IN THE NEWS

Computers fight smallpox

Grid-computing — a form of distributed computing that enables the extra unused power of computers around the globe to be harnessed towards a common goal — which is already being used to hunt for extra-terrestrials and a cure for cancer, is now being used in the fight against smallpox.

Although smallpox was eradicated in 1980, concerns over the potential use of the smallpox virus as a bioterrorist weapon have led to new approaches to find a cure for this fatal disease. The Smallpox Research Grid Project, launched in February, is a collaborative effort between scientists at institutes including Oxford University and the Memorial Sloan-Kettering Cancer Center, and companies that provide computer expertise and software, including IBM and United Devices Inc.

The idea is that the idle power of personal computers around the world can be used to screen chemical compounds for their ability to interact with the smallpox virus and stop it from replicating. The hope is that 35 million molecules can be tested and whittled down to the most promising candidates using molecular modelling, and these molecules would then be tested in the lab. As Tom Hawk, the general manager of grid computing told *CBS News*, "Wet-lab experiments still have to take place. I see this as a homing and narrowing process".

If you are interested in contributing the unused power of your computer to this project, just go to http://www.grid.org, register and download a screen-saver program from this site. Once installed, this program will be active whenever your computer is on but not in use. In this way, even when you are no longer working, your computer, as part of the computing grid, will be.

Jenny Buckland

REGULATORY LYMPHOCYTES

Tolerance or immunity — DCs decide

Researchers at the University of Queensland have shown that dendritic cells (DCs) that lack the NF-κB-family protein RELB (v-rel reticuloendotheliosis viral oncogene homologue B) and CD40 (tumour-necrosis factor receptor superfamily member 5, TNFRSF5) can suppress previously primed immune responses *in vivo*. According to their report, now published in *Immunity*, the DCs achieve this by inducing a population of $CD4^+$ regulatory T (T_{Reg}) cells.

The molecular mechanisms that control the functions of DCs in tolerance and immunity are not well understood, and advances in this field are of particular interest owing to the possible therapeutic applications of such findings for the immunotherapy of autoimmune diseases. Previous work has indicated that the ability of DCs to induce tolerance or immunity in response to an antigen is linked to the maturation state of the cell, with immature DCs being able to induce T-cell anergy *in vitro*. RELB activity is known to be required for DC maturation. So here, Martin *et al.* investigated whether abrogating the function of RELB in DCs would be sufficient to enable these cells to suppress immune responses *in vivo*.

RelB$^{-/-}$ bone-marrow-derived DCs, which lack cell-surface expression of CD40, were pulsed with antigen and transferred into naive wild-type mice. The *RelB*$^{-/-}$ DCs failed to prime an antigen-specific T-cell proliferative response in recipient mice, and they also suppressed a previously primed immune response when administered seven days after immunization. Similar results were obtained using DCs generated in the presence of BAY (a compound that blocks the nuclear translocation and activity of NF-κB-family proteins), which also lack CD40 expression, and with DCs from *Cd40*$^{-/-}$ mice.

So, DCs in which RelB function is blocked lack expression of CD40 and can suppress primed immune responses *in vivo* — but, do they do this by deleting effector T cells or by

INNATE IMMUNITY

Double protection

CCL28, a chemokine that is found in saliva and breast milk, has a dual role in mucosal protection according to a recent functional study published in *The Journal of Immunology*. Not only does this chemokine attract antibody-secreting cells, but it also has the unexpected capacity to kill microorganisms directly.

Several previous reports have indicated that chemokines and antimicrobial peptides — key weapons in the arsenal of the innate immune system — might be functionally related. Similar to chemokines, certain mammalian antibacterial peptides can attract leukocytes by acting on seven-transmembrane receptors. And, some chemokines have been reported to have antimicrobial activity at high doses *in vitro*. But, a physiological role for these activities has not been reported.

CCL28, which was discovered only recently, is expressed most abundantly at mucosal sites, and it is known to signal through the receptors CCR10 and CCR3. Kunio Hieshima and co-workers found that the epithelial cells of the salivary glands are the main source of CCL28, and they identified a population of CCR10- and CCR3-expressing cells in single-cell suspensions of mouse salivary glands. These cells, which have the morphology and cell-surface phenotype of plasma cells, respond vigorously to CCL28 in migration assays. So, one function of CCL28 is probably the recruitment of plasma cells to the salivary glands.

CCL28 was found to be present in human saliva and milk at high concentrations. The authors had also noticed that the carboxy-terminal segment of CCL28 has a high histidine content, and closer examination showed that it is similar in sequence to the antimicrobial peptide histatin-5. Together, this evidence provided the initial clue that CCL28 might have a second, more direct role in mucosal defences.

The authors tested the antimicrobial activity of CCL28 and found that it could kill various microbial pathogens — including the fungus *Candida albicans* and the bacteria *Streptococcus mutans, Klebsiella pneumoniae* and *Staphylococcus aureus* — apparently by disrupting the plasma membrane.

