those controlled by c-Rel. This is because IL-4–induced Bcl-3 expression is not accompanied by an induction of Bcl-x_L[7].

Bcl-3 could modulate cRel- or NF-κB–dependent expression of prosurvival genes by one of several potential mechanisms that involve its association with NF-κB1 or NF-κB2 homodimers (**Fig. 2**). Because NF-κB1 and NF-κB2 both lack a transcription-transactivating domain, it is thought that homodimers of these proteins function as transcriptional repressors when bound to DNA. However, upon binding to NF-κB2 homodimers, Bcl-3 functions as a transcriptional coactivator and converts NF-κB2 to a positive regulator of gene expression. Although Bcl-3 also binds to NF-κB1 homodimers, it remains unclear whether Bcl-3 is able to act as a transcriptional coactivator of NF-κB1. Alternatively, Bcl-3 could promote expression of survival genes by removing NF-κB1 homodimers from DNA, thereby allowing this repressor complex to be replaced by an NF-κB complex that has transactivating function such as a c-Rel–NF-κB1 heterodimer (**Fig. 2**).

Bcl-3 also seems to participate in lymphomagenesis. The finding that Bcl-3 inhibits apoptosis of antigen-stimulated T cells indicates that it might promote cell transformation by activating prosurvival genes. Expression of a transgene encoding Bcl-3 under the control of the IgH enhancer caused splenomegaly and an accumulation of mature B cells in lymph nodes, bone marrow and the peritoneal cavity[12]. However, as these mice did not to develop lymphoid neoplasms, deregulated Bcl-3 expression is but one change in the multistep process of leukemogenesis. Eμ–Bcl-2 transgenic mice also develop lymphadenopathy and have a very low incidence of lymphoma, which is dramatically increased when combined with an oncogene (for example, c-*Myc*) that deregulates cell cycle control[13]. Thus, like Bcl-2 overexpression, Bcl-3 may promote neoplastic transformation by keeping lymphocytes alive that would normally be doomed, thereby increasing their risk of accumulating additional oncogenic mutations.

In conclusion, the work of Mitchell *et al.* shows that Bcl-3 is a critical regulator of apoptosis in T lymphocytes, probably through its ability to modulate the expression of prosurvival NF-κB target genes.

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Blueprints for life or death

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NK cell receptors either activate or inhibit the fratricidal tendencies of NK cells. Structural analysis of receptor-ligand complexes of both types of receptors reveals striking similarities in form, despite the diverse function.

What does it take to switch a natural killer (NK) cell to an activated or to an inhibited state? Like so many checkpoints in the cellular immune system, the "red alert" or "stand down" status is determined by protein-protein interactions between cell surface receptors. Because the decisions are literally life or death, a degree of bureaucracy is justifiable, so the NK cell is equipped with separate switches to send the signal to activate or inhibit. Two papers in this issue of *Nature Immunology* provide the structural blueprints for how to operate an on or an off switch[1,2]. Until the last couple of years, NK cells were uncharted territory as far as structural biology was concerned, but things have moved apace and the publication of the current two sets of results mark the coming of age of this branch of structural immunology.

Whereas cytotoxic T cells identify infected cells directly through recognition of antigenic peptides displayed at the target cell surface by classical major histocompatibility complex (MHC) class I molecules, NK cells monitor the target cell surface for malfunction of this display system, a role described by the so-called "missing self" hypothesis[3]. Human NK cell activity is regulated by specific recognition of both classical and nonclassical MHC class I molecules on the target cells (**Fig. 1a**). The NK cell receptors that mediate these cell-cell recognition events belong to two distinct structural superfamilies: one group forms part of the immunoglobulin superfamily (IgSF), whereas the other set of receptors are dimers of subunits bearing C-type lectin-like domains[4,5]. Just to keep us on our toes, both groups of NK cell receptors contain activating and inhibitory members (**Fig. 1b**). The articles by Fan *et al.*[1] and Li *et al.*[2] encapsulate the full range of flavors: classical or nonclassical MHC class I binding, Ig or C-type lectin-like, inhibitory or activating.

Killer cell Ig-like receptors (KIRs) recognize distinct serotypic groups of classical MHC class I molecules and can have two or three Ig-like domains in their extracellular region. They can be further classified according to whether they have a short or a long cytoplasmic tail. The long cytoplasmic tails contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) and transduce inhibitory signals. In contrast, the short cytoplasmic tails mediate association with DAP12, which contains immunoreceptor tyrosine-based activation motifs (ITAMs) and transduces activating signals. Fan *et al.* have tackled the structure of a two Ig-domain inhibitory receptor, KIR2DL1, in complex with HLA-Cw4[1].

This is actually the second crystal structure of a KIR-MHC class I complex but, as is so often the case, the ability to compare and contrast two complexes spotlights the key features in the recognition system. Last year Boyington *et al.* reported the structure of the inhibitory receptor KIR2DL2 in complex with HLA Cw3[6]. We can also draw on a panel of uncomplexed KIR structures[7–9]. Add these data to the analysis of the KIR2DL1–HLA-Cw4 complex and the key design features of this type of switch are apparent. First, the

