

Global Gene Inhibition during Heat Shock via Reduced Stalled Pol II and Nucleosome Turnover

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An evolutionarily conserved cellular response to heat shock and other environmental stressors (e.g., cold, oxygen deprivation or heavy metal poisoning) involves transcriptional up-regulation of so-called 'heat shock' proteins (HSPs). The first such protein to be described, a 70 kilodalton variety called HSP70, was discovered in 1962 by Ferruccio Ritossa, after a technician accidentally set the temperature of a fruit fly incubator too high. HSP70 and many additional heat shock proteins act as molecular chaperones, which help other proteins to fold properly or avoid clumping, or assist with the assembly of oligomeric structures from simpler components, such as nucleosomes from histones and DNA. Upon heat shock, master transcription factors trigger fast and synchronous activation of HSPs by binding to promoters of HSP genes, where paused RNA polymerase II (Pol II) molecules wait vigilantly like a squad of rapid response sentinels. Simultaneously, heat shock causes global down-regulation of background transcription across the genome, presumably to prevent deleterious aggregations of denatured proteins.

The rapid, genome-wide and reasonably well-characterized transcriptional responses underlying heat shock make this process an ideal framework for investigating the general changes in chromatin landscape that accompany changes in gene regulation. This insight was one of the motivations behind a recent paper by graduate student Sheila Teves and Dr. Steven Henikoff, both of the Basic Sciences Division. Last month, *Science Spotlight* reported on a new methodology developed by the Henikoff Lab for quantifying epigenome structure at high spatial resolution. Prior to that, the Henikoff Lab had pioneered a powerful new technique to characterize nucleosome turnover kinetics via metabolic labeling of histones (Deal *et al.*, 2010). Teves and Henikoff have used these new technologies to profile low-salt soluble chromatin, Pol II and nucleosome turnover at single base-pair resolution in *Drosophila* cell culture engaged in classic heat shock.

Teves and Henikoff started out their study by providing a snapshot of the chromatin landscape for an HSP70 gene undergoing heat shock. They demonstrated loss of nucleosome occupancy within this gene, decrease in the subnucleosomal particle residing over the transcription start site (TSS) and evidence of active Pol II moving through the gene body. Loss of nucleosomes from HSP genes

during heat shock makes sense, since transcription factor binding is prevented when DNA is packaged into nucleosomes; instead, disruption or mobilization of nucleosomes facilitates gene activation. Next, the authors broadened their investigation by looking at genes across the *Drosophila* genome. They mapped all size classes of low-salt soluble chromatin, as well as bound Pol II, in windows around both the TSSs and transcription termination sites of all genes. Among other things, they discovered small subnucleosomal particles at the TSSs of genes exhibiting increased expression upon heat shock, which suggests that these particles may be involved in transcription initiation. They also found that stalled Pol II levels decreased genome-wide, indicating that reduced Pol II affinity may be a mechanism for global down-regulation of housekeeping gene expression during heat shock. A small number of genes involved in transcription regulation, hypoxia responses and heat shock were found to have increased nucleosome turnover downstream of the TSS. However, in general, the authors found that nucleosome turnover was reduced upon heat shock across a much larger number of genes. Moreover, using a Pol II elongation inhibitor, they experimentally demonstrated that this global reduction in nucleosome turnover closely resembles the change in nucleosome dynamics caused by direct inhibition of transcription elongation. These results provide important evidence of a causal relationship between transcriptional repression and nucleosome turnover in eukaryotes, where only correlative patterns had been detected previously.

[Teves SS, Henikoff S.](#) 2011. Heat shock reduces stalled RNA polymerase II and nucleosome turnover genome-wide. *Genes and Development* 25:2387-2397.

Also see: [Deal RB, Henikoff JG, Henikoff S.](#) 2011. Genome-wide kinetics of nucleosome turnover determined by metabolic labeling of histones. *Science* 328:1161-1164.

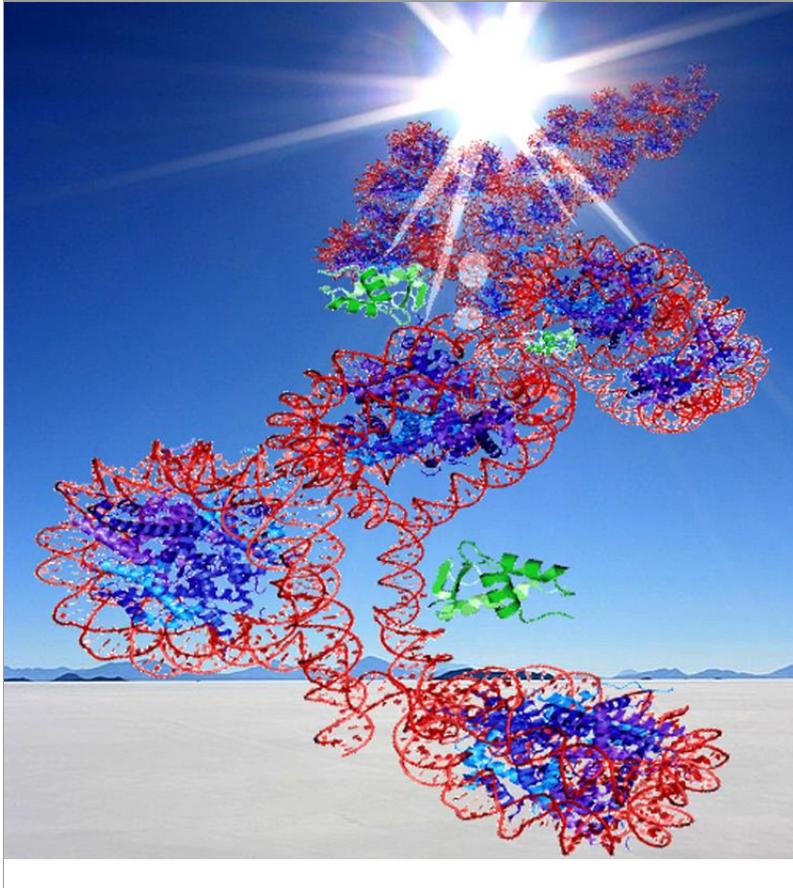


Image by Matt Arnegard

The dynamics of nucleosomes, the basic units of eukaryotic DNA packaging (depicted here), change dramatically with acute rises in body temperature.