IN THE NEWS

Yo-yo diets hit NK cells

It's an annual occurrence for some dieters: slim down for the beach in the summer months only to put the weight back on with the return of winter woollies. However, new research from the Fred Hutchinson Cancer Research Center, Seattle, USA, warns us that such yo-yo dieting might have a lasting negative impact on immune function. Conversely, maintaining the same weight over time seems to have a positive effect on the immune system, report Cornelia Ulrich and colleagues in the *Journal of the American Dietetic Association*.

In this study, overweight but otherwise healthy women were interviewed about their weight-loss history during the past 20 years. Women who had frequently (more than five times) lost weight had reduced natural killer (NK)-cell function compared with those who maintained the same weight for at least 5 years. Low NK-cell activity is associated with increased cancer rates and a higher susceptibility to viral infections. Ulrich says that although "there is clear evidence that weight loss is beneficial for your health ... this pattern of weight cycling where women go up and down" can cause problems (*The Times*). She added that exercise could be the answer, as it is known to lessen some of the negative effects of weight loss on the immune system and actually boost immunity. So, Katherine Tallmadge, a spokeswoman for the American Dietetic Association, urges "people not to do fad diets, and just try small changes that they are more likely to be able to live with" to minimize the impact on the immune system (*CNN News*). This view was mirrored by Nigel Denby of the British Diabetic Association, who said that sensible eating and increased exercise is "the perfect recipe for ... maintainable weight loss" (*BBC News*).

Lucy Bird

IMMUNE REGULATION

Expanding regulators

Until now, harnessing the potent suppressive activity of regulatory T (T_{Reg}) cells for the treatment of autoimmune disease and transplant rejection has been limited by the low numbers and diverse antigen specificity of these cells *in vivo*. In *The Journal of Experimental Medicine*, two papers describe *in vitro* methods for clonally expanding antigen-specific $CD4^+CD25^+$ T_{Reg} cells that effectively suppress disease in a mouse model of autoimmune diabetes.

In the report by Jeffrey Bluestone and colleagues, $CD4^+CD25^+$ T_{Reg} cells were purified from nonobese diabetic (NOD) mice or islet-antigen-specific TCR-transgenic mice (BDC2.5 mice) and expanded more than 200 fold in the presence of co-immobilized CD3- and CD28-specific antibodies plus a high dose of interleukin-2 (IL-2). The expanded $CD4^+CD25^+$ T_{Reg}-cell populations maintained antigen specificity and a T_{Reg}-cell phenotype — expressing high levels of CD25, CD62L, SOCS2, PD1, CTLA4, TRAIL and the T_{Reg}-cell lineage marker FOXP3. Expanded T_{Reg}-cell populations suppressed the *in vitro* proliferation of effector T cells more efficiently than T_{Reg} cells that were freshly isolated from NOD mice. The induction of suppressor activity was antigen specific and mediated through cell–cell interactions, and did not depend on the immunosuppressive cytokines IL-10 and transforming growth factor-β for effector function *in vitro*.

In contrast to the effective suppressive activity of both the expanded T_{Reg}-cell lines *in vitro*, they had marked differences in effectiveness *in vivo*. Expanded BDC2.5 T_{Reg} cells efficiently suppressed diabetes induced in lymphopenic NOD mice by the transfer of diabetogenic polyclonal cells or BDC2.5 effector T cells. By contrast, expanded polyclonal NOD T_{Reg} cells did not inhibit the transfer of disease, even when high numbers of T_{Reg} cells were used. Moreover, the BDC2.5 T_{Reg} cells efficiently blocked the development of spontaneous diabetes in T_{Reg}-deficient, CD28-deficient NOD mice.

In a similar study by Ralph Steinman and colleagues, $CD4^+CD25^+$ T_{Reg}-cell populations were expanded *in vitro* using dendritic cells (DCs) isolated from NOD mice and pulsed with specific autoantigen. Similarly,

IMMUNE REGULATION

Instructing T_H1/T_H2-cell differentiation

According to a new study reported in *Cell*, the development of T helper 2 (T_H2) cells is not just a default pathway that occurs in the absence of T_H1-cell-inducing signals but is an instructive process determined by Notch ligands.

Naive T cells develop into polarized effector cells that mediate effective immune responses. T_H1 cells are important for cellular immunity and are characterized by the production of interferon-γ (IFN-γ), whereas T_H2 cells are important for humoral immunity and produce the cytokines interleukin-4 (IL-4), IL-5 and IL-13.

IL-12 produced by antigen-presenting cells (APCs) can drive T_H1-cell differentiation, but in the absence of IL-12, T cells do not neccesarily develop along a default pathway into T_H2 cells, indicating that instructive factors for T_H2-cell differentiation exist. IL-4 is important for T_H2-cell induction, but the fact that T_H2 cells can develop in the absence of IL-4 signalling (in signal transducer and activator of transcription 6 (STAT6)-deficient mice) indicates that other T_H2-promoting signals exist.

This study explored the factors that are responsible for T_H2-cell differentiation. Notch receptors are known to be involved in cell-fate decisions, and the DNA-binding factor RBPJ-κ is a key component of Notch-signalling pathways. Because RBPJ-κ is expressed at a low level in naive $CD4^+$ T cells but is preferentially expressed by T_H2 cells, the authors proposed that the Notch-signalling pathway might regulate T-cell differentiation.

