(thymic-derived) IELs from wild-type mice express high levels of the GLP1 receptor (GLP1R). Mixed bone marrow chimaera experiments showed that loss of GLP1R on IELs protects against atherosclerosis in the *Ldlr*$^{-/-}$ model by mediating increased systemic levels of GLP1, which was associated with increased glucose tolerance. GLP1R$^{hi}$ IELs appear to regulate GLP1 levels through two main mechanisms: first, they 'mop up' GLP1; and, second, they seem to regulate GLP1 production, as β7-deficient mice had more GLP1-producing L cells.

The authors propose that integrin β7$^{+}$ IELs serve as gatekeepers of dietary metabolism by limiting GLP1 bioavailability. They suggest that this function would be beneficial in conserving energy in environments where food is scarce but detrimental to health in our present-day societies, in which diets are abundant in fat and sugar.

*Yvonne Bordon*

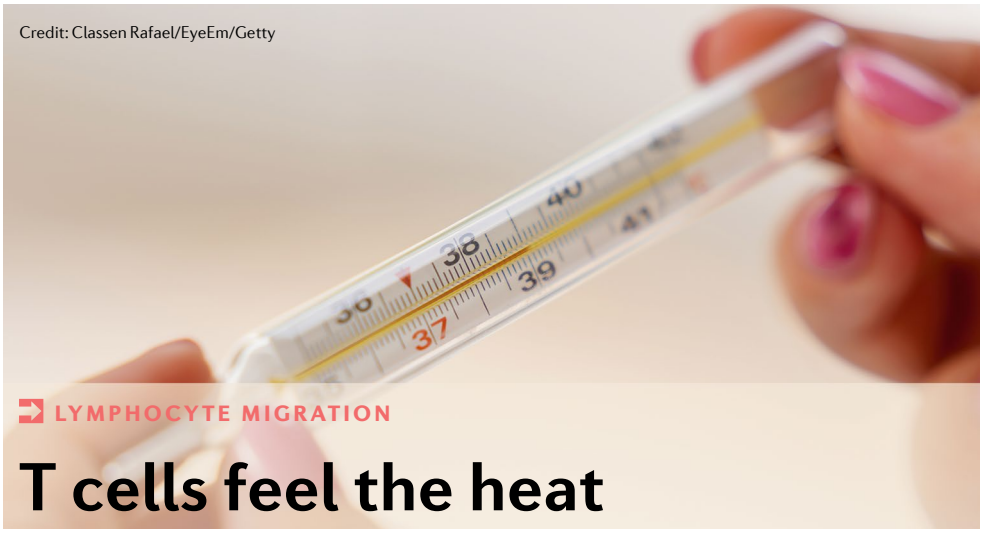
**ORIGINAL ARTICLE** He, S. et al. Gut intraepithelial T cells calibrate metabolism and accelerate cardiovascular disease. *Nature* https://doi.org/10.1038/s41586-018-0849-9 (2019)

or *Streptococcus pneumoniae*, and this increased survival was associated with both increased daytime sleep and decreased bacterial load. The expression of *nur* mRNA in *Drosophila* brain was induced by both sleep deprivation and peripheral infection. Indeed, *Drosophila* lines in which the *nur* gene was knocked out using CRISPR/Cas9 technology had a reduction in the infection-induced sleep that was observed in control flies.

As *nur* expression was detected in only a single neuron in each brain hemisphere after sleep deprivation or infection, it seems likely that the survival-promoting effect of NUR results from its sleep-inducing properties rather than its direct antimicrobial properties. Nevertheless, this study shows that a single factor can link sleep and immune function in *Drosophila*, which has potential implications for mammalian AMPs.

