Mad arrests

Shigella are pathogenic bacteria of the intestinal tract and are capable of causing bloody diarrhea. Hosts attempt to passively evade such pathogens by rapid cycling and shedding of gut epithelial cells. In *Cell*, Iwai *et al.* show that the bacterial virulence factor IpaB acts to counteract the cell cycle regulator Mad2L2, thereby arresting infected cells at the G2-M checkpoint. Mad2L2 is an inhibitor of the E3 ligase APC^{Cdh1}, which targets cyclin B1, Cdc20 and the kinase Plk1 for degradation. IpaB triggers premature activation of APC^{Cdc1} and prevents accumulation of the cyclins necessary to initiate anaphase. This cell cycle arrest increases the time by which intracellular bacteria can replicate before killing the host cell. By targeting the cell cycle, shigella also disrupt gut epithelial cell homeostasis, further complicating the immune response. ***LAD***

***Cell* 130, 611–623 (2007)**

TLR-specific immunodeficiency

Mutations in the signaling molecule UNC-93B, but not in the kinase IRAK-4, predispose humans to herpes simplex virus 1 (HSV-1) encephalitis (HSE). In *Science*, Casanova and co-workers link HSE susceptibility to a mutation in Toll-like receptor 3 (TLR3), which lies upstream of UNC-93B but not IRAK-4. Fibroblasts from two unrelated children harboring identical mutations in an extracellular leucine-rich repeat of TLR3 do not secrete type I interferon (IFN) after stimulation with the TLR3 ligand poly(I:C). This mutant TLR3 protein acts in a dominant negative manner, as its overexpression suppresses poly(I:C)-induced IFN production in control fibroblasts. Human peripheral blood cells and keratinocytes produce IFN after stimulation with poly(I:C) or other viral compounds. Thus TLR3 function in the central nervous system may be essential to control HSV-1, and neurotropic viruses may have exerted evolutionary pressure to maintain TLR3, an innate receptor apparently dispensable for resistance to many other microbial infections. *CB*

Science **317**, 1522–1527 (2007)

Gut population shift

The vast and diverse population of commensal bacteria in the animal intestine is essential for nutrient acquisition and for development of intestinal epithelial and immune cells. In *Cell Host & Microbe*, Finlay and co-workers show that host inflammation, even in the absence of pathogenic bacteria infection, alters the size and composition of the mouse commensal bacteria repertoire. Infection with *Citrobacter rodentium*, which elicits a vigorous T helper type 1 response, but not with *Campylobacter jejuni*, a noninflammatory pathogen, reduces the total number of gut microbes and allows 'preferential,' yet transient, outgrowth of facultative anaerobic γ-Proteobacteria. Gut inflammation induced by dextran sodium sulfate or genetic ablation of the immunosuppressive cytokine interleukin-10 also allows outgrowth of facultative anaerobic organisms and induces similar, albeit less profound, reductions in total gut microbial content. Identification of the host inflammatory component(s) promoting selective outgrowth of aerotolerant bacteria remains for future study. ***CB***

***Cell Host & Microbe* 2, 119–129 (2007)**

Written by Christine Borowski, Douglas C. Braaten & Laurie A. Dempsey

Hijacking integrins

Helicobacter pylori can cause gastric ulcers and cancer, but how this bacterium attaches to host epithelial cells to initiate infection remains unknown. In *Nature*, Kwok *et al.* identify the integrin $\alpha_5\beta_1$ as the ligand recognized by the *H. pylori* CagL protein. CagL is localized to the tip of specialized 'injection pili' that are used to introduce bacterial virulence factors, such as CagA, into host cells. CagL possesses an RGD motif recognized by $\alpha_5\beta_1$, which is found at focal adhesions and becomes activated upon CagL binding. CagA is transferred into host cells and phosphorylated by Src and other focal adhesion kinases, triggering cytoskeletal changes and loss of tight junctions. Such changes initiate the chronic inflammation that accompanies *H. pylori* infection. Blocking CagL-$\alpha_5\beta_1$ interaction offers a means to blunt virulence triggered by this pathogen. *LAD*

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HIV Env ends apoptosis

Although highly effective antiretroviral therapy for HIV infection reduces viral loads to undetectable levels in the blood, latently infected cells remain in 'reservoirs' for many months, posing a problem for eradicating infection entirely. In *PLoS Pathogens*, Stevenson and colleagues find that HIV-infected macrophages resist apoptosis because of signaling mediated by the HIV envelop protein (Env). Production of Env protein in infected cells induces macrophage colony-stimulating factor (M-CSF), which in turn downregulates tumor necrosis factor (TRAIL) receptor 1, thereby preventing TRAIL-induced apoptosis of the infected macrophages. Induction of M-CSF also upregulates transcription of the antiapoptotic factors Bfl-1 and Mcl-1. Neutralizing antibody to M-CSF or reduction of Bfl-1 and Mcl-1 by RNA interference render HIV-infected macrophages highly sensitive to TRAIL-mediated apoptosis. Treatment of infected macrophages with the anticancer drug imatinib, an M-CSF inhibitor, also induces apoptosis. These data demonstrate a mechanism of HIV persistence and a potential therapeutic target for eliminating HIV-infected macrophages. ***DCB***

***PLoS Pathog.* 3, 1281–1290 (2007)**

MyD88 versus ISP-1

Influenza virus infection induces two innate immune signaling pathways that are mediated by the nucleic acid sensing TLR7-MyD88 and RIG-I-ISP-1 receptor-adaptor pairs, but to what extent each one contributes to antiviral responses is not clear. In *Journal of Immunology*, a team led by Shizuo Akira evaluates the contributions of the specific signaling pathways mediated by MyD88 and ISP-1 in the context of influenza infection. At 24 hours after infection, mice genetically lacking either MyD88 or ISP-1 produce normal amounts of interferon (IFN)-α/β and chemokine CXCL10 mRNAs and they control virus infection normally, whereas mice lacking both adaptors do not. In contrast, adaptive immune responses evaluated several days after infection show significantly reduced production of virus-specific antibody and IFN-γ–producing $CD4^+$ T cells. These data demonstrate that innate and adaptive immune antiviral responses to influenza virus infection differ in that the former requires either the MyD88 or the ISP-1 pathway, whereas the latter specifically requires the MyD88-dependent pathway. *DCB*

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