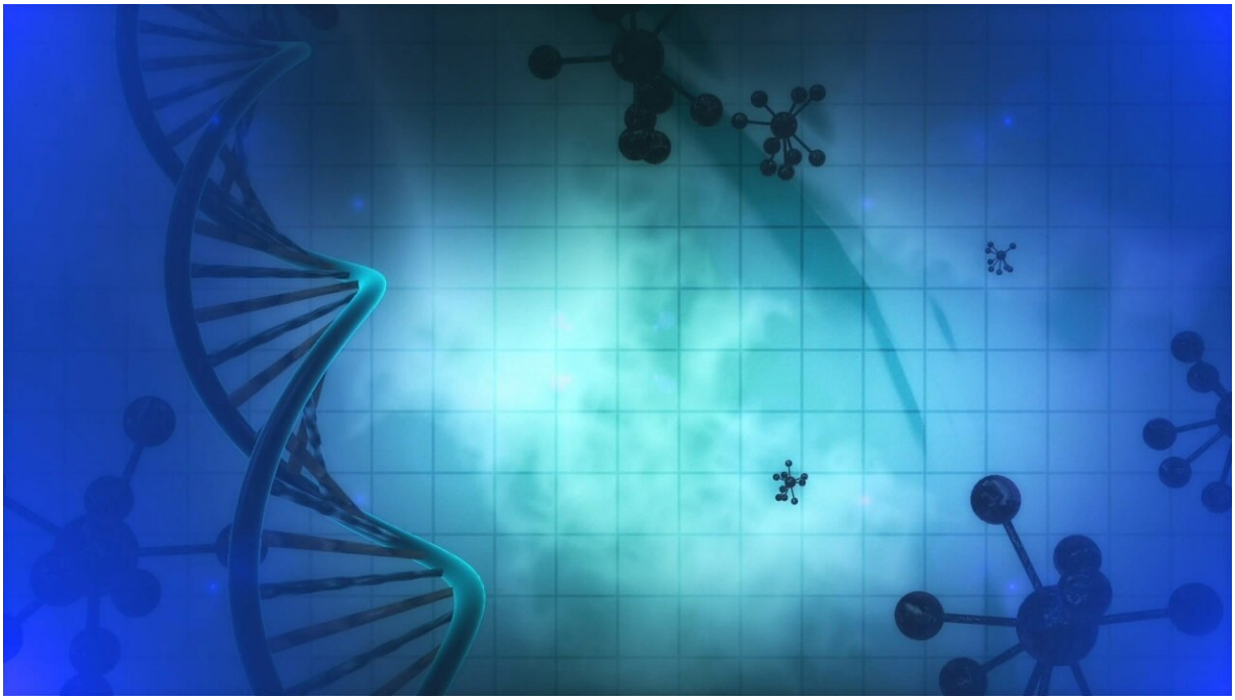

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The germline is the cell lineage of an organism that passes on its genetic material to its progeny. Genetic damage to the germline can cause developmental defects and even death of that same progeny. It is thought that biological mechanisms exist that ensure aberrant germline cells are eliminated to maintain germline integrity, although the specific molecular basis for this is unknown. In a new study published in

Communications Biology, researchers from the University of Tsukuba identified the transcription factor Myc as a central molecular actor within the process of preserving the genomic integrity of the germline after DNA damage.

To achieve their goal, the researchers studied the fruit fly Drosophila to understand how germline integrity is maintained. This fly model presents a sterility syndrome called P-M (paternal-maternal) hybrid dysgenesis (HD), which results from a high rate of mutations and rearrangements in the DNA, leading to germline-loss and sterility. At the molecular level, so-called P-elements are responsible for HD. P-elements are DNA segments of which the protein transposase. Transposases have an ability known as P-element mobilization wherein they move segments of DNA, which leads to mutations and DNA instability. When male fruit flies carrying P-elements are crossed with females lacking P-elements, P-element mobilization and thus DNA damage occurs in their progeny, resulting in sterility.

"The Drosophila P-M hybrid dysgenesis model has been known for decades, but the molecular basis of the resulting sterility is still not fully understood," says corresponding author Professor Satoru Kobayashi. "The goal of our study was to further our understanding of the molecular mechanisms governing the elimination of damaged germline cells during reproduction. Interestingly, in a separate set of experiments, we found that knockdown of the transcription factor Myc resulted in a similar germline-loss phenotype that we observe in hybrid dysgenesis. We wanted to know how Myc and hybrid dysgenesis were interconnected in the process of maintaining germline integrity."

The researchers first investigated the number of germline cells at different embryonic stages in HD progeny and in normal flies that did not produce Myc. They found that in both models the number of germline cells decreased at a similar stage of embryonic development,

suggesting that both processes are connected. The researchers then followed the expression of Myc in HD progeny and found that it was reduced in germline cells before the number of germline cells decreased, suggesting that HD causes Myc downregulation to result in a germline-loss phenotype. They then examined what happens if Myc continued to be expressed in HD progeny by overexpressing the transcription factor. While Myc overexpression in the HD germline led to increased germline cell numbers, the resulting germline exhibited a higher DNA mutation frequency and a lower capacity to develop into adulthood.

"These are striking results that show that Myc-dependent germline cell reduction serves to eliminate aberrant germline cells in which the genetic material has been damaged," says Professor Kobayashi. "We think that Myc is a central molecular actor in this process, serving as a quality-control during embryonic development."

More information: Ryoma Ota et al. Myc plays an important role in Drosophila P-M hybrid dysgenesis to eliminate germline cells with genetic damage, *Communications Biology* (2020). DOI: 10.1038/s42003-020-0923-3

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