*Kirsty Minton*

**ORIGINAL ARTICLE** Toda, H. et al. A sleep-inducing gene, *nemuri*, links sleep and immune function in *Drosophila*. *Science* **363**, 509–515 (2019)



Credit: Classen Rafael/EyeEm/Getty

LYMPHOCYTE MIGRATION

# T cells feel the heat

Fever is an evolutionarily conserved response to infection. But exactly how it confers survival benefits has been unclear. A new study reported in *Immunity* describes a molecular mechanism to explain how fever promotes T cell trafficking and enhances immune surveillance during infection, through a thermal sensory pathway involving heat shock protein 90 (HSP90) and α4 integrins.

Exposing mouse T cells to febrile temperatures (40 °C) for 12 hours led to significant increases in their ability to adhere to ligands for α4β1 integrin (VCAM1) and α4β7 integrin (MAdCAM1) but not to β2 integrin ligand (ICAM1). Chemokine-induced transmigration across VCAM1-coated or MAdCAM1-coated membranes was also markedly increased following pretreatment of T cells at 40 °C compared with 37 °C. This suggested that thermal stress specifically promotes α4 integrin-mediated T cell adhesion and transmigration.

As expected, T cells treated at temperatures >38.5 °C also showed a marked upregulation of various HSPs. However, immunoprecipitation studies revealed that only HSP90 selectively bound to α4 integrin — an interaction that was enhanced by exposure to febrile temperatures. Consistent with a functional role for HSP90–α4 integrin binding, HSP90 overexpression promoted α4 integrin-dependent T cell adhesion and transmigration at 37 °C.

Mutational studies showed that HSP90 binds to the α4 integrin cytoplasmic tail, with one mutation (R985A) specifically abolishing the interaction. Accordingly, T cells from mice expressing the R985A α4 integrin mutant (*Itga4*$^{R985A/R985A}$ mice) failed to show thermal stress-induced adhesion and transmigration in vitro. And following transfer into mice, wild-type T cells, but not *Itga4*$^{R985A/R985A}$ T cells, pretreated at 40 °C showed increased 'sticking' to high endothelial venules and homing to inguinal lymph nodes. Increased T cell trafficking to draining lymph nodes was also observed in wild-type mice after exposure to whole body hyperthermia for 6 hours compared with *Itga4*$^{R985A/R985A}$ mice treated the same way.

Delving deeper into the mechanism, the authors first used a fluorescence resonance energy transfer (FRET) system to show that HSP90 binding induces the active (extended) conformation of α4 integrins. Moreover, thermal stress or HSP90 overexpression promoted binding of talin and kindlin 3, which are the two critical co-activators of inside-out α4 integrin activation. Indeed, silencing of talin and kindlin 3 inhibited thermal stress-induced activation of α4 integrins. Second, they used a bimolecular fluorescence complementation technique to show that fever-induced binding of HSP90 induces dimerization and clustering of α4 integrins on the cell membrane. Dimerization of the two α4 integrin subunits was mediated by simultaneous binding by the amino-terminal domain and the carboxy-terminal domain of HSP90. Integrin clustering supported activation of a signalling pathway involving focal adhesion kinase (FAK) and Ras homologue gene family, member A (RHOA) GTPase to promote cell migration.

Finally, the authors tested whether the HSP90–α4 integrin axis is protective in the setting of oral *Salmonella enterica* subsp. *enterica* serovar Typhimurium infection. The infection was more severe, with more intestinal tissue damage and bacterial dissemination, in *Itga4*$^{R985A/R985A}$ mice than in wild-type mice. And increased severity was associated with a reduction in the number of T cells, and monocytes, accessing the inflamed tissue and some associated lymphoid tissues.

So, the fever-induced HSP90–α4 integrin axis is crucial for promoting immune cell trafficking to inflamed tissues to facilitate the clearance of bacterial infection. Whether this pathway can be targeted therapeutically — to enhance or temper immune trafficking — awaits further study.

*Lucy Bird*

**ORIGINAL ARTICLE** Lin, C. et al. Fever promotes T lymphocyte trafficking via a thermal sensory pathway involving heat shock protein 90 and α4 integrins. *Immunity* **50**, 137–151 (2019)