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Hide and seek

An online dictionary defines evasion as "the act of physically escaping from something (an opponent or a pursuer or an unpleasant situation) by some adroit maneuver". Unfortunately for us, successful infectious agents and tumors have developed such "adroit maneuvers", which they use to escape immune responses and maximize their probability of being transmitted to a fresh host. The fact that immunocompetent individuals can develop cancer and succumb to microbial infections indicates that the immune system is an imperfect "pursuer".

In this issue of *Nature Immunology*, we bring you a special Focus on immune-evasion strategies. Similar to our previous Focuses, our website (http://www.nature.com/natureimmunology/) will provide regular updates to our round-up of recent articles on immune escape and contains an annotated list of classic articles on immune evasion and links to major articles on this topic published by the Nature journals. Online access is free-of-charge for the next three months to all those who register.

Investigations into evasion tactics have proven to be extraordinarily fertile ground for fresh immunological insights, such as the discovery of an entirely new family of KIR-like genes (LIRs), based on their similarity to the NK cell decoy UL18, produced by cytomegalovirus. Perhaps more importantly, the study of immune-evasion strategies can provide us with more targets or better agents for immunotherapy. In designing this issue, we have deliberately chosen to include discussion of a wide array of systems, from tumor to microbial. As quickly becomes apparent, the obvious and not so obvious parallels among systems and mechanisms (summarized in an overview by Phillips) should help cross-pollinate the field and hasten improved approaches for immunotherapy.

When a pathogen invades a mammalian host, an innate immune response is triggered, after which an adaptive immune response ensues to eradicate the infection and establish memory. The evasion strategies that pathogens have devised are highly diverse, ranging from the passive to the aggressive. One of the most passive evasion strategies is to hide inside the host cell in a dormant form, as is the case with some bacteria (see the review by Dougan and colleagues). However, if the pathogen wants to come out of hiding, it must resort to other more aggressive mechanisms. To circumvent immune responses, for instance, *Leishmania* can actively and selectively inhibit IL-12p40 transcription (see the review by Sher and Sacks).

Pathogens, particularly viruses (see the review by Ware and colleagues), need to control cell death so that they can complete their replication cycles. Pathogens and tumors must also evade the antigen processing and presentation system (for coverage of viral tricks, see Yewdell and Hill's review; bacterial strategies are covered in the review by Normark and colleagues). Of course, if the pathogen chooses to down-regulate surface MHC class I proteins, it faces an additional problem, namely, susceptibility to NK cell attack. As always, viruses have evolved means to slip through these defenses as well (see the review by Strominger and colleagues). And to completely confound the host, extracellular pathogens such as trypanasomes have evolved complex antigenic variation systems that keep them one step ahead of their pursuers.

Hard evidence has accumulated that the immune system, often to its own detriment, helps "edit" its enemies (see the review by Schreiber and colleagues on tumor–immune system interactions). Selective pressure from CTLs actually encourages the outgrowth of retrovirus mutants that can escape CTL recognition, a phenomenon that is particularly well documented for HIV. Continuous immunosurveillance not only begets virus escape, but also affects tumor development. The concept of cancer immunosurveillance by the immune system was largely abandoned in the 1970s because the rate of tumor growth in immunodeficient and wild-type mice was thought to be similar. Schreiber and colleagues note in their review that the cancer immunosurveillance hypothesis is enjoying a renaissance—but with a few refinements. One of these is the reality of tumor editing by the immune system. The other is inclusion of numerous evasion mechanisms, such as MHC down-regulation (see Khong and Restifo's review), that are often analogous to those used by microorganisms.

How important are these immune-evasion strategies? We still lack a clear demonstration that the many mechanisms identified are critical for pathogen persistence. Much data purporting to demonstrate immune escape were drawn from *in vitro* findings. More *in vivo* experiments are needed to verify the physiological relevance of particular evasion strategies. Nevertheless, some immune-escape mechanisms *in vitro* are so strong that it is unlikely that the interaction is insignificant. Pathogens and tumors would hardly have developed an array of immunoevasion mechanisms if they did not provide some survival advantage. Although our knowledge of immune escape has advanced considerably in recent years, much more data is needed. It is our hope that by pulling together research on evasion from such diverse areas, we have provided a resource that can help hasten the day when the pursuer can be assured of catching its prey.