cropland requirements would be reduced by 450 million to 600 million hectares (about 20–30% of the projected 2050 cropland area for the reference diet) if any one of these alternative diets were adopted by the world’s population. The authors conclude that “the implementation of dietary solutions … is a global challenge, and opportunity, of great environmental and public health importance”.

How certain are these effects? The link found by Tilman and Clark between diets and health is astonishingly strong, and they used only data that had been corrected for other lifestyle factors. However, as the authors rightly stress, their data are not meant to compare the alternative diets with each other, nor to imply that other diets might not show even higher health benefits. Future research should aim to expand the empirical basis for the connection between diet and health, and to further investigate the mechanisms behind it.

Consistent with other LCA review studies, the authors’ data analysis shows that greenhouse-gas emissions are highest for ruminant meat, followed by other animal products, and lowest for most cereals, fruits, vegetables and pulses. However, LCA data purely reflect the current state of production systems, and cannot take into account potential efficiency improvements. Other uncertainties arise from the limited scalability of LCA data and agricultural systems in general. For example, it is not clear if vegetable production can be scaled up while maintaining low greenhouse-gas emissions (for example, because there are higher emissions from growth in greenhouses), and changes in livestock consumption and production will also lead to nonlinear effects, feedback and leakages not captured by LCA factors. Marine biologists will also question the scalability of fish production; current levels already overexploit natural stocks, and any increase beyond the sustainable global fisheries catch will have to come from aquaculture, as Tilman and Clark suggest — but expansion of aquaculture will have to rely mostly on land-based feed. However, although such scalability issues should receive further attention, the overall advantage of the alternative diets compared with the reference diet, in terms of emissions, is probably a robust finding.

Predictions of future land requirements for food products and the corresponding environmental consequences are much more uncertain than the emissions predictions, and strongly depend on assumptions about future crop yields, livestock technology and trade. The projected change in global cropland found by Tilman and Clark for the ir2050 reference diet is higher than the highest estimates in a recent comparison of global agro-economic models. However, the authors find that the reduction in global cropland that would be achieved by the alternative diets is rather constant when varying the most uncertain determinants of their projection in a sensitivity analysis.

With such clear health and environmental benefits of alternative diets, what could be done with this knowledge? First, it can be used by everybody to make informed consumption choices. But individual choices are strongly influenced by the ‘food environment’ — factors such as shop proximity, food prices, food and nutrition programmes, labelling schemes and community characteristics. Governments and other agencies play a part in shaping these environments to support healthier and more-sustainable food choices, and increased efforts to include both health and environmental factors in dietary guidelines will be key to promoting behavioural change.

Furthermore, addressing consumption should be accompanied by measures on the production side, because regulations at the source of a problem are often the most effective. For example, agriculture and land-use change should be subject to targets and regulations similar to those for the energy and industry sectors. Such interventions will also help to include environmental costs in the price of resource-intensive food products and would therefore further influence individual choices.

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IMMUNOLOGY

Tolerance lies in the timing

During immune-cell development, potentially self-reactive T cells are eliminated. It emerges that recruitment of a co-receptor bound to the T-cell receptor by the enzyme Lck is the rate-limiting step in this negative selection.

NICHOLAS R. J. GASCOIGNE

Immunological tolerance is a developmental process that enables the immune system to be poised to respond to potential pathogens without inappropriately responding to the body’s own molecules. As T cells of the immune system develop in the thymus, those whose T-cell receptor (TCR) binds to a ligand with high strength — an indication that the ligand belongs to a self-molecule — are induced to die. Writing in Cell, Stepanek et al. identify a molecular mechanism to explain the relationship between TCR recognition strength and this negative selection. The mechanism they propose is based on the ‘kinetic proofreading’ model originally put forward nearly 20 years ago for T-cell activation, which suggests that the induction of an activating signal requires the TCR to bind to its ligand for long enough that the resulting downstream signalling cannot be stopped by the eventual TCR–ligand dissociation. The novelty in Stepanek and colleagues’ work is that they have linked the half-life of this interaction to the recruitment of the signalling molecule Lck to the interaction complex, which turns out to be a rather rare event. Each mature T cell expresses a slightly different TCR that will bind to a complex formed of a specific short peptide (the antigen) and a major histocompatibility complex (MHC) protein on the surface of antigen-presenting cells. The strength of this binding determines the strength of the signal transmitted in the T cell. If the antigen is from a foreign organism, this signal needs to be strong enough to activate the cell to respond appropriately to the potential pathogen. But because the TCR repertoire is generated in immature T cells (thymocytes) in a fairly random way, some TCRs will recognize self-antigens, and these cells need to be deleted by negative selection during T-cell development. The challenge in understanding this process has been to determine how a continuous variable — the strength of MHC–peptide binding to the TCR — can be translated into a digital response, in which too-strong signalling leads to death, whereas signalling below this threshold induces positive selection, leading to thymocyte survival and differentiation into mature naïve T cells.

