IN THE NEWS

Soya scare?

Levels of the sex-hormone mimic genistein that are found in soya-based infant formula can impair immune function, according to a new study in mice. Although food-safety groups maintain that it is still safe to feed babies with the formula, concerns were raised in the media. After all, as *HealthScout* news pointed out, ~750,000 babies in the United States alone drink soya-based formula.

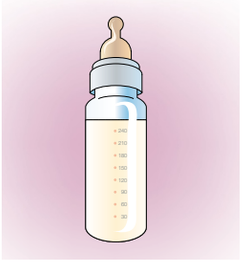
The paper published by Paul Cooke and colleagues at the University of Illinois, in the 28-May edition of the *Proceedings of the National Academy of Sciences*, shows that the thymi of mice that are fed or injected with amounts of genistein that are similar to those that are found in soya formula are shrunken and contain 80% fewer T cells.

Paul Cooke, taking a moderate position, told *BBC* news, "although there is nothing definitive, there is enough concern in this area that you would tend to shy away from it if you were a parent".

However, food-safety groups and food-industry bodies were quick to reassure parents. "If you look in the scientific literature for evidence of hormonal effects when human infants consume soya formula you don't find them," claimed Mardi Mountford of the International Formula Council (*HealthScout*).

Heather Payne of the Infant and Dietetic Food Association (UK) argued that because soya milk has been used for decades, any detrimental effects on human immune systems should have come to light by now.

Jennifer Bell



THYMIC DEVELOPMENT

Going back to our roots

Thymocytes require interactions with many types of epithelial cell in the thymus for their maturation and selection. However, the lineage relationships between these functionally and phenotypically distinct thymic epithelial cells (TECs) have remained unclear. Papers in *Immunity* and *Nature Immunology* now provide evidence for a common progenitor cell from which all TECs derive.

The thymic microenvironment is organized into distinct cortical and medullary areas, which are characterized by the presence of thymocyte precursors at defined stages of maturation, mesenchymal cells and several types of specialized epithelial cell. There has been much debate about the origin of TECs, but the lack of cell-specific cell-surface markers has prevented the isolation of putative thymic epithelial stem cells.

Bennett *et al.* carried out an extensive phenotypic characterization of the cellular composition of the embryonic day (E) 12.5 mouse thymus. Using monoclonal antibodies that are specific for keratin 5, keratin 8, MTS20 and MTS24 (markers that have been shown previously to be expressed by subsets of TECs), and for the differentiation antigens 4F1 and MTS10, several distinct epithelial subsets were identified. The lineage potential of these thymic subsets was assessed directly using a reaggregate fetal thymic organ culture (FTOC) model. Purified MTS20$^+$MTS24$^+$ or MTS20$^-$MTS24$^-$ cells were reaggregated, with or without mouse embryonic fibroblasts, for 24–48 hours and then either analysed directly or grafted under the kidney capsule of *nude* mice, which lack a thymus. MTS20$^+$MTS24$^+$ cells could differentiate into all known types of thymic epithelial cell, attract lymphoid progenitors and support T-cell development in *nude* mice. The MTS20$^-$MTS24$^-$ cells could perform none of these functions. Bennett and colleagues conclude that the MTS20$^+$MTS24$^+$ population has full thymic epithelial progenitor potential and is sufficient to establish a functional thymus *in vivo*.