Notch ligands belong to two main families — Jagged and Delta. Assessment of ligand expression revealed that the ability of dendritic cells to induce T_H2-type responses correlated with Jagged-1 expression, and the ability to induce T_H1-type responses correlated with Delta-4 expression. APCs expressing Jagged-1 were able to induce T_H2-cell differentiation of T cells from STAT6-deficient mice, indicating that induction is independent of IL-4–STAT6

they found that such antigen-specific T_{Reg} cells were more suppressive than freshly isolated T_{Reg} cells *in vitro* and efficiently prevented diabetes caused by diabetogenic T cells in NOD mice, even when low numbers of T_{Reg} cells were transferred.

For T_{Reg} cells to be of therapeutic use in patients with autoimmune diabetes, they must be able to block ongoing disease. To test this, Bluestone and colleagues expanded BDC2.5 T_{Reg} cells and transferred them into NOD mice with recent disease onset or chronic diabetes, together with a syngeneic islet-cell transplant. BDC2.5 T_{Reg} cells reversed diabetes in both settings and restored long-term immune homeostasis. Using a different model, Steinman and colleagues also showed that expanded T_{Reg} cells blocked ongoing disease, as they were effective even when administered 2 weeks after the transfer of diabetogenic T cells.

So, both these studies achieve effective *in vitro* expansion of T_{Reg}-cell populations that have enhanced suppressive function *in vivo*. As such, this work provides hope that the suppressive activity of T_{Reg} cells can be harnessed to treat autoimmune disease in humans in an antigen-specific manner.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPERS Tang, Q. *et al.* *In vitro*-expanded antigen-specific regulatory T cells suppress autoimmune diabetes. *J. Exp. Med.* **199**, 1455–1465 (2004). | Tarbell, K. V., Yamazaki, S., Olson, K., Toy, P. & Steinman, R. M. $CD25^+CD4^+$ T cells, expanded with dendritic cells presenting a single autoantigenic peptide, suppress autoimmune diabetes. *J. Exp. Med.* **199**, 1467–1477 (2004).

signalling. Further experiments showed that ligation of Notch instructs T_H2-cell differentiation by inducing the transcription factor GATA3 and by directly regulating transcription of the gene encoding IL-4 through targeting RBPJ-κ sites in a 3′ enhancer region.

This study challenges the dogma that the development of T_H2 cells is a default pathway that occurs in the absence of T_H1-cell-inducing signals. The molecular mechanisms controlling Delta-4-mediated induction of T_H1-cell differentiation remain undefined, and further studies will be required to determine how Delta and Jagged can mediate such different responses by engaging Notch receptors.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Amsen, D. *et al.* Instruction of distinct CD4 T helper cell fates by different Notch ligands on antigen-presenting cells. *Cell* **117**, 515–526 (2004).

IN BRIEF

INNATE IMMUNITY

Antagonistic antibody prevents Toll-like receptor 2-driven lethal shock-like syndromes.

Meng, G. *et al. J. Clin. Invest.* **113**, 1473–1481 (2004).

Infection with Gram-positive bacteria, such as *Bacteroides subtilis*, elicits inflammatory responses through the stimulation of Toll-like receptor 2 (TLR2) on host cells. The induction of hyper-inflammation through this pathway can cause septic shock, so the authors looked at whether targeting TLR2 might be an effective treatment. They raised an antibody against TLR2 that prevented the activation of TLR2-expressing cells through this pathway. When mice were pretreated with the antibody then challenged with a synthetic TLR2 agonist, levels of pro-inflammatory cytokines and chemokines were reduced compared with untreated mice. Pre-treated mice were also less susceptible to lethal toxaemia induced by infection with *B. subtilis*.

ASTHMA AND ALLERGY

Acidic mammalian chitinase in asthmatic T_H2 inflammation and IL-13 pathway activation.

Zhu, Z. *et al. Science* **304**, 1678–1682 (2004).

Lower life forms produce chitinases as a protective mechanism in response to infection with parasites that have chitin coats. Recently, humans have also been shown to express a chitinase known as acidic mammalian chitinase (AMCase). Given the link between antiparasite and allergic responses, which both have a T helper 2 (T_H2)-cell bias, the authors looked at whether AMCase might be involved in asthma pathogenesis. They showed in a mouse model of lung inflammation that lung epithelial cells and macrophages both express AMCase and that this depends on IL-13 production by T_H2 cells. Administration of an antibody specific for AMCase reduced lung inflammation by inhibiting the ability of IL-13 to induce chemokine responses. AMCase expression could also be detected in human lung tissue from patients with asthma. This study indicates that chitinases might be mediators of T_H2-cell responses and therefore potential therapeutic targets to control these responses.

SIGNALLING

Rac1 and Toll–IL-1 receptor domain-containing adapter protein mediate Toll-like receptor 4 induction of HIV-long terminal repeat.

Equils, O. *et al. J. Immunol.* **172**, 7642–7646 (2004).

Patients infected with HIV commonly suffer microbial infections that cause increased HIV-1 replication. Previous studies indicate that lipopolysaccharide (LPS) stimulation of Toll-like receptor 4 (TLR4) induces transcription of the HIV long-terminal repeat (HIV-LTR). In this paper, Equils *et al.* show that LPS induces RAC1 activation and that RAC1 stimulates HIV-LTR *trans*-activation. RAC1-induced HIV-LTR activation depends on Toll/IL-1-receptor-domain-containing adaptor protein (TIRAP), but RAC1 activation is probably downstream of MyD88. This study therefore provides insight into the signalling pathways likely to be important in microbial-induced HIV-1 replication.