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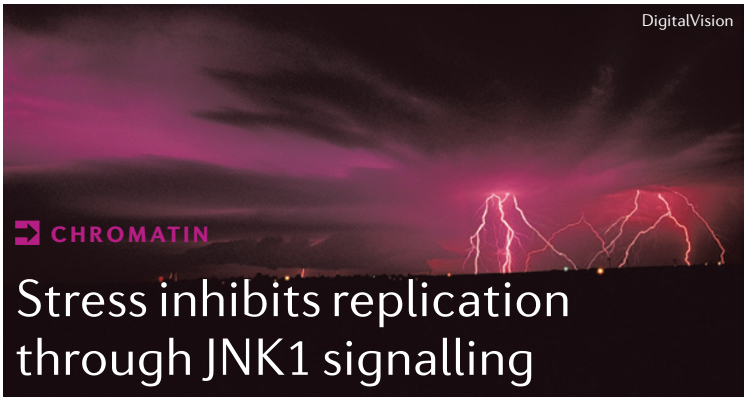

Stress inhibits replication through JNK1 signalling

> “phosphorylation of CDT1 on Thr29 by JNK1 blocks replication initiation in response to environmental stress.”

To protect the integrity of the genome in conditions of environmental stress, cells temporarily inhibit DNA replication. Miotto and Struhl now identify a signalling pathway linking environmental stress to the initiation of DNA replication. They show that JUN N-terminal kinase 1 (JNK1)-mediated phosphorylation of the replication licensing factor CDT1 prevents CDT1 from recruiting the histone H4 acetylase HBO1 (also known as MYST2) to replication origins, abrogating the acetylation that is required for replication initiation.

The authors treated HeLa cells with chemicals that cause different types of stress to study the effects of stress on replication licensing. They found that HBO1 did not associate with replication origins under stress conditions but maintained its association with other genomic sites, consistent with its known role as a transcriptional co-activator.

Previous work had shown that HBO1 is recruited to replication origins by CDT1. As CDT1 is degraded to prevent reinitiation of replication when cells enter S phase and in conditions of DNA damage, the authors tested whether the observed failure to recruit HBO1 to replication origins resulted from CDT1 degradation. They found that CDT1 levels are not affected by osmotic stress, and although treatment with a proteasome inhibitor restored CDT1 levels, this did not affect HBO1 recruitment under osmotic stress. This suggested that the failure to recruit HBO1 in stress conditions is independent of CDT1 stability and, instead, results from defective HBO1 recruitment.

So, what regulates HBO1 recruitment under stress conditions? Miotto and Struhl postulated that a stress-induced post-translational modification may influence the CDT1–HBO1 interaction. Therefore, they tested the known post-translational modifications of CDT1 and found that CDT1 was phosphorylated in response to osmotic stress. By inhibiting various kinases that are known to be activated in response to different stress conditions, they identified JNK1 as the relevant kinase. They found that chemically inhibiting JNK1 prevented HBO1 disassociating from replication origins under osmotic stress, and confirmed that this effect was specific to JNK1 by small interfering RNA-mediated knockdown of JNK1. CDT1 has several known phosphorylation sites; by testing different mutants, the authors found that a Thr29Ala mutation in CDT1 blocked JNK1-mediated phosphorylation of CDT1 and, furthermore, that overexpression of the Thr29Ala-mutant CDT1 rescued HBO1 binding at replication origins,

Thus, phosphorylation of CDT1 on Thr29 by JNK1 blocks replication initiation in response to environmental stress. This inhibition is transient, so replication can proceed when the stress is relieved. As HBO1 is also known to be involved in regulating the transcriptional response to stress — it is recruited to target genes in stress conditions and acts as a co-activator of the transcription factor adaptor protein 1 (AP1) — these results show how HBO1 acts as a coordinator of the cellular response to environmental stress.

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ORIGINAL RESEARCH PAPER Miotto, B. & Struhl, K. JNK1 phosphorylation of Cdt1 inhibits recruitment of HBO1 histone acetylase and blocks replication licensing in response to stress. *Mol. Cell* 18 Aug 2011 (doi:10.1016/j.molcel.2011.06.021)