

configurations involving H^+ and H^- ions and neutral hydrogen, H^0 . Under all circumstances, they find that states involving either H^+ or H^- are more stable than those involving H^0 . Whether the H^+ or H^- charge state is more stable depends on the chemical potential of the reservoir of electrons in the material — called the Fermi energy — which determines how easily the conversion between an H^+ and an H^- ion can be made (by adding or removing two electrons). A high Fermi energy means that the system lowers its energy by accepting electrons to become H^- ; as the Fermi energy is lowered, a transition point is reached at which both states have the same energy; beyond this, the H^+ state becomes energetically preferred. Remarkably, Van de Walle and Neugebauer have found that the energy at the transition has almost the same value for a wide variety of materials.

In fact, this universal alignment is not immediately obvious, as there is an additional step to be taken to align the Fermi energy for the transition between H^+ and H^- states in different materials: a reference energy relating electronic states in different materials must be established⁵. In earlier work summarized in ref. 6, Van de Walle and colleagues showed that there is a natural line-up of the band energies at interfaces between materials that can be used to place all the materials on the same scale. Van de Walle and Neugebauer have now calculated the relative positions of the valence-band maximum (the highest energy of the outermost electrons in the atoms of the material) on this scale for a range of materials, including silicon, gallium arsenide and water. Then, when the transition-point energy is plotted on the same scale, the striking constancy of its value from one material to another is clearly seen (Fig. 2 on page 627).

How could such a simple result be found for such varying situations? Indeed, universal rules have been proposed before, for transition-metal impurity states in semiconductors^{7,8}. In some cases there is a natural explanation: the energies obey universal rules because the states are highly localized and hardly change from one host material to another. But for hydrogen the situation is quite different, as its ions form strong bonds and even disrupt molecules or crystalline solids.

A good example of the disruptive influence of hydrogen is seen in crystalline silicon. In its positive-charge state, the H^+ ion prefers to sit in the middle of a Si-Si bond, causing the bond to lengthen. In the negative state, however, the lowest-energy position for an H^- ion is at an interstitial site in an open space in the diamond-like lattice, as far as possible from the Si atoms. In the more typical example of a partially ionic semiconductor, hydrogen breaks an intrinsic bond in the material and forms a new strong bond with

either the anion (in its positive-charge state) or the cation (in its negative-charge state). These two configurations are very different and depend on the semiconductor material. It is even more striking to consider the insulator SiO_2 , in which hydrogen breaks a Si-O bond. Either SiH^+ or OH^- is formed, each complex bonded to other atoms in the network.

Nevertheless, Van de Walle and Neugebauer¹ propose a simple explanation for the universal alignment that they see. In an overall neutral state, the energies of the hydrogen bonds are almost the same, whether hydrogen is bound to the anion or to the cation in a material. The primary factor determining the transition-point energy is the 'dangling bond' that remains: the H^- charge state binds to the cation, leaving an unfulfilled, dangling bond on the neighbouring anion (and vice versa for H^+). The dangling bond accepts an electron, or, for H^+ bound to an anion, it gives up an electron. This fixes the transition energy at the 'mid-gap' position — effectively an average of the energies to add or subtract an electron — and leads to a natural alignment of transition energies that is not sensitive to the details of the band structure of the material.

This remarkable alignment uncovered by Van de Walle and Neugebauer might prove a

useful guide in understanding more about the physics at interfaces between different materials. There are many examples: the interface between semiconductors and aqueous solutions in photocells; the transfer of protons in fuel cells and hydrogen storage materials; and the interface between computational silicon elements and biological sensors. This work, then, bears not only on the interfaces of materials, but on the interfaces of scientific disciplines. ■

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Signal transduction

A regulator branches out

Alain Israël

The cellular signalling pathway that leads to activation of the NF- κ B protein has been studied for many years, and one might think that there's little left to learn. But it still has some surprises in store.