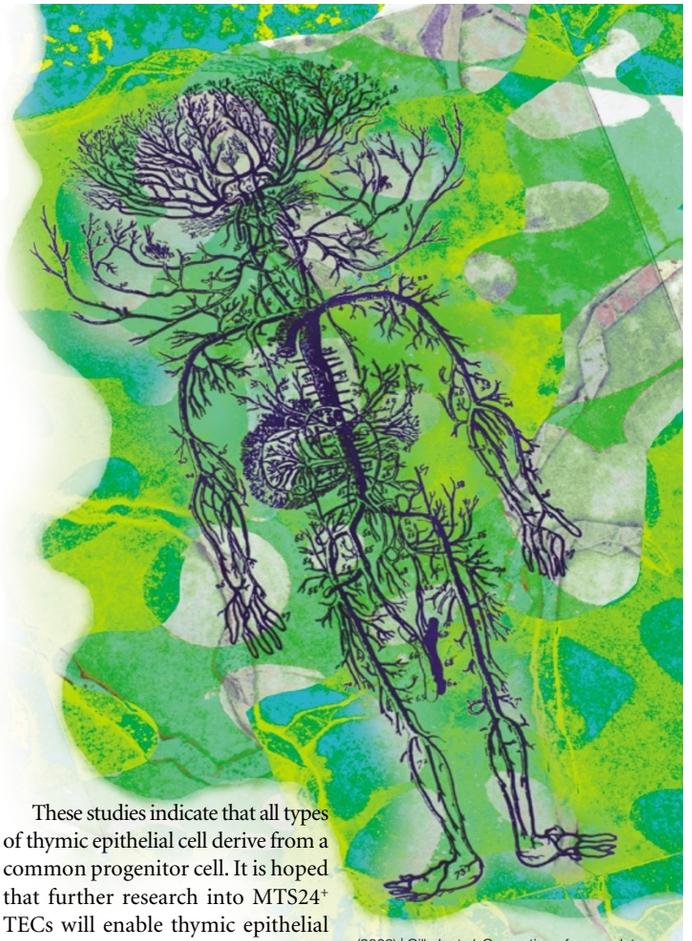
Gill *et al.* also investigated the role of MTS24$^+$ TECs in thymocyte development. E15.5 FTOCs that were depleted of lymphoid cells were treated with purified MTS24-specific monoclonal antibodies before being reconstituted with haematopoietic precursors. Antibody-treated cultures developed 88% fewer thymocytes than control cultures and thymocyte development was blocked at an early stage. In addition, the ability of E15.5 MTS24$^+$ cells to generate functional thymic microenvironments was investigated by assessing the development of ectopic thymi after transplantation of these cells under the kidney capsule of recipient mice. Thymi that had a normal distribution of thymocyte subsets and normal architectural organization developed in mice that received MTS24$^+$CD45$^-$ MHC class-II$^+$ cells, whereas no thymi developed in mice that received MTS24$^-$CD45$^-$ MHC class-II$^+$ cells. The authors conclude, in agreement with the findings of Bennett *et al.*, that the MTS24$^+$ thymic subset is sufficient to establish and maintain a complete thymic epithelial microenvironment and that these cells have full thymic epithelial progenitor potential.

HIV

Silencing HIV-1

RNA interference (RNAi) is a mechanism of post-transcriptional gene silencing that has been described both in animal and in plant cells. Short double-stranded RNA (dsRNA) duplexes lead to specific deletion of RNAs containing the same sequence. In plants, RNAi is an important defence against dsRNA-containing viruses and transposons, but whether this process can be used as a tool in human antiviral responses is unclear. A recent paper in *Nature Medicine* describes how RNAi can be targeted to inhibit HIV-infection in human cells, so possibly forming the basis of new antiviral therapies.

To assess the effects of RNAi on HIV-1 infection, Novina and colleagues targeted both cellular and viral RNAs. The HeLa-derived cell line Magi-CCR5 (which expresses human CD4, and the chemokine receptors CCR5 and CXCR4) was transfected with short interfering RNA (siRNA) specific for the gene of interest and then infected with HIV-1. Cells transfected with siRNA specific for CD4 (the principle receptor for HIV-1) expressed CD4 mRNA at a level eight times lower than control cells, which led to a



These studies indicate that all types of thymic epithelial cell derive from a common progenitor cell. It is hoped that further research into MTS24$^+$ TECs will enable thymic epithelial stem cells to be identified.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Bennett, A. R. *et al.* Identification and characterization of thymic epithelial progenitor cells. *Immunity* **16**, 803–814 (2002) | Gill, J. *et al*. Generation of a complete thymic microenvironment by MTS24$^+$ thymic epithelial cells. *Nature Immunol.* **3**, 635–642 (2000)

FURTHER READING Anderson, G. & Jenkinson, E. J. Lymphostromal interactions in thymic development and function. *Nature Rev. Immunol.* **1**, 31–40 (2002)

fourfold reduction in HIV-1 entry. Therefore, siRNA-directed silencing of CD4 specifically inhibited HIV entry and hence replication.

