IN THE NEWS

Flu vaccine shortages

"The flu is not a severe cold: it can be a serious illness, and three to four thousand deaths [in the United Kingdom] are linked to flu every year", according to Chief Medical Officer Sir Liam Donaldson (*Department of Health*). "If you suffer from a chronic illness like asthma or diabetes, or are 65 years or older, you are particularly at risk from flu", he states. A similar warning is given in the United States, although vaccination is recommended for a wider group of people, including pregnant women and individuals of 50 years or older (*New York State Office for Aging*).

However, the Medicines and Healthcare Products Regulatory Agency (UK) has recently suspended the manufacturing licence of the influenza-vaccine maker Chiron Corporation because of concerns about the way the vaccine is manufactured. This decision is likely to have a particularly severe impact in the United States, where Chiron is responsible for nearly 50% of the influenza vaccines distributed, and Dr Anthony Fauci (Director of the National Institute of Allergy and Infectious Disease) has said that there will be "significant shortages" (*The New York Times*). In the United Kingdom, Chiron supplies a smaller proportion of the influenza vaccines, and a Department of Health spokesperson said, "We are confident that we have sufficient vaccines for this winter's campaign" (*BBC News*).

As a result of the vaccine shortage, the Centers for Disease Control and Prevention (USA) is planning to teach people how to protect themselves through hygiene and 'cough etiquette'. It has said that you should avoid touching your eyes, nose or mouth and that if you do get flu, stay at home so that you don't infect others (*The New York Times*).

Karen Honey

MUCOSAL IMMUNOLOGY

IL-15 triggers destruction

The destruction of the intestinal epithelium by interleukin-15 (IL-15)-activated intraepithelial cytotoxic T lymphocytes (CTLs) is one of the main pathological events of coeliac disease — a T-cell-mediated disease of the small intestine induced by wheat gliadin. Two papers that were recently published in *Immunity* now provide insight into the mechanisms of this cytotoxicity: the triggering of NKG2D (natural-killer (NK) group 2, member D) on the cell-surface of intraepithelial CTLs by its ligand MICA (MHC-class-I-polypeptide-related sequence A) or MICB present on the cell-surface of intestinal epithelial cells (IECs) initiates signalling pathways that lead to the killing of IECs, and this is coordinated by IL-15.

CTLs have been shown to express NK-cell receptors such as NKG2D, and signals transduced by these receptors can modulate the cytotoxicity of CTLs. So, Meresse *et al.* set out to investigate whether NKG2D expression by intraepithelial CTLs was important in coeliac disease. Intraepithelial CTLs isolated from biopsies of patients with active coeliac disease expressed markedly higher levels of NKG2D than the same cells from healthy individuals. In contrast to peripheral-blood-derived CTL clones (which cannot mediate target-cell lysis after stimulation through NKG2D alone), ligation of NKG2D alone was sufficient to induce lysis of target cells by intraepithelial CTLs from patients with active coeliac disease. Further analysis indicated that intraepithelial CTLs from healthy individuals could acquire this phenotype — high levels of NKG2D expression and the ability to lyse target cells after ligation of NKG2D alone — when cultured with IL-15. However, both exposure to IL-15 and recent stimulation through the T-cell receptor was required to enable peripheral-blood $CD8^+$ memory T cells to elicit NKG2D-mediated lysis of target cells. These observations indicate that the high levels of IL-15 and the constant exposure to antigen in the intestine of patients with active coeliac disease are probably responsible for the NKG2D-mediated cytolytic phenotype of the intraepithelial CTLs isolated from these individuals.

IL-15 was shown to increase not only the expression of NKG2D but also the expression of signal-transduction adaptor molecule DAP10, further priming the cells to be responsive to NKG2D signalling. In the intestine of patients with active coeliac disease such signals could be provided by the NKG2D ligands MICA and/or MICB, the expression of which were found to be upregulated on the cell-surface of IECs from such individuals.

Similarly, in the second study, Hüe *et al.* observed that, compared with cells from healthy individuals, the level of expression of MICA was markedly increased on the cell-surface of IECs from patients with active coeliac disease. Furthermore, the level of MICA expression correlated with the severity of disease. In cultures of biopsies taken from coeliac patients on gluten-free

diets (who are therefore free of active disease), wheat gliadin was shown to induce the expression of MICA by IECs. The gliadin peptide p31–49 (known to cause damage of the small intestine by itself) could also induce MICA expression by IECs, and this was abolished in the presence of IL-15-neutralizing antibody.

In contrast to the report of Meresse *et al.*, Hüe *et al.* observed that intraepithelial CTLs from both healthy individuals and those with active coeliac disease expressed similar levels of NKG2D. Furthermore, when stimulated through NKG2D alone, intraepithelial CTL cell lines derived from patients with active coeliac disease could induce lysis of target cells only in certain situations — for example, if cells were recently exposed to high concentrations of IL-15. However, in all cases, NKG2D ligation markedly amplified CD3-mediated lysis of target cells, indicating a role for NKG2D signalling in the regulation of intraepithelial CTL cytotoxicity.

The results obtained from these studies indicate that NKG2D–MICA/MICB interactions are crucial for mediating destruction of IECs in active coeliac disease and that IL-15 regulates the frequency of this interaction. Further studies are required to confirm the precise relationship between IL-15, NKG2D and MICA/MICB in coeliac disease, but both groups suggest that targeting this axis could provide a novel therapy for coeliac disease.

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References and links

ORIGINAL RESEARCH PAPERS Meresse, B. *et al*. Coordinated induction by IL-15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease. *Immunity* **21**, 357–366 (2004) | Hüe, S. *et al*. A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. *Immunity* **21**, 367–377 (2004).