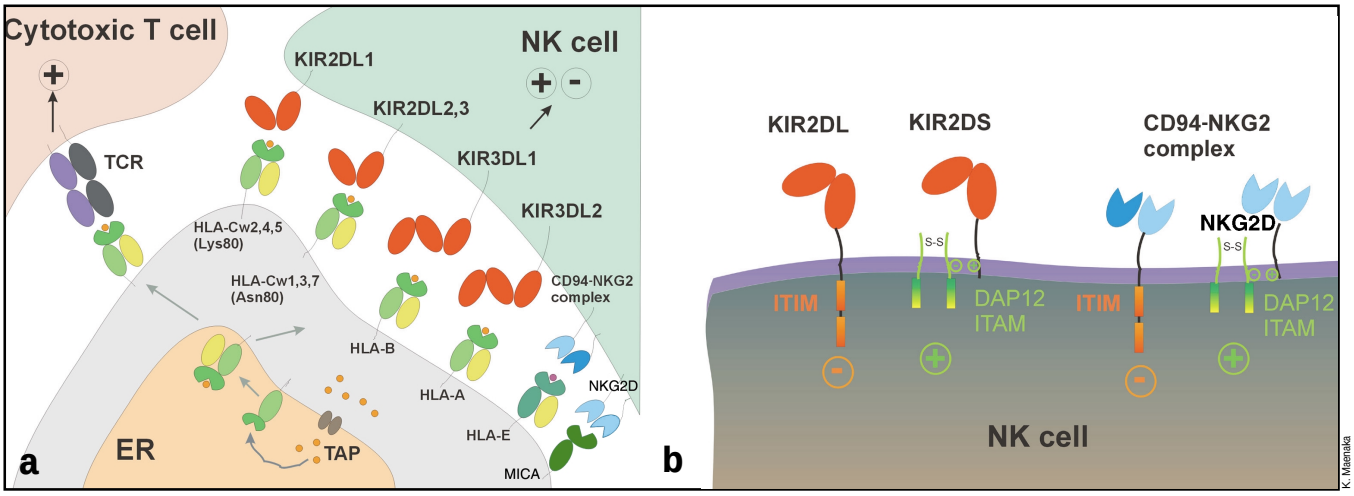

Figure 1. NK cell receptor interactions. (**a**) The interactions of NK and T cell receptors with classical and nonclassical MHC class I molecules. (**b**) Inhibitory and activating NK cell receptors.

footprint of the KIR on the MHC class I peptide–binding groove matches between the two complexes, as does the involvement of the KIR's "elbow" (a region spanning the two Ig-like domains). This conserved architecture locks the relative orientation of the two Ig-like domains of the KIR to give the appropriate fit. So one basic blueprint describes how to put a KIR-MHC class I complex together, at least for the two Ig-domain KIRs.

Unfortunately for aspiring switch builders, the common blueprint doesn't extend to the detail of the residue-to-residue interactions that form the recognition interface. This is rather surprising, given the high number of residues that are identical in the KIR2DL2–HLA-Cw3 and KIR2DL1–HLA-Cw4 interface. Indeed, the specificity of these particular KIR-MHC pairings has always been ascribed to residue 44 of the KIR and residue 80 of the HLA-C. The structures support this but the mechanism is subtle and differs between the two complexes. In KIR2DL1, specificity for HLA-Cw4 residue 80 is conferred by shape and charge matching in a distinct pocket, whereas the preference of KIR2DL2 for HLA-Cw3 residue is defined by a direct hydrogen bond.

The C-type lectin-like group of NK cell receptors are type II transmembrane receptors, usually expressed as homo- or heterodimers. Each subunit comprises a single C-type lectin-like domain connected by a neck region of variable length to a single membrane-spanning region and a short intracellular NH_2-terminal segment. In humans these molecules interact with nonclassical MHC class I molecules. One such interaction involves HLA-E and the heterodimeric receptor CD94-NKG2A. In contrast, NKG2D is a homodimer and has as its cognate ligand MICA. Li *et al.* have determined the structure of the NKG2D-MICA complex; this provides the first structural blueprint of an NK cell–activating switch[2]. The structure of MICA in isolation is available[10] as is that of murine NKG2D, published in the March issue of *Nature Immunology*[11]. MICA is rather an exotic example of an MHC class I molecule because it has dispensed with the usual requirement for β_2-microglobulin. In the isolated MICA structure this allowed the relative orientation of the $\alpha1\alpha2$ and $\alpha3$ domains to deviate dramatically from the MHC class I norm[10]. The equal exposure of both the classical peptide-binding surface and the under surface of the $\alpha1\alpha2$ domains, plus the virtual obliteration of the peptide-binding groove (by an apparent disordering of the central section of the $\alpha2$ helix), prompted speculation that receptor binding might not involve the usual areas. The current structure determination quashes such theories, at least for NKG2D binding. Yet again, the footprint of the NK cell receptor lies on the top of the "peptide-binding groove" in roughly the same place as that of the KIRs.

Two of the distinctive features of the isolated MICA structure have fallen back into line in the complexed structure. The relative orientations of the $\alpha1\alpha2$ and $\alpha3$ domains now lie closer to the standard distribution seen in MHC class I structures. The familiar helical element of $\alpha2$ is also restored so that MICA does exhibit a very limited "peptide-binding groove", although this is not occupied by anything other than water in the complex. The two NKG2D subunits each predominately contact either the $\alpha1$ or the $\alpha2$ domain of MICA. Thus, although essentially the same surface from each NKG2D subunit is used, the contacts it makes are very different. Again the details of the docking would not have been predictable.

A comparison of the MHC class I–binding modes for these two structurally very different NK cell receptor families reveals one common theme. Both bind on top of the MHC class I peptide-binding groove. By analogy with the binding of the T cell receptor, this may set an intercellular spacing that determines the clustering of auxiliary molecules in this flavor of immunological synapse. Again, like the T cell receptor–MHC complex structures, there is no evidence from the NK cell receptor complexes for anything other than a 1:1 binding mode. Similarly, the blueprints for the design of an activating or an inhibitory switch look basically similar for the extracellular region. As for many switches, the differences are in the internal wiring.

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