IN THE NEWS

Bird flu scare

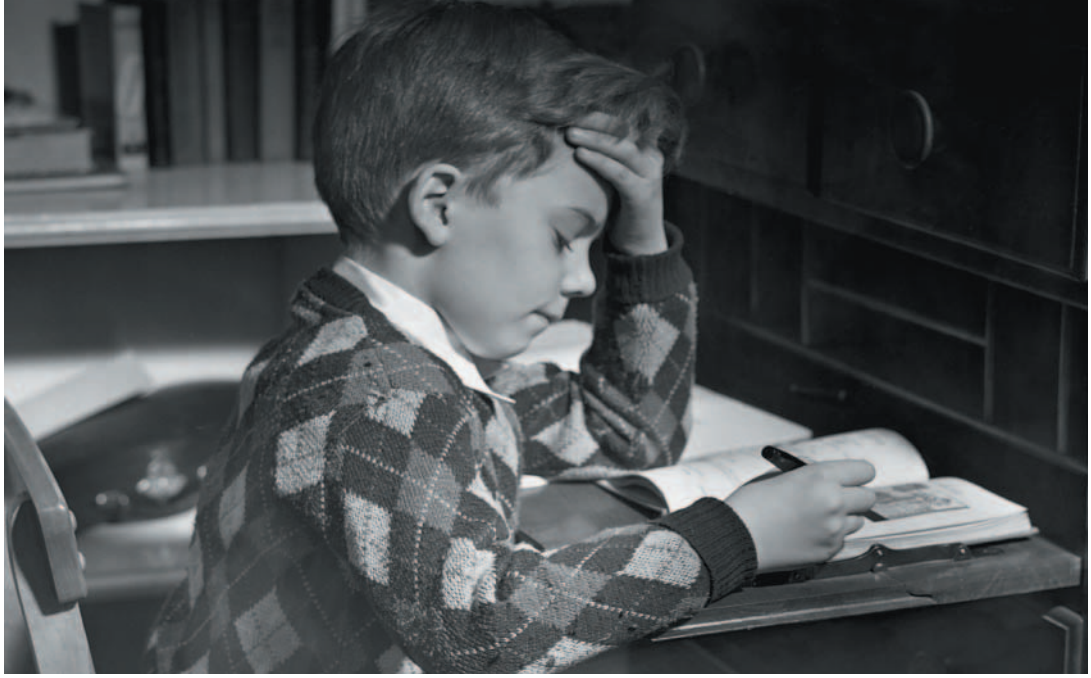
The World Health Organization (WHO) issued a warning in late November that the bird flu virus that has recently plagued Asian countries might unleash a flu pandemic that could kill millions of people. WHO is concerned that "much of the world is unprepared for a pandemic" and will be issuing guidelines for "enhancing preparedness" to reduce its potential impact (*WHO*). "China is taking the threat of a pandemic very seriously", said Julie Hall, a WHO advisor in Beijing, and Chinese health officials are making plans to deal with mass infections by a new virus form, including mass production of vaccines and antiviral drugs (*Times Online*).

Last year, bird flu killed 32 people in Thailand and Vietnam, and millions of chickens across Asia. Experts fear that a new and highly virulent form of human flu could emerge following a genetic change in bird flu, allowing the virus to spread as easily among humans as it does among birds (*The Guardian*).

On a positive note, researchers in China have developed a new test that can detect bird flu in humans within hours, compared with up to a week for previous tests, thereby providing early diagnosis that will be crucial to controlling bird-flu outbreaks (*Reuters*).

Fresh insights about bird flu might also be provided by the unveiling of the chicken-genome sequence, which was recently published in *Nature* (9 Dec 2004). Ewan Birney, from the European Bioinformatics Institute in Cambridge, UK, says that "we don't know which genes are really involved in helping prevent transmission of the flu virus", and with the chicken genome sequenced, we now have "a better platform to do this sort of research in the future" (*BBC News*).

Lucy Bird



REGULATORY T CELLS

What determines what you become when you grow up?

Results from previous studies have led to the hypothesis that $CD4^+CD25^+$ regulatory T (T_{Reg}) cells differentiate in the thymus as a consequence of high-affinity peptide–MHC–T-cell receptor (TCR) interactions. However, a report published in *The Journal of Experimental Medicine* provides contrasting data, and the authors suggest that encounter with a high-affinity ligand during thymocyte development might only seem to induce T_{Reg}-cell differentiation.

It has been shown that the proportion of T_{Reg} cells in mice that express a transgenic TCR and its cognate peptide ligand is greater than in mice that express the transgenic TCR alone. This has led to the hypothesis that agonist peptides induce T cells that express the cognate TCR to differentiate into T_{Reg} cells. So, to investigate how the dose of agonist peptide affects the efficiency of T_{Reg}-cell differentiation, van Santen *et al.* generated mice that express a TCR (known as the AND-TCR) specific for residues 88–103 of moth cytochrome C (MCC) and express I–E^k-bound MCC peptide 96–101 ($MCC_{96–101}$). Expression of the MHC-class-II-bound peptide was driven by a promoter that is inhibited in a dose-dependent manner in the presence of tetracycline, and expression was restricted to the epithelial cells of the thymus. Mice were given graded doses of tetracycline in their drinking water for their lifespan, and increased levels of thymic expression of I–E^k-bound $MCC_{96–101}$ correlated with a decrease in the percentage of $CD4^+CD8^-$ thymocytes and, within this population, a decrease in the percentage of AND-TCR^+ cells. However, within the AND-TCR^+CD4^+ thymocyte subset, the proportion of cells expressing CD25 increased. These cells were phenotypically T_{Reg} cells: for example, they expressed high levels of mRNA encoding the transcription factor FOXP3, and they inhibited the proliferation of $CD4^+CD25^-$ T cells.

These findings seemed consistent with the idea that agonist peptides induce T cells expressing the cognate TCR to differentiate into T_{Reg} cells in a dose-dependent manner. However, when the numbers of AND-$TCR^+CD4^+CD25^+$ and AND-$TCR^+CD4^+CD25^-$ thymocytes were compared with the level of I–E^k-bound $MCC_{96–101}$, it was found that the number of AND-$TCR^+CD4^+CD25^+$ thymocytes increased only slightly as I–E^k-bound $MCC_{96–101}$ expression increased — certainly not to the level that was expected from the increase in the percentage of these cells. This indicates that the observed increase in the percentage of AND-$TCR^+CD4^+CD25^+$ thymocytes was a result of preferential deletion of AND-$TCR^+CD4^+CD25^-$ thymocytes and not a result of increased numbers of AND-TCR^+ thymocytes being directed to become T_{Reg} cells.

This study provides evidence that is in contrast to the current hypothesis that high-affinity agonist peptides promote thymocytes that express the cognate TCR to differentiate into T_{Reg} cells. Instead, the authors suggest that, in this system, other signals promote T_{Reg}-cell differentiation and that studies elucidating the signals that induce FOXP3 expression will probably determine which signals induce T_{Reg}-cell differentiation. It will be important to establish whether these observations hold true for other systems.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER van Santen, H. M., Benoist, C. & Mathis, D. Number of T_{Reg} cells that differentiate does not increase upon encounter of agonist ligand on thymic epithelial cells. *J. Exp. Med.* **200**, 1221–1230 (2004).