Indeed to promote sensitivity to antiandrogen therapy at late stages.

**Nuclear hormone receptor regulation by RB/E2F in other cancers**

Finally, if RB modulates the expression and activity of AR in prostate cancer, are other nuclear hormone receptors regulated by RB/E2Fs in other cancers, and does the efficacy of relevant endocrine therapies depend upon RB status? Early loss of RB is generally linked to responsiveness to conventional genotoxic therapies in various tumor types, but is the opposite true for endocrine therapy? For example, does RB loss mitigate against hormone therapy in breast cancer, as has been suggested previously (14)? Previous work has also identified a direct interaction between RB and the glucocorticoid receptor (15). Does this come into play in modulating stress responses in cancer etiology? Overall, the work of Sharma and colleagues (4) raises many intriguing questions that have major implications for how we diagnose and treat prostate cancer, but to what extent we must reconsider a role for RB in the late stages of and for therapy of other human cancers remains to be seen.

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**Which species are in your feces?**

Colby Zaph

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Nosocomial infections (i.e., infections acquired as a result of treatment in a hospital or health care unit) result in approximately 100,000 deaths and cost more than 25 billion dollars per year in the US alone. These infections are caused primarily by bacteria and affect mainly immunosuppressed patients. However, not all patients acquire infections, and the events leading up to infection are unclear. In this issue of the JCI, Ubeda et al. report how acquisition of one such infection, vancomycin-resistant *Enterococcus faecium* (VRE), is linked to a shift in the microbial flora following antibiotic treatment. This study highlights the potential for high-throughput sequencing of intestinal microbiota to be a means to identify high-risk populations.

Nosocomial infections are infections acquired as a result of treatment in a hospital or health care unit. They are increasingly becoming a significant public health problem. It is thought that 5%–10% of patients entering hospitals worldwide develop a hospital-acquired infection (HAI) (1). The global growth of antibiotic-resistant bacterial strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE), has complicated the control of HAIs and highlights the need for a better understanding of how HAIs develop, are acquired, and may be controlled.

Intestinal *Enterococcus* infections are among the most common type of infection acquired by hospitalized patients. While enterococcal infections are much less capable of causing disease than HAIs such as *Clostridium difficile* and *S. aureus*, they still cause complications, prolong hospital stays, and can be fatal, particularly those caused by VRE. Fatal VRE infections, which occur upon bacterial invasion of the bloodstream, primarily affect immunocompromised patients such as those undergoing bone marrow or hematopoietic stem cell transplantation (HSCT) (2). It has been estimated that up to 50% of HSCT patients acquire VRE, and infection with VRE is independently associated with increased mortality in these patients (3). Identifying high-risk patients and developing novel methods to combat VRE are critical components in combating HAIs. The study by Ubeda et al. in this issue of the JCI begins to address this in both mice and humans using high-throughput sequencing analysis of commensal flora populations (4).

**Commensal flora and susceptibility to infection**

Over the past several years, interest in understanding the relationship between the commensal flora and disease states has increased markedly. It is clear that changes in the flora have a dramatic effect on the...
Antibiotic treatment leads to long-term changes in the commensal flora and susceptibility to VRE. (A) In the steady state, interactions between commensal bacteria and host cells in the intestine — primarily epithelial cells — result in the production of antimicrobial effector proteins (AMPs), such as REGIIIγ and RELMβ, that shape the commensal populations. The production of AMPs in this context may be dependent on NF-κB, which is presumed to be activated by TLR recognition of commensal bacterial products. In this state, mice are resistant to VRE infection. (B and C) Following transient antibiotic treatment, the numbers and diversity of the bacterial populations are severely reduced. Antibiotic treatment — presumably through a reduction in commensal bacteria — also results in decreased expression of AMPs. These changes result in long-lived increased susceptibility to VRE.

Antibiotics drastically change the microbiome

High-throughput pyrosequencing of bacterial 16S rDNA sequences allows for nonbiased, global analysis of the relative composition of bacterial populations in vivo. Using this technique, Ubeda et al. characterized the effects of several antibiotic regimens on the composition of the intestinal microbiome in mice (4); that is, they investigated how antibiotic treatment affected the relative frequencies of bacterial populations by quantifying the genomes of all the microorganisms that live in the intestine of a healthy adult mouse (the microbiome). Interestingly, a transient 7-day antibiotic treatment resulted in a dramatic shift in the commensal populations, with the outgrowth of several minor populations of bacteria, including Enterobacteriaceae, Clostridium, and Enterococcus species, bacteria that tend to be causative agents of nosocomial infections. Furthermore, several populations (primarily from the Bacteroidetes phylum) failed to recover after antibiotic withdrawal. These changes in the flora allowed normally resistant mice to become susceptible to VRE infection. Thus, the composition of the bacterial flora was critical in restraining the outgrowth of potentially pathogenic species, a pattern that has also been observed in animals with Salmonella typhimurium infection (19–21).