Signalling molecules usually contribute to more than one type of process in living organisms, but the NF- κ B family of proteins is particularly multi-talented. It is involved in immune and inflammatory responses, in cell survival and proliferation, and in cancer — and these are just a few of its functions. The NF- κ B proteins are part of a molecular cascade that starts with signals outside a cell and culminates, in the cell nucleus, with the binding of NF- κ B dimers to DNA and the activation of gene expression. It had been thought that some components of this pathway work solely to regulate the movement of NF- κ B to the nucleus. But on pages 655 and 659 of this issue, Yamamoto and colleagues¹ and Anest and co-workers² report a surprising new role for one such component³, an enzyme called IKK- α .

Cells must keep their NF- κ B proteins on a tight leash to prevent them from activating gene transcription wantonly. So, in the

absence of specific extracellular signals, the proteins are kept in the cytoplasm by inhibitors that come in two flavours: the I κ B molecules, which act only as NF- κ B inhibitors, and the p105 and p100 proteins, which serve both as inhibitors and as precursors of NF- κ B DNA-binding subunits (Fig. 1). When cells receive appropriate cues, the I κ B kinase (IKK) complex becomes active and labels the inhibitors with phosphate groups. This phosphorylation leads either to the complete degradation of the I κ B inhibitors, or to the partial degradation of the p100 or p105 proteins. Free NF- κ B dimers are thereby generated, which contain a DNA-binding subunit (p50 or p52) and a transcription-activating subunit, such as p65 or RelB. The dimers then move to the nucleus, where they switch on their target genes.

There are three known subunits in the IKK complex — two protein kinases (IKK- α and IKK- β) and a structural/regulatory subunit (NEMO/IKK- γ)³. Yamamoto *et al.*¹

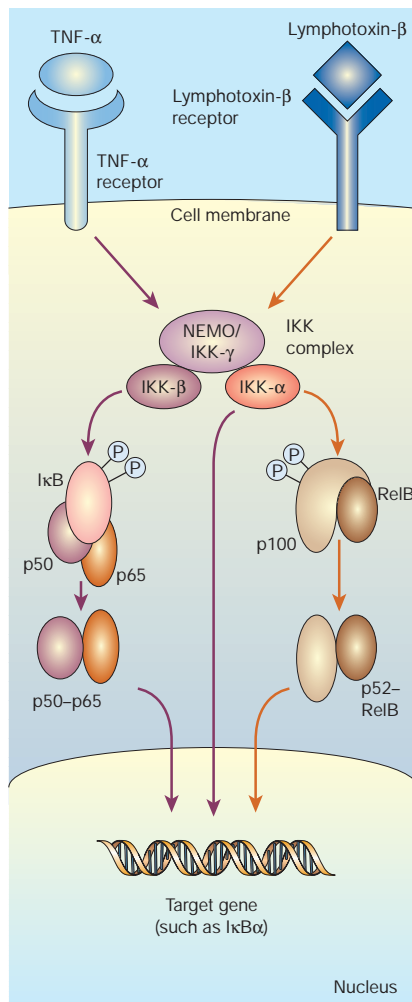


Figure 1 The classical NF- κ B cascade, the alternative — and a new twist. NF- κ B proteins are dimers, comprising a DNA-binding subunit (such as p50 or p52) and a transcription-activating subunit (such as p65 or RelB). In cells that have not received appropriate external cues, the proteins are kept inactive either by a member of the I κ B family in the classical pathway, or by an inactive precursor (in this case, p100) in the alternative pathway. In response to proteins such as tumour-necrosis factor- α (TNF- α) or lymphotoxin- β (top), the I κ B kinase (IKK) complex is activated. It phosphorylates I κ B and/or p100, leading to degradation of I κ B and the processing of p100 into a smaller, p52 form. The p50-p65 and p52-RelB dimers (two forms of NF- κ B) then move to the nucleus and activate gene expression. Yamamoto *et al.*¹ and Anest *et al.*² have found that IKK- α can itself move into the nucleus in response to TNF- α , where it associates with certain NF- κ B-responsive genes and phosphorylates a histone protein, one of the components of chromatin. How it enters the nucleus and associates with the appropriate genes remains unknown. (Note that the partners of IKK- α in the complex targeted by lymphotoxin- β have not been formally identified.)

and Anest *et al.*² have now identified a wholly unexpected new substrate for the IKK- α component. They show that, in response to extracellular cytokine proteins that influence the inflammatory response — such as tumour-necrosis factor- α (TNF- α) — IKK- α itself moves into the nucleus. Once there, it associates with the promoters (regulatory regions) of several NF- κ B-responsive genes, and phosphorylates a component of chromatin.

