within 4 years, all islands had lost their top predators: the jaguar, puma, and harpy eagle. Thus, as habitat area shrinks, predators are lost before their prey, and parasitoids are lost before their hosts—just as one would expect from the decrease in population densities as one ascends the trophic ladder, and from the inverse relation between extinction probability and population size.

Those species that do manage to persist on small islands tend to become far more abundant than populations of the same species on larger, more species-rich islands. The increase in abundance is by a factor of 2 for birds, 10 for iguanas and capuchin monkeys, 30 for howler monkeys, 35 for rodents, 100 for leaf-cutter ants, and a large but unmeasured factor for tarantulas. Part of the explanation for increased abundance is ecological release from competition: When competing species are removed, the resources that would have gone to them become available to the persisting species. The other part of the explanation is escape of prey from control by predators or parasitoids that limit their abundance on larger islands. For instance, on small islands leaf-cutter ants escape control by armadillos, army ants, and phorid flies, and birds escape control by monkeys, but on medium-sized islands the armadillos themselves escape control by jaguars, and the monkeys escape control by harpy eagles. The superabundance of small herbivorous animals on small islands acts through a trophic cascade to weed out palatable plant species and to convert the landscape into a forest of "herbivore-proof" plants. This mirrors the way in which goats convert islands into landscapes of goat-proof plants, and the exploding deer population—following the decline of wolves, bears, and human hunters in the eastern United States—has eliminated dozens of palatable woodland plant species.

Although this issue's report by Terborgh *et al.* emphasizes control of prey by their predators, and of plants by their herbivores, there is far more to the Lake Guri Project than those two conclusions. The project reminds me of a kaleidoscope that gets shaken up hundreds of times, with some general tendencies emerging among the resulting patterns, but with fascinating differences of detail because of effects of chance, yielding bizarre communities that would never exist at equilibrium. For instance, a herd of capybaras, trapped on one island too remote for them to escape by swimming, has converted that island's understory into bare ground covered with capybara dung. Howler monkeys similarly trapped on remote islands have soared in abundance and proceeded to shut down their per capita output of baby howlers fourfold. Capuchin monkeys survived on only two medium-sized islands, where they have gone on to clean out 90% of bird population densities. The forest on two islands with agoutis is turning into a forest of plant species whose seeds agoutis like to bury. Leaf-cutter ants forage mainly just at night on islands plagued with phorid flies that parasitize them, but the ants run around boldly in daylight on an island with few flies.

Perhaps the most important message of Lake Guri concerns the virtues of unplanned natural experiments. Professors of field biology urge their students to avoid "bird watching" not driven by hypotheses formulated in advance, and to go into the field only after designing a well-controlled experiment to discriminate between competing hypotheses. All too often, the sad result is that the student succeeds in answering that original question, and thereby fails to notice some much more interesting question at the same field site. Unplanned natural experiments create ecological communities that we would never have dreamed of creating, or that laws, moral scruples, or practical obstacles would have prevented us from creating even if we had dreamed of them. Who would or could locally exterminate jaguars, armadillos, or army ants, or make populations of capybaras or tarantulas explode in numbers? Nowhere else can one find such bold, large-scale experiments as on habitat fragments created by nature.

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PERSPECTIVES: IMMUNOLOGY

A Molecular Gut Reaction

Florence Lambolez and Benedita Rocha

The mucosal surfaces of the body are the regions where individuals and the environment meet. For example, the gut mucosa is in continuous contact with food antigens, the enteric commensal bacteria that constitute the gut flora, and potential pathogens that enter the host through the intestine. The gut epithelium and its mucous layer form a major barrier, trapping invading pathogens, which are then eliminated when the gut epithelium is shed. Maintaining the integrity of gut epithelium as well as ensuring its continuous turnover are essential for local defense. In the gut, local defense depends in part on T lymphocytes called intraepithelial lymphocytes (IELs) that are nestled among gut epithelial cells. These T cells modulate homeostasis of the gut epithelium through local production of cytokines (*1*), but exactly how they do this is unclear. On page 1936 of this issue, Leishman *et al.* (*2*) reveal the two molecules that enable IELs both to maintain the gut epithelium and to regulate its turnover.

IELs have unique properties. First, although they are T cells, they include a major subpopulation that is generated locally rather than within the thymus (*3*). During maturation of the thymus, T lymphocytes that recognize self antigens are eliminated. The "locally generated" IELs include T lymphocytes that express self-reactive T cell receptors (TCRs) (*4, 5*). Second, unlike thymus-derived naïve T cells, IELs are not in a "resting" state. Instead, they more closely resemble "effector" T cells, the lymphocytes present in other organs that are activated during acute immune responses. Before naïve T cells undergo division and differentiation into effector lymphocytes, they must be stimulated by antigen. In contrast, both effector T cells and IELs do not need this "priming" and, upon encounter with antigen, immediately produce cytokines that result in killing of infected target cells (*6*). Yet there must be some way that these effector cells are controlled locally. If antigen stimulation induces T cell division, what prevents IELs from dividing extensively and disrupting the gut epithelium? If self-reactive IELs have the potential to kill gut epithelial cells, what prevents them from doing so? According to Leishman and colleagues, unique local characteristics appear to modulate IEL behavior.

