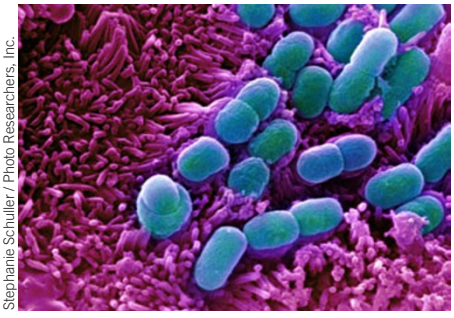
findings, this lipodystrophy in the knockout mice probably indicates that local FGF21-mediated increases in PPAR-γ activity in fat tissue in response to food intake may translate into an acute increase in adipogenesis and adiposity. However, it should be noted that pharmacological treatment with exogenous FGF21 leads to weight loss in rodents and monkeys, indicating that systemic FGF21 is probably acting on many tissues with the overall chronic effect of reduced adiposity.

PPAR-γ is the major target of thiazolidinediones (TZDs), a class of antidiabetic drugs that include rosiglitazone. The authors also found that FGF21-knockout mice are resistant to many, though not all, of both the beneficial and adverse effects of rosiglitazone. Thus, these findings also provide further insight into the mechanism of action of TZDs and perhaps suggest ways to maintain the benefits of these drugs while avoiding their pitfalls.—*RL*

■ IMMUNITY

Controlling commensals



Stephanie Schuller / Photo Researchers, Inc.

There is a growing appreciation of the complex interplay between the microbiota and the host immune system and its role in disease. A recent study provides new understanding of host immune pathways that normally keep commensal gut bacteria under control (*Immunity* **36**, 1–11).

The Toll-like receptor adaptor protein MyD88 is crucial for the regulation of intestinal homeostasis, but the mechanisms by which it does so have remained elusive. Donna Kirkland *et al.* characterized details of a pathway by which MyD88 protects mice treated with dextran sulfate sodium (DSS) from lethal colonic inflammation. Mice lacking MyD88 died after DSS-induced colonic damage but were protected by antibiotic treatment, which depletes commensal bacteria. Moreover, commensal bacteria were present in tissues outside the colon in the MyD88-deficient, DSS-treated mice, suggesting that in the absence of MyD88 and after colonic damage these bacteria can escape and disseminate to other tissues.

The authors then showed that MyD88 activation in B cells was needed for host protection from lethal bacterial dissemination after DSS treatment. This B cell–intrinsic MyD88 signaling pathway seemed to mediate its protective effects via the production of IgA, IgM and complement.

This study thus illustrates how loss of a protective immune signaling pathway can allow commensal bacteria to become pathogenic. —*MS*

■ IMMUNITY

Infectious tolerance?

Helicobacter pylori infection of neonatal mice is known to induce differentiation of regulatory T cells (T_{reg} cells), which protect against the gastric pathology seen in older mice infected with this pathogen. Oertli *et al.* now report that modulation of dendritic cells (DCs) by *H. pylori* is important for the induction of immune tolerance in infected neonates (*J. Clin. Invest.* doi:10.1172/JCI61029).

The researchers showed that although *H. pylori* did not affect the basal activation state of DCs, it did impair their maturation induced by diverse stimuli. These maturation-impaired, infected DCs induced T_{reg} cells more potently than their uninfected counterparts and failed to activate effector T cell responses. When the researchers depleted DCs in neonatally infected mice, more leukocytes infiltrated the gastric mucosa, fewer bacteria colonized the stomach and mild gastritis was present, indicating that *H. pylori* suppression of DC function induces tolerance to bacterial colonization and prevents gastric pathology. In a small number of biopsies of human gastric mucosa, the researchers found more DCs in *H. pylori*–infected individuals than in uninfected controls, and the gastric mucosa DCs had an impaired maturation phenotype in both groups, suggesting that *H. pylori* infection may similarly affect DCs in humans.

How the bacteria impede DC maturation is not known, but the authors also showed that *H. pylori*–infected DCs produced interleukin-18 (IL-18), which was required for the observed induction of T_{reg} cell differentiation. As IL-18 also has a role in T helper type 1 induction, how *H. pylori* modulates the balance of T cell differentiation to promote immune tolerance in neonatal mice and how this balance shifts in infected older animals remains to be elucidated.—*AF*

Written by Victoria Aranda, Alison Farrell, Randy Levinson, Juan Carlos López, Carolina Pola and Meera Swami.

New from NPG

Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity
Henao-Meija, J. *et al. Nature* doi:10.1038/nature10809 (1 February).
The authors uncover a pathway in which the NLRP3 and NLRP6 inflammasomes modulate the gut microbiota to regulate the progression from nonalcoholic fatty liver disease to the chronic inflammatory condition nonalcoholic steatohepatitis, and they also show this pathway causes features of the metabolic syndrome.

Expression of tumour-specific antigens underlies cancer immunoediting
DuPage, M. *et al. Nature* doi:10.1038/nature10803 (8 February).

Cancer exome analysis reveals a T-cell–dependent mechanism of cancer immunoediting
Matsushita, H. *et al. Nature* doi:10.1038/nature10755 (8 February).
Two recent studies compare the antigens expressed on tumors in immunocompetent and immunodeficient mouse hosts to characterize new details about the process of cancer immunoediting, which enables tumor cells to escape immune surveillance.

Genome-wide association study identifies a variant in *HDAC9* associated with large vessel ischemic stroke
The International Stroke Genetic Consortium *et al. Nat. Genet.* doi:10.1038/ng.1081 (5 February).
This genome-wide association study replicates two previous associations for cardioembolic stroke and one for large vessel stroke, and identifies a new association between the gene encoding histone deacetylase 9 and large vessel stroke. In addition, the results indicate that different stroke subtypes have different underlying genetic architectures.

SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates
Lahouassa, H. *et al. Nat. Immunol.* doi:10.1038/ni.2236 (12 February).
The authors show that SAMHD1 restricts HIV-1 infection of myeloid cells by hydrolyzing dNTPs, resulting in insufficient dNTP concentrations for viral replication. These results suggest that nucleotide depletion may be a general strategy for protecting host cells from agents like HIV that replicate through a DNA intermediate.