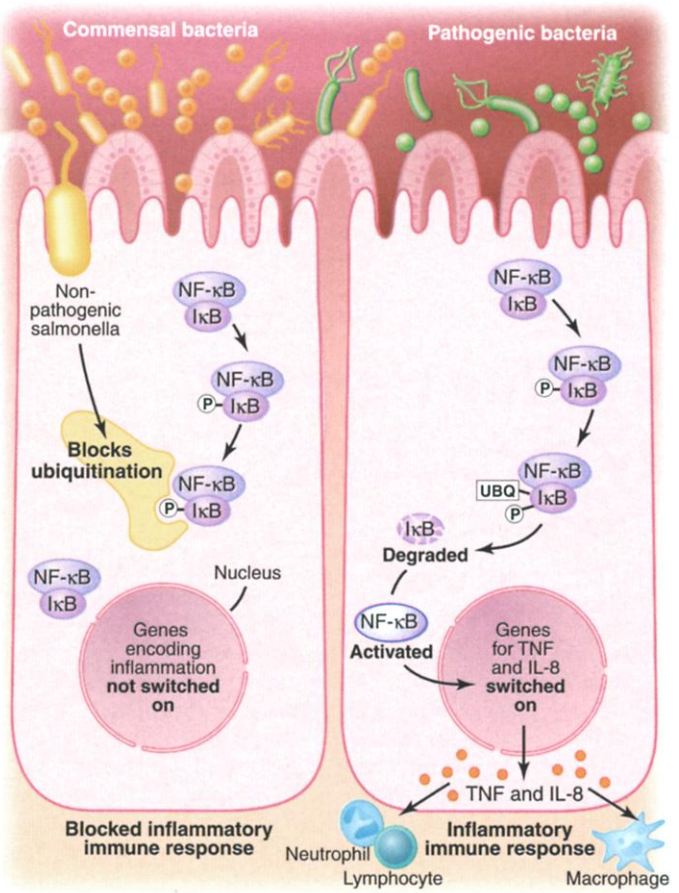
PERSPECTIVES: MICROBIOLOGY

How to Get Along—Friendly Microbes in a Hostile World

Ramnik J. Xavier and Daniel K. Podolsky

The mucosal surface of the gastrointestinal tract interfaces with the complex environment of the gut lumen. This environment contains potentially antigenic dietary constituents, a daunting variety of usually harmless microflora, and bacterial pathogens that either directly invade the mucosa or produce toxins that damage it. To withstand this hostile milieu, the epithelial cells of the gut mucosa have evolved features that make the intestinal epithelium an active immunologic as well as anatomic barrier. For example, these nonclassical immune cells express major histocompatibility complex class I and II molecules, consistent with their ability to participate in adaptive immune recognition of pathogenic bacteria. These cells also express Toll-like receptors on their apical surface that enable them to detect bacterial products and to initiate an innate immune response (*1, 2*).

These capabilities of the gut epithelium result in a continuous, very low level of inflammation within the intestinal mucosa, which is upregulated in response to pathogens or noxious antigens. However, the presence of molecules on the surface of gut epithelial cells that engage antigens also creates a paradox: Why is there an almost complete absence of inflammatory cells such as neutrophils in the gut mucosa, and why is an immune response not mounted to the numerous indigenous bacteria that normally live in the gut? Neish *et al.* (*3*), reporting on page 1560 of this issue, provide a solution to this puzzle. They show that a nonpathogenic strain of *Salmonella* is able to abrogate synthesis of inflammatory cytokines by gut epithelial cells. The bacteria accomplish this by blocking degradation of IκB, an inhibitor of the master transcription factor NF-κB. The investigators propose that through this method the normal gut microflora are able to induce a distinctive form of tolerance in gut epithelial cells. It is intriguing that many of the drugs used to treat inflammatory bowel disease also block NF-κB activation.



A bug's life. Nonpathogenic *Salmonella* bacteria interfere with NF-κB activation in gut epithelial cells. The transcription factor NF-κB is activated by binding of bacterial products such as lipopolysaccharide to the surface of gut epithelial cells. Commensal bacteria that normally inhabit the gut such as nonpathogenic *Salmonella* have devised schemes to interfere with NF-κB activation and hence with the expression of genes involved in the inflammatory response. Nonpathogenic *Salmonella* block ubiquitination (UBQ) and degradation of IκB, an inhibitor that binds to and sequesters NF-κB in the cytoplasm. When IκB is degraded, NF-κB is released and moves to the nucleus where it switches on target genes involved in inflammation. This strategy may explain the virtual absence of inflammation in the gut mucosa despite its constant exposure to a variety of indigenous bacteria.