Although the concentrations of CCL28 in milk and saliva are lower than the doses that have been found to be effective in killing assays, the authors point out that the chemokine is probably concentrated on epithelial-cell surfaces by binding heparan sulphate. Of note, the closest relative of CCL28, CCL27, does not share its antimicrobial activity.

So, did chemokines emerge initially as antimicrobial peptides before evolving their chemotactic

inducing T_{Reg} cells in recipients? The authors investigated this by collecting $CD4^+$ T cells from the spleens of mice that had been injected with antigen-pulsed BAY-treated DCs and transferring these T cells into primed recipient mice. Antigen-specific T-cell responses were suppressed in mice that received the $CD4^+$ T cells. This shows that T_{Reg} cells were induced in the mice that received the treated DCs and that these T cells could transfer tolerance to recipient primed mice (a concept known as infectious tolerance). Further experiments showed that these T_{Reg} cells produced interleukin-10 (IL-10) in an antigen-specific manner, and that production of this cytokine was responsible for the observed suppression.

These results show that RELB, by controlling DC maturation and expression of CD40, could be important for determining the response of T cells to DCs in lymphoid organs, resulting in either tolerance or immunity.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Martin, E. *et al.* Antigen-specific suppression of a primed immune response by dendritic cells mediated by regulatory T cells secreting interleukin-10. *Immunity* **18**, 155–167 (2003)

FURTHER READING Thompson, A. G. & Thomas, R. Induction of immune tolerance by dendritic cells: implications for preventative and therapeutic immunotherapy of autoimmune disease. *Immunol. Cell Biol.* **80**, 509–519 (2002)

WEB SITE

Ranjeny Thomas's lab: http://130.102.98.253/cicr/Research_groups/Immunobiology/DCBGroup/dendritic_cell_biology_group.htm

functions, or is the microbicidal activity of CCL28 a later adaptation, arising by convergent evolution? The evolutionary origin of the dual functionality of CCL28 remains an intriguing unresolved issue.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPER Hieshima, K. CCL28 has dual roles in mucosal immunity as a chemokine with broad-spectrum antimicrobial activity. *J. Immunol.* **170**, 1452–1461 (2003)

FURTHER READING Nakayaka, T. *et al.* Profile of chemokine receptor expression on human plasma cells accounts for their efficient recruitment to target tissues. *J. Immunol.* **170**, 1136–1140 (2003)

IN BRIEF

IMMUNE REGULATION

Malaria blood-stage suppression of liver-stage immunity by dendritic cells.

Ocaña-Morgner, C. *et al. J. Exp. Med.* **197**, 143–151 (2003)

Malaria infection is initiated when an infected mosquito injects sporozoites into a mammalian host. The sporozoites invade the liver, where development and replication lead to the production of merozoites, which can infect erythrocytes — the blood stage of the infection. Using a rodent malaria model, this study shows that the blood stage of the infection actively suppresses immune responses targeted at the liver stage of the disease. Irradiated sporozoites injected into mice induce a $CD8^+$ T-cell response, whereas non-irradiated sporozites do not. When equal numbers of irradiated and non-irradiated sporozoites are injected, a $CD8^+$ T-cell response does not develop, which indicates that the non-irradiated sporozoites are mediating a suppressive effect. This suppressive effect — inhibition of IFN-γ secretion by T cells — was found to be mediated by dendritic cells (DCs). Blood-stage parasites inhibit DC maturation, enhance IL-10 production and decrease IL-12 production, but the suppressive factor released by DCs has not been identified yet.

REGULATORY LYMPHOCYTES

Activation of human $CD4^+$ cells with CD3 and CD46 induces a T-regulatory cell 1 phenotype.

Kemper, C. *et al. Nature* **421**, 388–392 (2003)

T regulatory 1 (T_R1) cells are a type of regulatory $CD4^+$ T cell that produce IL-10 and can suppress the function of T helper cells, but the differentiation pathway of these cells remains unclear. Now, Claudia Kemper and colleagues show that complement regulatory protein — a transmembrane protein that inhibits complement activation on host cells — has a role in stimulating the development of T_R1 cells. Co-engagement of CD3 and CD46 in the presence of IL-2 induces a T_R1 phenotype of human $CD4^+$ T cells. Supernatant from these T_R1-cell cultures suppresses the proliferation of bystander cells, a process that is inhibited by neutralizing IL-10-specific antibody.

EVOLUTION

Urochordates and the origin of natural killer cells: identification of a CD94/NKR-P1-related receptor in blood cells of *Botryllus*.

Khalturin, K. *et al. Proc. Natl Acad. Sci. USA* **100**, 622–627 (2003)

Botryllus schlosseri is a colony-forming invertebrate chordate that can undergo transplantation reactions. When two colonies meet, they either fuse or develop a cytotoxic lesion at the point of contact. The authors screened for genes with levels of expression that were either up or downregulated after allorecognition between colonies. Of the 1,200 transcripts analysed, 50 were differentially regulated. One of these (*BsCD94-1*) was found to be a protein containing a C-type lectin domain, with homology to the natural killer (NK)-cell receptor CD94. CD94.1-expressing blood cells in *Botryllus* resemble granulocytes and might be ancestral NK cells.