Consistent with previous studies (10), these changes in bacterial populations observed by Ubeda and colleagues were long-lived and failed to return to normal, even after several months (4). One striking finding in the study of Ubeda et al. was...
that, even 2 months after antibiotic treatment, mice were still susceptible to VRE infection. These results suggest that transient antibiotic treatments result in long-term changes in the commensal bacterial populations that predispose the host to certain infections. Although the molecular mechanisms associated with this increased susceptibility remain unclear, the potential identification of a signature at the level of bacterial populations may provide a novel analytical tool to identify patients predisposed to fatal VRE infections.

Relevance to human disease
To directly test whether a bacterial population signature could identify patients predisposed to fatal VRE infections, Ubeda et al. examined the microbiomes of human volunteers treated with ciprofloxacin, who lost bacterial diversity but did not acquire overgrowth by a single species (10). This highlights the important role of the host immune response in regulating commensal bacterial populations (Figure 2). The production of immune mediators in the gut — such as IgA (22); effector T cell– and DC-derived cytokines, including IL-17A, IL-22, and IL-23 (23, 24); and regulatory molecules, including TGFβ and retinoic acid (25) — may all contribute to maintaining a balanced commensal flora. Thus, the status of the immune system is also a critical component in commensal homeostasis, further highlighting the closely linked host-commensal relationship.

Future studies
The study by Ubeda and colleagues (4) raises questions about the current use of antibiotics and how at-risk patients are identified. Antibiotic treatment of high-risk patients will not stop, but a closer examination of the effects of different classes of antibiotics on commensal populations and their subsequent consequences on infections should be investigated. While Ubeda et al. focused on VRE (4), other HAIs may not behave similarly, and thus global strategies may not apply. However, the use of high-throughput sequencing allows for a nonbiased global analysis of commensal populations, thereby potentially identifying distinct signatures in other HAIs. Furthermore, it is clear that the interactions between the commensal flora and the host immune system are bidirectional, with important ramifications for intestinal homeostasis. Future studies correlating intestinal and peripheral immune responses with commensal signatures may provide novel methods not only to affect the commensal flora, but also to regulate immune responses through manipulation of commensal populations.

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A lineage of CD4+ T cells known as Th17 cells, which are derived by exposure of naive CD4+ T cells to IL-6 and TGF-β, have been implicated in several autoimmune diseases. In this issue of the JCI, studies by Acharya et al. and Melton et al. show that TGF-β is activated at the DC/CD4+ T cell synapse by αv integrins and that this activation is required for Th17 differentiation and autoimmunity in the central nervous system. Thus, these studies offer a potential therapeutic target in fighting autoimmune diseases.

Th17 cells are a recently identified and critical component of the adaptive immune system (1–3). They are characterized by the production of IL-17A and IL-17F as well as other cytokines such as IL-22. These effector cytokines have been shown to be critical for clearance of certain bacteria and fungal pathogens (4). In addition, vaccine-induced Th17 cells have been shown to have broad protective roles against extracellular pathogens such as Streptococcus pneumoniae and to control Th1 cell migration in the context of vaccination against the intracellular pathogen Mycobacterium tuberculosis (4). However, this protective aspect of the Th17 lineage comes at a cost, as these cells have been implicated in autoimmune diseases such as multiple sclerosis, psoriasis, and rheumatoid arthritis (1–3).

Several groups have shown that naive CD4+ T cells differentiate into Tregs in the presence of TGF-β (5, 6). However, in the presence of TGF-β and IL-6, naive CD4+ T cells differentiate into Th17 cells (6–8). Early work by Li et al. (9) showed that the source of TGF-β in this context was the CD4+ T cell. However, TGF-β is secreted from cells in an inactive form, in which bioactive TGF-β is in complex with its latency-associated peptide (LAP) through noncovalent bonds. Two studies in this issue of the JCI demonstrate that DCs activate TGF-β in an integrin-dependent fashion (10, 11), suggesting that the activation of TGF-β occurs at the DC/T cell synapse (Figure 1) and that this activation is required to drive the differentiation of Th17 T cells.

**TGF-β and integrins**

TGF-β is a multifunctional cytokine involved in many aspects of immunology, angiogenesis, and epithelial growth as well as in pathogenic states such as fibrosis (12). Activation of TGF-β has been an area of intense study. Mechanisms identified as leading to the disruption of the noncovalent interaction between LAP and bioactive TGF-β and thus activation of TGF-β...