IN THE NEWS

Mixed messages

There has been intense media interest in the AIDS epidemic recently, in light of the XIV International AIDS Conference in Barcelona (7–12 July). However, it is not clear whether the news is good or bad.

The authors of a United Nations report (3 July) and a study published in the *Lancet* (4 July) suggest that 40 million people are infected with HIV and that 70 million will die from AIDS over the next 20 years. Peter Piot, Executive Director of UNAIDS warns that, "we're only at the beginning of this epidemic" (*UN News Service*), and Stephen Lewis, special envoy of the Secretary General for HIV/AIDS in Africa, presented the worrying statistic that in sub-Saharan Africa, 67% of HIV$^+$ 15–24-year olds are female (UN Press Briefing).

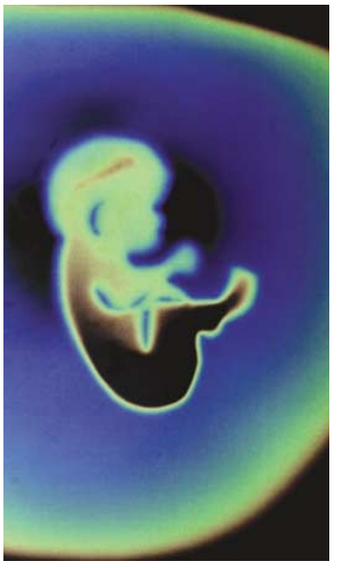
On a more optimistic note, the *Lancet* report proposes that 28 million new infections could be avoided by education programmes. The proposed introduction of an HIV$^+$ character to the South-African version of *Sesame Street* is one such initiative (*MediaGuardian*). The prevention of AIDS-related deaths will also require that anti-HIV drugs are more widely available. To this end, a court ruling in South Africa has ordered the government to stop denying nevirapine — which blocks mother-to-child transmission of HIV — to pregnant women (*Reuters*). Similarly, the world's largest HIV vaccine trial is awaiting final approval in Thailand. It is hoped that any success of the vaccine will not be confused with the recent controversy over V-1 Immunitor, a Thai food supplement made from the blood of HIV-infected individuals (*New Scientist*).

So, it seems that although the statistics are alarming and there is no room for complacency, preventive measures are having some impact and new developments look promising.

Kirsty Minton

REPRODUCTIVE IMMUNOLOGY

Placental presentation



Immunologists have never found it easy to explain why the semi-allogeneic fetus is not attacked in placental mammals by the maternal immune system. How is a response against paternal antigens avoided? Most researchers agree that local effects at the maternal–placental interface are important. Hobbs *et al.* suggest in *Cell* that the vertebrate-specific amino-terminal domain of the TATA-box-binding protein (TBP) regulates a placenta-specific β_2-microglobulin (β_2m)-dependent process that is used to evade a maternal rejection response.

The authors generated mice that have a modified *Tbp* allele ($Tbp^{\Delta N}$) that lacks the amino-terminal domain. More than 90% of $Tbp^{\Delta N/\Delta N}$ fetuses died in mid-gestation. Histopathology indicated that fetal death was the result of a placental insufficiency. Moreover, the physiology of mutant fetuses was normal, and the rare homozygous adults were healthy. This indicates that the mutation primarily affects a process that is required for placental, but not fetal, development.

Next, the authors showed that the defect could be complemented by an immunodeficient maternal environment. When the $Tbp^{\Delta N}$ mutation was bred into recombination-activating gene 1 ($Rag1$)$^{-/-}$ or severe combined immunodeficient (SCID) mice, most of the $Tbp^{\Delta N/\Delta N}$ fetuses survived, which indicates that the maternal immune response has an important role. This was confirmed by the observation that the defect can also be complemented by knockout of β_2m. As β_2m is required for the assembly and surface expression of MHC class I molecules, the defect

T-CELL SIGNALLING

Conformational change

We all know how T-cell receptors (TCRs) initiate antigen-induced signal transduction — right? Ligand-induced receptor clustering results in cross-phosphorylation of cytoplasmic immunoreceptor tyrosine-based activation (ITAM) motifs of associated CD3 chains, which recruit signalling molecules. But, what about the possibility of a ligand-induced conformational change in the TCR? G-protein-coupled receptors do it, and now in *Cell*, Gil *et al.* report that the TCR can do it too. They show that ligand engagement of TCR–CD3 induces a conformational change in CD3ε that recruits the adaptor protein NCK.

