at gap junctions, where they belong. Although it’s possible that CAR–driven signals induce connexin gene expression, the recent discovery that the two proteins bind to each other suggests instead that CAR might pin down connexins in adjacent gap junctions, thereby preventing their mislocalization and subsequent degradation.

The findings might explain the association between cardiac arrhythmia and CAR loss seen in patients who develop autoantibodies against CAR or who become infected with Coxsackievirus. The group is now trying to confirm that this arrhythmia is due to a connexin disturbance at the AV node. HB

The lowdown on sugar highs

Short-lived sugar highs might give a quick energy boost, but according to El-Osta et al. (page 2409), they also leave a lasting bad impression on heart vessels of diabetes patients. The findings might explain why diabetics are at higher risk for heart disease.

Diabetes is a major cause of heart attack and stroke—events that are triggered by atherosclerotic plaques and inflammation in the arteries. In diabetic patients who have had extended periods of high blood glucose levels, arterial damage persists long after insulin therapy reduces their mean glucose levels. The authors now provide a molecular explanation for this phenomenon.

The group found that short-lived sugar highs, which occur even in insulin-treated diabetics, trigger histone modifications—an established effect of long-lasting sugar highs. Persistently high sugar levels are known to create reactive oxygen species that induce the generation of methylglyoxal—an activator of the histone methylating enzyme Set7. The authors found that brief blood sugar peaks also activated Set7, which bound to the promoter of the gene for NF-κB, thereby increasing its expression. NF-κB then switched on genes for proteins that help recruit and attach plaque-forming monocytes to vessel walls. These gene expression changes, which were seen in both human heart endothelial cells and mouse aortas, persisted for at least six days after glucose levels returned to normal. These changes were prevented by blocking methylglyoxal production.

Current treatments for diabetes are aimed at reducing mean glucose levels in patients but not the temporary rises in blood sugar levels that occur between insulin injections. This study suggests that adjusting the timing of the treatment regimen to avoid these spikes might be more effective in reducing the risk of heart disease. HB

Egr-2 prevents self-reactions

Self-tolerance is well known to be enforced in part by an external force of regulatory T cells. Now, Zhu et al. (page 2295) show that T cells also have their own internal barrier to self-reactivity—a transcription factor called Egr-2.

The team had previously found that Egr-2 is made by T cells that are repeatedly stimulated by their cognate antigen. The cells then become unresponsive, much like T cells that are constantly exposed to self-antigens in the periphery.

The authors now find that, in mice, Egr-2 expression is also turned on in effector T cells that develop as a result of exposure to gut bacteria or to certain self-antigens. The Egr-2–expressing cells reacted to strong T cell receptor stimulation in vitro but did not trigger autoimmunity or responses against the gut bacteria in mice, suggesting that Egr-2 might only temper T cell reaction to the relatively weak signals of self-antigens. But how repeated antigen stimulation induces Egr-2 and how the transcription factor distinguishes weak, self-signals from strong, non-self signals are not yet known.

The deletion of Egr-2 triggered the accumulation of effector T cells and the development of lupus and its accompanying inflammation. The T cells amassed due to reduced expression of the gene for the cell cycle inhibitor p21Cip1, one of the few known Egr-2 targets. The rapidly proliferating T cells overexpressed genes for inflammatory cytokines, but the authors have yet to determine which Egr-2–induced genes normally suppress these cytokine genes.

Persistent viral antigens are known to induce tolerance in effector T cells, resulting in chronic infections. The group is now investigating whether deletion of Egr-2 in these cells prevents chronic infection. HB