Most of the bacteria that constitute the gut microflora are commensals, that is, they coexist with intestinal epithelial cells without harming them. However, some are symbionts, that is, both bacteria and host cells benefit from the association. For example, some symbiotic gut bacteria induce intestinal epithelial cells to express glycans (sugar chains), which they are able to usurp as a fuel source. Clearly, a dynamic molecular cross talk exists between the microflora and mucosal epithelial cells of the gut (*4*).

The characteristics that determine whether a microbe is a commensal or a pathogen are still unclear. Pathogenic bacteria have developed strategies that permit them to colonize and invade the gut mucosa. These include novel attachment devices, gene injectors (type III translocation proteins), secreted proteins, and molecules that block phagocytic cells. For example, pathogenic (EPEC) strains of *Escherichia coli* bind to human gut epithelial cells with the protein intimin after they have translocated the receptor for intimin (Tir) into the host cell membrane (*5*). The Neish study is among the first to report that the normal microflora of the gut are able to exploit the molecular pathways of intestinal epithelial cells to prevent a host inflammatory response.

It has become increasingly evident that NF-κB is a major player in the inflammatory immune response of the gut (*6*). This transcription factor is normally bound to its inhibitor IκB, such that its nuclear localization signal is masked and NF-κB is retained in the cytoplasm. Phosphorylation of IκB by IκB kinases α and β (IKKα and IKKβ) results in its ubiquitination and degradation, leading to the release of NF-κB, which then moves to the nucleus where it switches on expression of various cytokine and chemokine genes that encode mediators of the inflammatory response.

A number of bacterial pathogens have evolved strategies to commandeer NF-κB activation. For example, the Yop protein of the plague bacillus *Yersinia enterocolitica* directly interferes with the activity of

The authors are in the Gastrointestinal Unit, Massachusetts General Hospital, 55 Fruit Street, GRJ-719, Boston, MA 02114, USA. E-mail: podolsky.daniel@mgh.harvard.edu

CREDIT: K. SUTLIFF

IKKβ in epithelial cells (*7*). Neish *et al.* now show that nonpathogenic bacteria have also evolved ways to interfere with NF-κB activation. These investigators took advantage of a cultured cell line derived from a human colon cancer that has most of the features of normal colon epithelium. When they added nonpathogenic (commensal) *Salmonella* to the apical surface of this cell layer, they found that the bacteria prevented ubiquitination and hence degradation of phosphorylated IκB; NF-κB remained bound to IκB in the cytoplasm, and so the genes encoding inflammatory cytokines were not switched on (see the figure). The observations of Neish *et al.* need to be confirmed in vivo and the bacterial products that prevent ubiquitination of IκB identified. Future studies should also address how the default "no NF-κB activation" state maintained by nonpathogenic bacteria is overridden so that the gut epithelium is able to mount an immune response against pathogenic bacteria.

What is the physiological significance of the effect of commensal bacteria on NF-κB activation? Two recent reports suggest that oral administration of nonpathogenic bacteria (probiotics) may be effective in the treatment of some patients with inflammatory bowel disease (*8, 9*). Although the way in which probiotics work is largely unknown, these bacterial species may also be able to abrogate NF-κB activation and quell the host's inflammatory response. A better understanding of how the normal gut microflora remains largely invisible to the host intestinal epithelium may provide a clearer picture of the molecular pathways of chronic inflammation. Indeed, dysregulated interactions between microbe and host might underlie many of the poorly understood chronic inflammatory disorders of the gastrointestinal tract.

References

1. R. Medzhitov, P. Preston-Hurlburt, C. A. Janeway Jr., *Nature* **388**, 394 (1997).
2. E. Cario *et al.*, *J. Immunol.* **164**, 966 (2000).
3. A. S. Neish *et al.*, *Science* **289**, 1560 (2000).
4. L. Bry, P. G. Falk, T. Midtvedt, J. I. Gordon, *Science* **273**, 1380 (1996).
5. L. M. Higgins *et al.*, *Science* **285**, 588 (1999).
6. M. Karin and Y. Ben-Neriah, *Annu. Rev. Immunol.* **18**, 621 (2000).
7. K. Orth *et al.*, *Science* **285**, 1920 (1999).
8. B. J. Rembacken *et al.*, *Lancet* **354**, 635 (1999).
9. P. Gionchetti *et al.*, *Gastroenterology* **119**, 305 (2000).

