Mechanism for stress-induced epigenetic inheritance uncovered in new study

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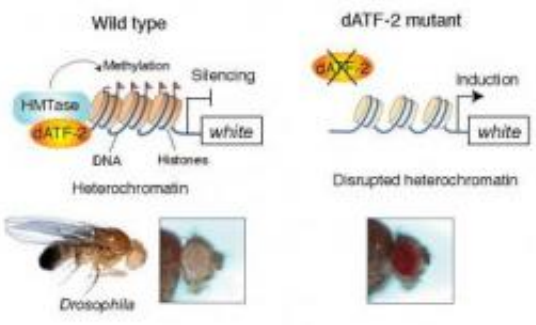
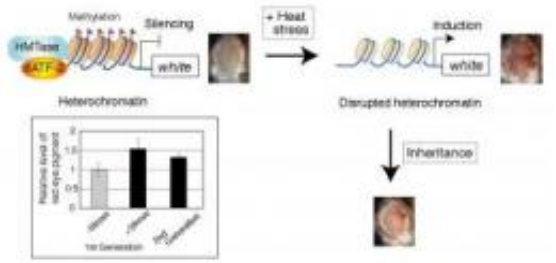


dATF-2 is essential for heterochromatin formation. In the Drosophila line, in which the white gene required for the production of red eye pigment is located close to the heterochromatin, the white gene expression is silenced by heterochromatin, leading to white eye (left). In the dATF-2 mutant, the heterochromatin is disrupted, leading to red eye (right). Credit: RIKEN

Researchers at RIKEN have uncovered a mechanism by which the effects of stress in the fly species Drosophila are inherited epigenetically over many generations through changes to the structure of chromatin, the material that makes up the cell nucleus. Published in the journal *Cell,* the results highlight the role of the transcription factor dATF-2 in chromatin assembly, marking a major advance in our understanding of non-Mendelian inheritance.

Recent years have seen growing interest in the phenomenon of epigenetic inheritance: the idea that our genome, through epigenetic tags

and other structural modifications, transmits more information than the sequence of letters encoded in its DNA base pairs alone. Stresses of various kinds have been shown to induce such epigenetic change, yet the underlying mechanisms involved remain unknown.

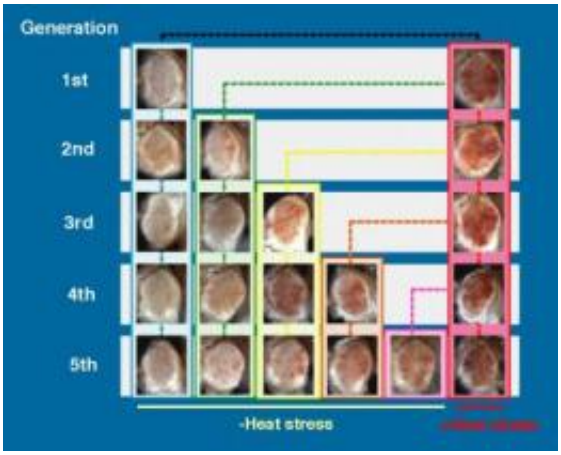


Disrupted heterochromatin by stress via dATF-2 is inherited. Exposure of flies to heat stress during early embryogenesis caused the disruption of heterochromatin, leading to red eye (upper). When the heat-stressed flies were mated with non-stressed flies, the generated progenies exhibited slightly the red eye phenotype (lower right). The amount of red eye pigment was quantified and shown (lower right). Credit: RIKEN

To clarify these mechanisms, the researchers investigated the activity of activation transcription factor-2 (ATF-2), a member of a family of transcription factors which regulate gene expression in response to changes in the cellular environment. Earlier research had suggested that in the absence of stress, ATF-2 plays a role in silencing certain genes through the formation of heterochromatin, a tightly-packed variety of chromatin whose state is epigenetically heritable. When the stress is turned on, ATF-2 changes its function and induces gene expression.

Studying mutations to the ATF-2 gene in Drosophila (dATF-2), the researchers observed a disruption to the heterochromatin structure and reduced methylation of histone proteins, the main component of

chromatin (Fig. 1). Further analysis revealed that heat shock and osmotic stress during early embryogenesis results in phosphorylation of dATF-2 and triggers its release from the heterochromatin.



Multigenerational inheritance of the disrupted heterochromatin by stress. When the flies were exposed to heat stress only at 1st generation, its effect that can be judged by red eye phenotype was seen in the second generation flies, but not in the successive generations (green). When flies were exposed to heat stress at first and second generations, its effect was observed in the successive three generations (yellow). Credit: RIKEN

Most interestingly, the researchers discovered that the disruption to heterochromatin caused by the release of dATF-2 was transmitted to the next generation of cells, without any change to their DNA sequences (Fig. 2). In the case of heat shock, sustained stress over multiple generations resulted in the altered chromatin state being inherited by subsequent generations as well (Fig. 3). The findings thus provide the first example of multigenerational transmission of stress-induced epigenetic change, highlighting the role played by ATF-2 and opening promising new avenues for further study.

Provided by RIKEN