CHROMATIN

The inheritance of stress

Alterations to epigenetic states allow the organism to adapt to environmental changes. Seong *et al.* now reveal an activating transcription factor 2 (ATF2)-dependent mechanism by which stress can induce changes in heterochromatin that are inherited by successive generations in a non-Mendelian manner.

Previous work in fission yeast had shown that Atf1 (the yeast homologue of ATF2) is involved in the nucleation and spread of heterochromatin, which is characterized by compact chromatin and gene silencing. To test the function of ATF2 in higher organisms, the authors used a position effect variegation model (the *Drosophila melanogaster* w^{m4} line), in which an inversion has moved the *white* gene from a euchromatic region (which is characterized by open chromatin and gene expression) to be juxtaposed to a heterochromatic region. This causes the *white* gene to become silenced in a variable manner, depending on the extent of heterochromatin spread, and leads to a variegated pattern of *white* gene expression in the fly eye. They found that crossing w^{m4} flies with *ATF2*-mutant flies reduced *white* silencing; this indicates that ATF2 functions in heterochromatin formation in *D. melanogaster*. The RNA interference (RNAi) pathway has a well-established role in heterochromatin formation; however, using RNAi mutants, the authors show that the involvement of ATF2 in this process is independent of RNAi, similarly to yeast Atf1.

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MACMILLAN SOUTH AFRICA

ATF2 contains phosphorylation sites for stress-activated protein kinases, such as p38, which is downstream of MAPK/ERK kinase kinase 1 (MEKK1; also known as MAP3K1). The authors found that both osmotic stress and heat shock led an increase in ATF2 phosphorylation and also to heterochromatin disruption, which they measured by *white* expression and by reduction in the levels of histone H3 Lys9 dimethylation (H3K9me2) at specific heterochromatic sites. To confirm that ATF2 phosphorylation was indeed essential for stress-induced heterochromatin disruption, they mutated ATF2 p38 phosphorylation sites to Ala; as expected, there was no decrease in H3K9me2 levels in stress conditions. Owing to redundancy in p38 protein kinases in *D. melanogaster,* the authors studied the role of the upstream kinase MEKK1 in ATF2 phosphorylation. In *MEKK1*-mutant flies, heterochromatin did not become disrupted, indicating a requirement for MEKK1 in stress-induced phosphorylation of ATF2.

Because the authors had found that stress disrupts heterochromatin in germ cells as well as somatic cells, they tested whether stress-induced changes are inherited. They found that stress-induced heterochromatin disruption can be inherited across multiple generations; however, unless stress is re-induced, the disruption to heterochromatin fades. Thus, stress-induced heterochromatin disruption is unstable, suggesting that there is a mechanism that normally maintains heterochromatin in germ cells that can become overwhelmed in conditions of extreme stress. Interestingly, they found that stress-induced heterochromatin is inherited in a non-Mendelian manner: they observed *white* gene expression caused by heterochromatin disruption when only one parent was stressed, regardless of whether the *white* gene was inherited from the stressed or unstressed parent. This resembles the phenomenon of paramutation, which has been extensively studied in plants — a paramutagenic allele causes another allele in the same nucleus to become silenced, suggesting a *trans*-allelic interaction.

This work shows how the environment can signal information, such as stress, to chromatin through ATF2 phosphorylation and suggests an interesting way by which the environment can heritably alter gene expression.

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