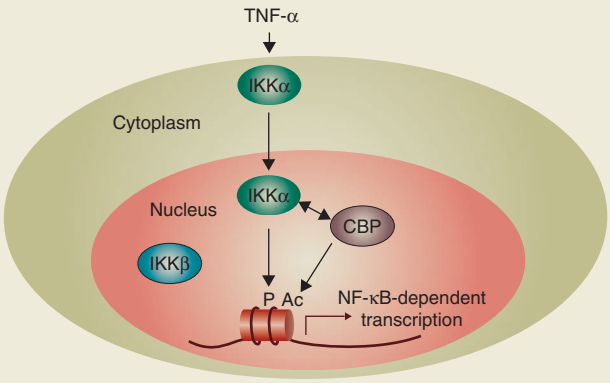
IKKα: a chromatin modifier



Nuclear IKKα is necessary for histone H3 phosphorylation at NF-κb-dependent promoters.

Activation of the transcription factor NF-κB depends on inducible phosphorylation and subsequent degradation of NF-κB inhibitors, known as IκBs. Two reports by Anest *et al.* (*Nature* DOI: 10.1038/nature01648) and Yamamoto *et al.* (*Nature* DOI: 10.1038/nature01576) now describe how IκB kinase (IKK) provides an additional layer of regulation through NF-κB-mediated transcription. They show that a subunit of IκB kinase can phosphorylate histone H3 and may therefore modulate chromatin accessibility at NF-κB-responsive promoters.

IKK is composed of two catalytic subunits, IKKα and IKKβ, and is crucial for cytokine-induced IκB degradation and subsequent activation of NF-κB. Previous studies have shown that IKKβ is essential for degradation of IκB. In contrast, IKKα, although not necessary for proteolysis of IκB, is still important for NF-κB-dependent transcription. However, exactly how IKKα regulates NF-κB-dependent transcription is unclear. Previous work showing that IKKα shuttles between the nucleus and the cytoplasm hinted at the possibility of a novel nuclear function for IKKα.

Here, both Anest *et al.* and Yamomoto *et al.* start by confirming that IKKα is a nuclear protein. To address whether nuclear IKKα regulates cytokine-inducible NF-κB gene transcription, the groups used chromatin immunoprecipitation (ChiP) assays to examine the promoter occupancy of NF-κB target genes. These experiments showed that after cytokine stimulation, IKKα is recruited to NF-κB target-promoters in a NF-κB-dependent manner. Furthermore, they showed that the kinetics of IKKα recruitment parallel phosphorylation of histone H3-Ser 10 at the promoter, an event that is known to correlate with active gene expression. Both studies also showed that IKKα is most probably the physiological kinase responsible for cytokine-induced phosphorylation of histone H3, as phosphorylation of histone H3 at Ser 10 was markedly reduced in *IKKα*$^{-/-}$ murine embryonic fibroblasts and IKKα directly phosphorylated Ser 10 *in vitro*. Thus, these findings suggest that IKKα may affect gene expression by regulating chromatin structure at promoters.

Histone phosphorylation at Ser 10 is often accompanied by increased acetylation at histone H3-Lys 14. Indeed, both reports show that in addition to decreased levels of phosphorylated H3-Ser 10 in *IKKα*$^{-/-}$ cells, levels of H3 acetylation are also reduced at NF-κB-responsive promoters. Furthermore, Yamomoto *et al.* find that IKKα interacts with the histone acetyl transferase, CBP, but that recruitment of CBP to the promoter is not dependent on IKKα. Collectively, these data suggest that phosphorylation of histone H3 at Ser 10 by IKKα is required for subsequent H3-Lys 14 acetylation by CBP and that both events are necessary for efficient activation of NF-κB-mediated transcription.

It is unclear whether phosphorylation of histone H3 at Ser 10 by IKKα will be important for transcription of all, or only a subset of, NF-κB targets. Whether IKKα will be required for NF-κB-independent gene transcription also remains an open question. Furthermore, Anest *et al.* find that IKKβ is also recruited to NF-κB promoters, but that IKKβ does not seem to phosphorylate histone H3 at Ser 10, hinting at a potentially novel function for IKKβ in the NF-κB pathway.

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chromosomal instabilities that are associated with increased risk of B-cell lymphomas[9]. Again, this points to the importance of maintaining an appropriate heterochromatic structure. Experiments have shown that flies with abnormal methylation induced by the mouse DNA methyltransferase 3a show inappropriate chromosome condensation that could be subsequently rescued by knocking out *Su(var)3-9* (ref. 11). So, it seems probable that the crosstalk between cytosine methylation and histone modification is important for the maintenance of chromosomal stability on the basis of increasing evidence that these two systems are mechanistically linked[10].

The paper by Sansom *et al.*[7] demonstrates for the first time that lack of the MBD2 protein, which is a methyl-CpG-binding protein and a potential transcriptional repressor, inhibits intestinal adenoma development in *min* mice. This is consistent with earlier work from the Jaenisch laboratory[12], in which decreased methylation resulted in less intestinal tumorigenesis in *min* mice. Thus, the failure to methylate DNA, or the failure to interpret the methylation signal by one of the methylated DNA-binding proteins, results in fewer epithelial-derived tumours. At first glance this result seems to be at odds with the two papers discussed above, which demonstrated that reduced methylation increases soft-tissue sarcoma and risk of developing lymphomas. So why should perturbing DNA methylation or reading of the methylation signal result in increased tumour formation in some cases and decreased tumour formation in others? In addition, why do the *min* mice not develop lymphomas when they have less methylation[12] or defects in methylation signal interpretation[7]? Perhaps the answer lies in the fact that the reduction of methylation level in the earlier study[12] was significantly less than that found with the new hypomorphic *Dnmt1* allele used in the studies by Eden *et al.* and Gaudet *et al.* Similarly, the failure of *MBD2* knockout mice to develop lymphomas may be a result of a lower penetrance because of redundancy with other proteins that might be more relevant to heterochromatic regions than to promoters. It is noteworthy that MBD2 has been implicated in the silencing of tumour suppressor genes in both human colorectal carcinoma and prostate cancer cells[13,14]. Another possibility is that reduction of methylation and deficiency of MBD2 in *min* mice affects genes downstream in the tumorigenesis pathway or