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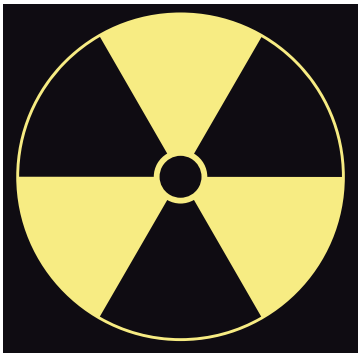
CHROMATIN

JAK2 goes nuclear

> an unprecedented role for JAK2 in the nucleus

Janus kinase 2 (JAK2) is a non-receptor tyrosine kinase known to initiate cytoplasmic signalling cascades that regulate various processes, including cell cycle progression, apoptosis, mitotic recombination, genetic instability and heterochromatin modifications. In *Nature*, Tony Kouzarides and colleagues now report an unprecedented role for JAK2 in the nucleus by showing that it phosphorylates the core histone H3 to prevent it from binding to heterochromatin protein 1α (HP1α).

Using confocal immunofluorescence, the authors observed that JAK2 is present in the nucleus of different haematopoietic cell lines. They found that JAK2 specifically phosphorylates histone H3 both *in vitro* and *in vivo*. Phosphorylation occurs at a tyrosine residue (Y41) that lies in the first H3 helix, in a region known to control nucleosome remodelling. Levels of phosphorylated H3Y41 (H3Y41ph) increase when JAK2 is activated by cytokines, whereas phosphorylation is rapidly lost on treatment with JAK2 inhibitors, which suggests that JAK2 directly phosphorylates H3Y41 *in vivo*.



As the JAK pathway has been previously reported to alter heterochromatin structure by disrupting the localization of HP1, the authors investigated whether JAK2-dependent H3 phosphorylation might regulate H3–HP1 binding. They found that the HP1α isoform binds to an H3 peptide containing Tyr41 *in vitro*, and that this binding is inhibited upon Tyr41 phosphorylation. Furthermore, analysis of permeabilized nuclei prepared from haematopoietic cells cultured in the presence or absence of JAK2 inhibitors showed that blocking JAK2 activity decreases the level of H3Y41ph and increases the proportion of chromatin-bound HP1α. Thus, JAK2-mediated phosphorylation of H3 modulates HP1α binding to chromatin *in vivo*.

But what is the biological relevance of H3Y41 phosphorylation? The authors analysed mRNA expression profiles of haematopoietic cells treated with or without JAK2 inhibitors to identify JAK2 targets. Cytoplasmic JAK2 is known to signal through signal transducer and activator of transcription 5 (STAT5). In addition to known targets of the canonical JAK2–STAT5 signalling pathway, they found that genes lacking a predicted binding site for STAT5, including the haematopoietic oncogene LIM domain only 2 (*LMO2*), were also regulated by JAK2. Chromatin immunoprecipitation revealed that downregulation of *LMO2* is accompanied by lower levels of H3Y41ph and increased HP1α binding at sites surrounding the *LMO2* transcription start site. This suggests that JAK2-mediated H3Y41 phosphorylation excludes HP1α from the *LMO2* promoter and reveals a link between the *JAK2* and *LMO2* genes, which are both involved in normal haematopoiesis and leukaemia.

Thus, this study shows for the first time that JAK2 has a nuclear function. It directly phosphorylates histone H3 and prevents HP1α from binding chromatin at a site near H3Y41. H3Y41 phosphorylation might regulate chromatin architecture at specific promoter regions and promote gene expression.

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ORIGINAL RESEARCH PAPER Dawson, M. A. *et al.* JAK2 phosphorylates histone H3Y41 and excludes HP1α from chromatin. *Nature* 27 Sep 2009 (doi:10.1038/nature08448)