Chromatin is the compact form of DNA that is found, in association with certain proteins, in the nuclei of eukaryotic organisms; its highly organized structure is important in regulating gene expression. At the heart of chromatin are the histone proteins (H1, H2A, H2B, H3 and H4), which are dynamic components of the gene-transcription machinery. Histones that are located at gene-regulatory regions undergo several types of modification that affect the expression of the corresponding genes⁴. For instance, the phosphorylation of histone H3 at a particular serine amino acid (serine 10) is important in inducing the transcription of so-called immediate early genes (genes that are rapidly turned on and off in response to extracellular signals)⁵. Yamamoto *et al.* and Anest *et al.* now show that IKK- α phosphorylates histone H3 at serine 10.

How does this fit in with what we already know about the NF- κ B signalling cascade? Interestingly, it had already been suggested that the two kinases of the IKK complex have different roles. IKK- β is involved in the degradation of the I κ B inhibitors in response to pro-inflammatory cytokines such as TNF- α (left-hand pathway in Fig. 1). But IKK- α , besides being involved in an NF- κ B- and kinase-independent manner in regulating skin-cell differentiation⁶, is also thought to be part of an alternative pathway. This pathway, activated in response to specific stimuli such as lymphotoxin- β , a member of the TNF family, causes partial degradation of the p100 protein and the movement of NF- κ B dimers such as p52-RelB to the nucleus (right-hand pathway in Fig. 1)³. These results have led to the suggestion that IKK- α is not involved in TNF- α -induced activation of NF- κ B target genes. But other data have challenged this view⁷, including a report⁸ that it is required for TNF- α -induced expression of the gene that encodes the NF- κ B inhibitor I κ B α ; this gene is also a target of NF- κ B.

The new findings^{1,2} suggest that IKK- α is indeed required for TNF- α -induced gene expression — but in a non-classical way. Recruitment to the promoters of NF- κ B target genes has so far been formally demonstrated only for members of the NF- κ B family such as p65, the major transcription-activating subunit^{9,10}. It has also been reported for more general transcription regulators that associate with NF- κ B components¹⁰.

But this is the first time that an upstream component of the signalling cascade has been shown to behave in this way.

There are a few differences between the results obtained by the two groups. Yamamoto *et al.*¹ studied the promoter of the I κ B α gene in HeLa cells, and detected IKK- α , but not IKK- β . Anest *et al.*², by contrast, looked at mouse embryo fibroblast cells and found that IKK- β was recruited to the same promoter, with kinetics similar to that of IKK- α . (In fact, they also found that the third component of the complex, NEMO/IKK- γ , was recruited to that promoter, at later times.) But both groups show that IKK- β is not essential for the phosphorylation of histone H3.

These findings raise a number of questions. For instance, what protein (or proteins) conveys IKK- α to the gene promoters? The new data^{1,2} suggest that p65 might be responsible, although the authors did not detect a direct interaction between the two proteins. Also, does IKK- α regulate NF- κ B-independent promoters? Does IKK- α -mediated phosphorylation of histone H3 regulate other histone modifications that induce gene expression? What role does IKK- β (and NEMO/IKK- γ) play when it is recruited to chromatin? Do other NF- κ B-activating stimuli induce the recruitment of any of these proteins? In this context, Saccani *et al.*⁹ found that IKK- α is not recruited to the promoter of I κ B α in cells stimulated with lipopolysaccharide, part of the cell wall of many bacteria — implying that such recruitment is not a general mechanism. In another seemingly contradictory result, Cao *et al.*¹¹ showed that cells with an inactive version of IKK- α respond normally to TNF- α , interleukin-1 and lipopolysaccharide. But the regulation of specific NF- κ B-responsive genes such as I κ B α has not been studied in this genetic setting.

Whatever the answers to these questions, the discovery that IKK- α has this activity will open up a new avenue of research into the NF- κ B cascade, bringing the nuclear events associated with activation of this signalling pathway back into focus. ■

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