T lymphocytes recognize antigenic peptides through their TCRs. Thymus-derived T cells also express CD8, a corecep-

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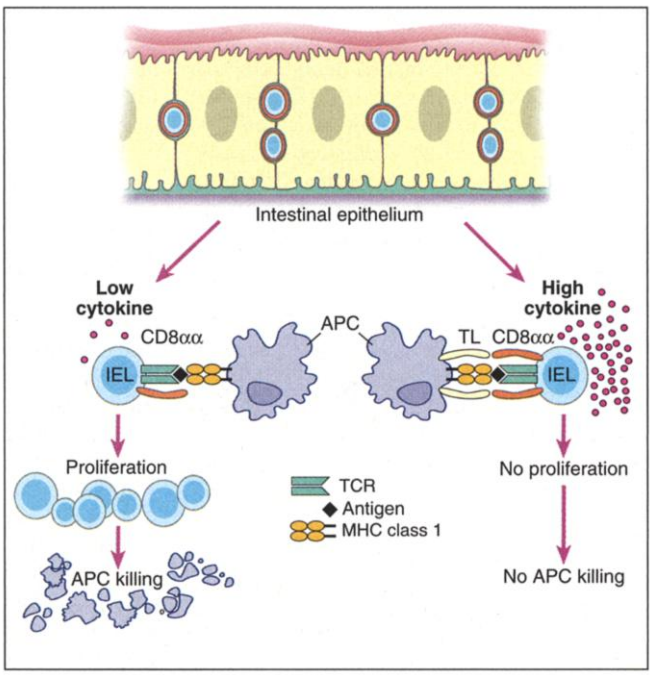
tor that considerably enhances TCR-mediated responses. The CD8 complex of these cells is a heterodimer comprising CD8α and CD8β chains. This heterodimer interacts with classical major histocompatibility (MHC) class I molecules, which are expressed by virtually all cells in the body. These MHC class I molecules present antigenic peptides to CD8αβ T cells. Most IELs, however, express a different CD8 complex—a CD8αα homodimer composed of two α chains. Leishman *et al.* demonstrate a high-affinity interaction between the CD8αα homodimer and an unusual (nonclassical) MHC class I molecule called thymus leukemia antigen (TL). The TL molecule has two interesting characteristics: It does not present antigenic peptides (in contrast to its classical MHC class I relatives), and it is expressed almost exclusively by epithelial cells of the small intestine (*7*). Strong interactions between CD8αα and TL enable IELs to interact directly and locally with the gut epithelium, but independently of antigen recognition and TCR specificity.



TL death us do part. Interactions between CD8αα and TL regulate the behavior of intraepithelial lymphocytes (IELs). Epithelial cells of the small intestine (yellow) express the TL molecule and are overlaid by a layer of mucus (pink). IELs (blue), localized among the gut epithelial cells, express CD8αα (red). **(Bottom, left)** If isolated IELs are stimulated by antigen-presenting cells (APCs) that express antigen but lack TL, they divide and kill target cells but secrete low amounts of cytokines. **(Bottom, right)** If APCs express both antigen and TL, IELs secrete high amounts of cytokines but do not divide and do not kill target cells.

What are the consequences of this interaction? Leishman *et al.* (*2*) compared IEL responses to antigen-presenting cells that did or did not express the TL molecule (see the figure). Surprisingly, they found that CD8αα-TL interactions could either enhance or suppress IEL responses. Such interactions considerably enhance cytokine release by IELs but inhibit their proliferation and cytotoxicity. These apparently paradoxical effects make a lot of sense in the particular environment of the small intestine. By inhibiting proliferation, CD8αα-TL interactions prevent IELs from dividing and disrupting the gut epithelium. In addition, by blocking T cell killer activity, these interactions prevent the elimination of healthy epithelium by self-reactive IELs (*2*). In contrast, by favoring interferon-γ production, the binding of CD8αα to TL may promote turnover of gut epithelium (*1*).

These results indicate that the small intestine and IELs have developed a unique way to control local homeostasis and to ensure continuous epithelial cell renewal. The mechanisms by which CD8αα-TL interactions induce such paradoxical effects on IEL responses remain to be discovered. Hints may come from certain types of inflammatory bowel disease that are associated with a deficiency in regulatory T lymphocytes, or overproduction of the inflammatory cytokine interleukin-10 (*8*). It is possible that in these disorders there is a severing of the interaction between CD8αα and TL. If so, then these diseases may yield valuable information about the maintenance of gut homeostasis.

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PERSPECTIVES: NETWORK ANALYSIS

The Structure of the Web

Jon Kleinberg and Steve Lawrence

In the span of a decade, the World Wide Web has grown from a small research project into a vast repository of information and a new medium of communication. Unlike other great networks of the past century—such as the electric power grid, the telephone system, or the highway and rail systems—the Web does not have an engineered architecture. Rather, it is a virtual network of content and hyperlinks, with over a billion interlinked "pages" created by the uncoordinated actions of tens of millions of individuals.

Because of the decentralized nature of its growth, the Web has been widely believed to lack structure and organization as a whole. Recent research, however, shows a great deal of self-organization. Analyses of the Web's network of hyperlinks have revealed an intricate structure that is proving to be valuable for organizing information, improving search methods, and understanding the Web in a broader technological and social context.

A recent study (*1*) indicates that the Web contains a large, strongly connected core in which every page can reach every other by a path of hyperlinks. This core contains most of the prominent sites on the Web. The remaining pages can be characterized by their relation to the core: Upstream nodes can reach the core but cannot be reached from it, downstream nodes can be reached from the core but cannot reach it, and "tendrils" contain nodes that can neither reach nor be reached from the core.

In fairly large snapshots of the Web, these four components—core, upstream, downstream, and tendril regions—have roughly comparable sizes. Moreover, the core is very compact: The shortest path from one page in the core to another involves 16 to 20 links on average, a "small-world" situation in which typical distances

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