Next, the viral structural protein Gag was targeted by transfecting cells with siRNA specific for the p24 component of this polyprotein. p24-siRNA-transfected cells showed a fourfold decrease in viral protein compared with controls, implying that viral amplification was inhibited by this approach.

The authors also carried out transfection assays on human T cells, to assess the effect of RNAi on viral infectivity in a more physiological context. H9 cells were transfected with siRNA against green fluorescent protein (GFP) and were infected with an HIV-1 strain in which the *nef* gene had been replaced with GFP. Again, silencing of viral gene expression occurred, resulting in reduced GFP and HIV-1 protein expression.

But can siRNA-directed silencing reduce viral production in an established infection? Novina *et al.* tested the effect of p24-siRNA on previously infected Hela-CD4 cells and on a latently infected T-cell clone (ACH2) and again saw silencing of p24 expression. So, HIV-1 gene expression can be silenced by this approach even after viral integration has occurred in an established infection.

This study extends work by Lee and colleagues, published in *Nature Biotechnology*, who used a vector-based RNAi strategy to silence an HIV-1 gene, and establishes that siRNA technology can be used to suppress multiple steps of the HIV-1 life cycle.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Novina, C. D. *et al.* siRNA-directed inhibition of HIV-1 infection. *Nature Med.* 2002 June 3 (DOI:10.1038/nm725)

FURTHER READING Lee, N. S. *et al.* Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells. *Nature Biotechnol.* **20**, 500–505 (2002)

IN BRIEF

HAEMATOPOIESIS

Essential and instructive roles of GATA factors in eosinophil development.

Hirasawa, R. *et al. J. Exp. Med.* **195**, 1379–1386 (2002)

Targeted deletion of a high-affinity GATA-binding site in the GATA-1 promoter leads to selective loss of the eosinophil lineage *in vivo*.

Yu, C. *et al. J. Exp. Med.* **195**, 1387–1395 (2002)

These papers show that the transcription factor GATA1 has a pivotal role in eosinophil development. Hirasawa *et al.* transduced human myeloid progenitors that were isolated from cord blood with GATA1 and found that they developed into eosinophils, even under culture conditions that favour the development of myeloid cells. Furthermore, they show that *Gata1*$^{-/-}$ mice lack eosinophil progenitors in the fetal liver. Yu *et al.* show that deletion of a positive regulatory element in the *Gata1* promoter blocks eosinophil development. Together, these results indicate that GATA1 has an essential role in the specification of the eosinophil lineage.

ALLERGY

Human epithelial cells trigger dendritic-cell-mediated allergic inflammation by producing TSLP.

Soumelis, V. *et al. Nature Immunol.* **3**, 673–680 (2002)

Allergic inflammation is associated with the dysregulated production of T helper 2 (T_H2) cytokines, such as IL-4, IL-5 and IL-13. The activation of dendritic cells (DCs) seems to be an important part of this process, but it is unknown what drives DCs to preferentially stimulate T_H2-cell development. This study shows that human epithelial cells produce an IL-7-like cytokine, known as thymic stromal lymphopoietin (TSLP), which activates DCs and causes them to polarize naive CD4$^+$ T cells for the production of T_H2-associated cytokines. So, TSLP is a key trigger for DC-mediated allergic inflammation and might represent a new target for blocking inflammation, particularly in allergic diseases.

T-CELL DEVELOPMENT

Dynamics of thymic–stromal-cell interactions visualized by two-photon microscopy.

Bousso, P. *et al. Science* **296**, 1876–1880 (2002)

Two-photon laser-scanning microscopy (TPLSM) allows immunologists to investigate the behaviour of immune cells in three dimensions in real-time analyses. Here, Bousso and colleagues use TPLSM to assess the interactions of thymocytes and stromal cells during positive selection in a reaggregated thymic organ culture system. Thymocyte–stromal-cell interactions were diverse, involving both dynamic and stable interactions, but the basis for this observed diversity is unclear. The next step will be to assess the signals that are received through the T-cell receptor of a single thymocyte during thymocyte development.