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 woolies. 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 necessarily 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