Using a yeast two-hybrid system, Gil and colleagues showed that non-ITAM regions of CD3ε interact with NCK after TCR–CD3 triggering. Precipitation experiments confirmed that CD3ε is the only CD3 subunit that interacts with NCK. NCK co-precipitates with TCR–CD3 from anti-CD3-stimulated, but not unstimulated, Jurkat T cells. This result was confirmed *in vivo*. It seems that the engagement of TCR–CD3 modifies this complex to recruit NCK to CD3ε. A cell-free assay was used to discount contributions from other cellular factors, and a monovalent Fab of anti-CD3 antibody was used to rule out receptor crosslinking, which indicates that a conformational change is responsible.

The authors went on to show that the amino-terminal SRC-homology 3 domain (SH3.1) of NCK binds to the proline-rich sequence (PRS) of CD3ε. Using deletion mutants of the CD3ε cytoplasmic tail, they showed that deletion of the PRS abolishes NCK binding. The expression of isolated domains of NCK was used to determine that only SH3.1 can bind CD3ε and that this binding is inducible.

How is NCK binding associated with TCR tyrosine phosphorylation? Surprisingly, the conformational change that allows NCK binding occurs independently of phosphorylation. Furthermore, after engagement of TCR–CD3, CD3ε can associate with NCK before the

probably involves inappropriate antigen presentation.

The authors suggest that the TBP amino-terminus downregulates antigen presentation by MHC class I. They speculate that the amino-terminus might have co-evolved with the MHC system to regulate its expression. In mice, the placenta is simply the first vital location of this function. It will be interesting to determine whether mutant adults have defects in other MHC class-I-dependent responses, such as susceptibility to intracellular pathogens.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Hobbs, N. K. *et al*. Removing the vertebrate-specific TBP N-terminus disrupts placental β_2m-dependent interactions with the maternal immune system. *Cell* **110**, 43–54 (2002)

FURTHER READING Erlebacher, A. Why isn't the fetus rejected? *Curr. Opin. Immunol*. **13**, 590–593 (2001)

tyrosine phosphorylation of CD3ζ and other substrates is detected. The common belief that ITAM phosphorylation is the earliest event in TCR signalling needs rethinking. The early association of NCK with TCR–CD3 is physiologically relevant, because inhibition of this interaction decreases the number of T-cell–APC conjugates and inhibits maturation of the immunological synapse.

On the basis of these results, Gil *et al.* propose that ligand engagement of TCR–CD3 exposes a PRS in CD3ε that recruits NCK. This is consistent with the observation that the entire cytoplasmic tails of CD3 subunits have been conserved throughout evolution, and not just the ITAMs. They suggest that full T-cell activation requires a combination of ligand-induced crosslinking, leading to phosphorylation, and ligand-induced conformational change, allowing NCK binding. This is a radical change to our assumptions about TCR signalling.

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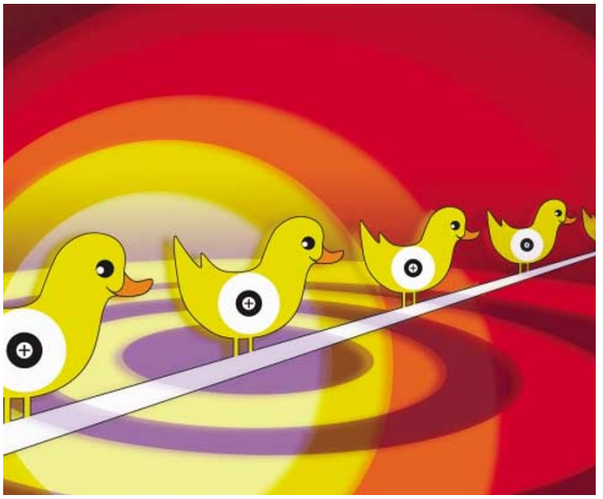
ORIGINAL RESEARCH PAPER Gil, D. *et al*. Recruitment of Nck by CD3ε reveals a ligand-induced conformational change essential for T-cell receptor signalling and synapse formation. *Cell* **109**, 901–912 (2002)



HIV

A new therapeutic target?