In addition to the TCR, developing thymocytes express cell-surface co-receptor proteins, called CD4 and CD8, which bind to MHC class II (MHCII) and class I (MHCI) proteins, respectively. Thymocytes bearing TCRs

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Figure 1 | Dwell time determines selection outcomes in thymocytes. T-cell receptors (TCRs) recognize antigen molecules bound to major histocompatibility (MHC) proteins. The strength of signal transmitted by this interaction determines whether a developing thymocyte is selected to survive (positive selection, induced by not-too-strong signals) or die (negative selection, induced by strong signals indicative of self-antigens). Signal strength is also influenced by the recruitment of T-cell co-receptors to the complex.

1. Stepak et al. show that co-receptors that are not bound by the protein Lck bind only briefly to MHC before dissociating (indicated by arrows). By contrast, co-receptors with bound Lck stay associated with the TCR–MHC complex for longer, owing to interactions between the active site of Lck and the CD3 protein that is associated with the TCR. This longer dwell time leads to the sustained signalling required to induce negative selection. (P denotes protein phosphorylation.)

The authors then mathematically modelled the effect of differential co-receptor–Lck coupling on T-cell activation. The model that best fits the data proposes that the probability of a Lck-bound co-receptor being recruited to the TCR–MHC–peptide complex is the crucial factor in kinetic proofreading, because only Lck-bound co-receptors stay bound to the signalling complex long enough to transmit a negative-selection signal (Fig. 1). The probability of CD8–Lck being recruited is lower than that of CD4–Lck, so the TCR complex will need to ‘examine’ more CD8 molecules than CD4 molecules before it finds one that bears active Lck. Thus, a longer TCR–MHC–peptide dwell time is required when CD8 is involved.

Although this model provides a molecular mechanism for how developing thymocytes translate TCR dwell time into distinct signalling and functional outcomes, and how this varies between MHCI- and MHCII-restricted thymocytes, there are some points that it does not resolve. For example, antigen-independent co-receptor interaction with MHC molecules can concentrate MHC at the interface between an antigen–presenting cell and a thymocyte, with the effect of speeding the rate at which the TCR can bind to MHC–peptide. Because of the higher affinity of CD8 for MHCI than of CD4 for MHCII, this effect will be more marked for MHCI-restricted TCRs and might lower the threshold affinity, but not dwell time, for signalling. Moreover, concentration at this interface also applies to the co-receptor and its associated Lck, so CD8 should be more concentrated than CD4, and the density of CD8–associated Lck at the interface could be higher than estimates obtained from whole-cell analyses.

Another potentially confounding point is that formation of the TCR signalling complex has been identified as a two-step interaction, in which the co-receptor binds to MHC to stabilize the complex only after TCR binding and early signalling events lead to Lck interaction with the TCR complex. According to this model, Lck-bound co-receptors preferentially associate with TCRs that have just bound MHC–peptide, which would make the proportion of Lck molecules that are associated with co-receptors less important than in Stepak and colleagues’ model.

Despite such unresolved details, the new model is an attractive variant of the kinetic-proofreading model for T-cell activation, taking into account features of Lck and co-receptor interactions that were not previously accommodated. In particular, co-receptor–Lck interactions change during T-cell differentiation, in parallel with changes in antigen sensitivity, and the co-receptor-scanning model provides a simple mechanistic explanation for this phenomenon.

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