PERSPECTIVES: ASTRONOMY

Monsters at the Heart of Galaxy Formation

John Kormendy

Black holes 10^6 to $10^{9.5}$ times as massive as the sun were first invoked in the 1960s to explain the enormous energy output of active galactic nuclei (AGNs) such as quasars (*1–4*). These supermassive black holes (BHs) stand in sharp contrast to ordinary BHs, which have masses of only a few solar masses ($M_\odot$) and which are well known to form when massive stars die. The origin of supermassive BHs is unknown, and their existence long remained a hypothesis. By the mid-1980s, BH "engines" had become part of the theoretical framework for understanding AGN activity (*5, 6*), but evidence for their existence was still lacking. In the following decade, much effort was invested in looking for dynamical evidence of dark objects in galactic nuclei (*7, 8*). That evidence is now strong, and in two objects—our Galaxy and NGC 4258—the dark mass must live inside such a small radius that astrophysically plausible alternatives to a BH can be excluded (*9*).

Enhanced online at www.sciencemag.org/cgi/content/full/289/5484/1484

Until recently, BHs were studied mainly to understand the spectacular but restricted phenomena of AGNs. But the situation is changing rapidly. Surveys with the Hubble Space Telescope (HST) are finding BHs in every galaxy that has an elliptical-galaxy–like "bulge" component (*10, 11*). These observations strengthen hints from ground-based spectroscopy (*12*) that BHs are standard equipment in galaxy bulges. They indicate that BH growth and galaxy formation are closely linked. These results have profoundly changed astronomers' views of BHs: More than just exotica needed to explain rare AGNs, BHs are becoming an integral part of our understanding of galaxy formation.

This change in perspective was much in evidence in an all-day session on BHs held on 6 June 2000 at the 196th meeting of the American Astronomical Society. Detections of at least 15 new BHs were reported, bringing the total number available for study to at least 34. The big news was a new correlation between BH mass, $M_\bullet$, and host galaxy properties, announced independently by Karl Gebhardt and coworkers (*13, 14*) and by Laura Ferrarese (*15*) and collaborators. Both groups have found that BHs are more massive in galaxies whose stars have larger random velocities σ (see the right panel of the figure). A similar correlation (*7, 16*) was previously observed between BH mass and the total luminosity L_{bulge} of the bulge (a surrogate for its total mass): More massive BHs live in more massive bulges (see the left panel of the figure). This is not surprising because many properties of astronomical objects scale with mass and because more massive galaxies are expected to have more fuel to feed BHs. But the scatter in the $M_\bullet$-L_{bulge} correlation is substantial, and a few galaxies have anomalously large or small BHs. In contrast, the new correlation has essentially zero scatter. The figure shows all BHs detected to date. If the sample is restricted to the galaxies with the most accurate mass measurements, then the scatter in the right panel is consistent with the error bars.

In astronomy, tight correlations have a history of leading to fundamental advances. The correlation between $M_\bullet$ and σ implies a connection between galaxy formation and the process that feeds BHs, building them up to their present masses while making them shine as quasars. To be accreted onto a BH, fuel must be robbed of almost all of its angular momentum. This is difficult, so the process of "feeding the monster" is poorly understood (*17*). But tying BH growth to galaxy formation is useful progress.

Why is a BH that is unusually massive for its luminosity also high in σ, so that exceptions in the left panel of the figure are not exceptions in the right panel? There are several possibilities (*18*). For example, the stellar mass-to-light ratio could be anomalously large; equilibrium demands more velocity for more mass. This, however, proves not to be the main effect. Instead, bulges with unusually high velocity dispersions are observed to be unusually compact. That is, they have higher surface brightnesses and smaller radii than is normal for their luminosities. Therefore, the stars are closer together, so their gravitational forces on each other are larger and they must move faster. This means that when a galaxy is hotter than average, it has undergone more dissipation than average and has collapsed inside its dark halo to a smaller size and higher

The author is at the Department of Astronomy, University of Texas at Austin, RLM 15.308, Austin, TX 78712, USA. E-mail: kormendy@astro.as.utexas.edu