Viruses have evolved various mechanisms to avoid recognition and destruction by the host immune system. By studying these mechanisms, we have learned much about how the immune system functions, and in the process, new therapeutic targets for drug development have been identified. HIV-1 has proven to be a difficult nut to crack in this regard, but a new study in *Nature* describes the identification of a human protein, CEM15, the function of which is suppressed by viral Vif, leading to the production of infectious virions. This interaction might be a new therapeutic target for drug development.

The Vif-deficient virions that are produced by primary T cells are non-infectious, such that T cells, and T-cell lines such as CEM, are referred to as non-permissive (NP). By contrast, other cell types, such as CEM-SS (a subclone of the CEM cell line), are termed permissive (P), because they can produce infectious Vif-deficient virions. Cell-fusion experiments have shown that the NP phenotype is dominant over the P phenotype. These data imply that a factor in the NP cells is able to influence the production of infectious Vif-deficient virions. Malim and colleagues set out to identify this factor by using a PCR-based complementary DNA subtraction strategy to compare CEM (NP) and CEM-SS (P) cells. Subtracted cDNAs were used as probes in northern-blot experiments using RNA from both NP and P cells. The authors identified a cDNA that corresponds to a gene that they have named *CEM15*, and the transcript was identified in all of the NP cells that were tested. Ectopic expression of CEM15 in a P cell line had no effect on the quantity of Vif-deficient HIV-1 particles produced by these cells, but instead of being infectious, the virus particles were non-infectious.

What is CEM15? Analysis of the CEM15 protein sequence showed that it has marked homology to APOBEC1 (a cytidine deaminase that specifically edits APOB mesenger RNA).

So, CEM15 seems to be responsible for the inability of NP cells to produce infectious Vif-deficient virions, which indicates that CEM15 is the cellular target of Vif. Because of the homology to APOBEC1, the authors speculate that CEM15 might affect Vif-deficient virions by means of interactions with viral RNA. Importantly, the CEM15–Vif interaction might prove to be an important therapeutic target for the development of new drugs to alter virus infectivity. But, the function of CEM15, and how Vif suppresses this function, remain to be determined.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Sheey, A. M., Gaddis, N. C., Choi, J. D. & Malim, M. H. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* July 14 2002 (DOI 10.1038/nature00939)

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ANTIGEN PRESENTATION

Mapping the maze

CD1 molecules are MHC class-I-like glycoproteins that bind lipid-based antigens, but the binding mechanisms that are used by CD1 molecules to accommodate lipid antigens that seem to be too large for the binding groove have remained unclear. Gadola *et al.*, reporting in *Nature Immunology*, describe the crystal structures of human CD1B complexed to glycolipid antigens. These new structures reveal that the binding groove is more complex than was previously supposed, which helps to explain the ability of CD1 molecules to bind long lipid chains.

Gadola *et al.* developed an *in vitro* system for refolding denatured CD1B molecules in the presence of defined glycolipids. The complexes produced were cystallized and the structures analysed in detail. Compared with MHC class I, the binding groove of CD1B is a complex maze of interconnecting pockets and tunnels — three distinct pockets, named A′, C′ and F′, were defined, as well as a connecting tunnel, termed T′. CD1B can bind long lipid chains by accommodating alkyl chains of up to 70 carbons in length in a superchannel formed by the connection of A′, T′ and F′. The C′ pocket can accommodate shorter alkyl chains of ~16 carbons. An exit portal for the C′ pocket, located below the α2 helix, indicates that longer chains might also be accommodated. These structures show how CD1B can adapt to bind lipid ligands of various sizes.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Gadola, S. D. *et al.* Structure of human CD1b with bound ligands at 2.3Å, a maze for alkyl chains. *Nature Immunol.* July 15 2002 (DOI 10.1038/ni821)