Immunity and Invasive Success

Stuart E. Reynolds

Science **340**, 816 (2013);
DOI: 10.1126/science.1238998

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

ECOLOGY

Immunity and Invasive Success

The Asian harlequin ladybird has successfully invaded ecosystems around the world with the help of a pathogen that it carries.

Stuart E. Reynolds

Biological invasions can be serious threats to local and even global biodiversity, but despite much study, little is known about the factors that enable particular introduced species to be successful invaders (*1*). On page 862 of this issue, Vilcinskas *et al*. (*2*) report an important advance in understanding these factors. They show that the almost worldwide invasive triumph of the harlequin ladybird *Harmonia axyridis* (*3*) depends on the presence of a coexisting pathogen within the invading insect and also the insect's immunity to the pathogen.

This discovery recalls some famous invasions in human history. In *Guns, Germs, and Steel* (*4*), Diamond explored why small numbers of invaders from a technically more "advanced" continent were often able to overthrow much larger numbers of long-established residents of a less "advanced" one. He noted that, among other factors, the diseases of advanced human societies have been instrumental in enabling them to conquer less advanced ones. In the 16th century conquest of the Americas, smallpox, measles, and other diseases imported by the Europeans decimated the aboriginal peoples, spreading even in advance of the arrival of the invaders. Long coexistence had led the genomes of the European pathogens to be lavishly provided with virulence genes and those of the European hosts to be replete with defenses against them. The immune systems of native Americans were adapted to defending against a different set of associated pathogens and were unequal to the task of defending against European germs. This was thus a case, at least in part, of conquest by an invading host-pathogen alliance.

Biological invasions may also be promoted by the presence within the invading population of endemic pathogens to which invaders but not hosts are resistant or tolerant (*5*, *6*). For example, populations of the native European crayfish *Austropotamobius pallipes* have been locally extinguished by the crayfish plague *Aphanomyces astaci* carried by the introduced North American crayfish *Pascifastacus leniusculus* (*7*).

Department of Biology and Biochemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK. E-mail: s.e.reynolds@bath.ac.uk

Concealed weapon. Vilcinskas *et al*. show that the invasive Asian harlequin ladybird, *H. axyridis*, carries a pathogen that is lethal to other ladybird species.

The example reported by Vilcinskas *et al*. allows the mechanism of toleration by the invader to be explored. The authors have found that invasive harlequin ladybirds are chronically infected with a blood parasite, a microsporidian from the genus *Nosema* that is tolerated by *H. axyridis* but lethal to closely related ladybirds such as *Coccinella septempunctata* and *Adalia bipunctata*.

Microsporidia are intracellular, spore-forming fungal parasites. Chronic asymptomatic microsporidian infections are relatively common among some insects, whereas in other insect hosts the parasites are lethal. It is not known how *Nosema* is transmitted among ladybirds, but two features of the host's ecology may facilitate the spread of the parasite. First, extensive intraguild predation occurs, in which ladybird larvae attack and consume each other. Feeding by C. *septempunctata* on eggs and larvae of *H. axyridis* is known to be lethal (*8*). Second, in winter harlequin ladybirds form large aggregations, and this close proximity may facilitate conspecific transfer of infection (see the figure).

The presence of microsporidia in the invading ladybirds is only half of the story, however. Why is *H. axyridis* able to tolerate *Nosema*, whereas other ladybirds are not? We might similarly ask why during the invasion of the Americas, Europeans were able to resist their own diseases when native inhabitants were not. Long exposure to a parasite leads a host to acquire defenses that, if they do not enable it to rid itself of infection, at least allow it to tolerate the parasite.

A similar reasoning appears to explain why *H. axyridis* is not killed by *Nosema*. The harlequin ladybird's innate immune system is constitutively activated by the presence of the microsporidian and secretes huge amounts of an antimicrobial alkaloid, harmonine, into the insect's hemolymph. Other ladybirds lack this chemical. Further, the harlequin ladybird genome contains an exceptionally large number of antimicrobial peptide genes. These defenses do not kill the parasites, but the low abundance of *Nosema* transcripts in *H. axyridis* RNA suggests that the parasite is kept in a quiescent state. Perhaps when released from such controls in other species of ladybirds, the microsporidians are much more damaging to their hosts.

It has been proposed (*9*) that invasive species should invest more in their immune systems than noninvasive species, because in newly colonized habitats the invaders must resist parasites to which they are not preadapted. At first glance, the findings for *H. axyridis* appear to bear this out: Immune defenses are expensive, and harmonine is accumulated to very high levels in harlequin ladybirds. But here the necessity for greater expenditure on immune defenses appears driven by the need not only to resist novel parasites in the new environment but also to

Published by AAAS

tolerate old parasites brought from the old one. The expensive immune defenses of *H. axyridis* have, thus, allowed *Nosema* to be used as a biological weapon against sympatric competitors, a trait only revealed as a preadaptation to invasiveness when the insect was introduced by human agency into new ecosystems far from home.

References

1. J. G. Ehrenfeld, *Annu. Rev. Ecol. Evol. Syst.* **41**, 59 (2010).
2. A. Vilcinskas, K. Stoecker, H. Schmidtberg, C. R. Röhrich, H. Vogel, *Science* **340**, 862 (2013).
3. J. J. Sloggett, *Entomol. Sci.* **15**, 261 (2012).
4. J. Diamond, *Guns, Germs, and Steel* (Norton, New York, 1997).
5. J. Prenter, C. Macneil, J. T. A. Dick, A. M. Dunn, *Trends Ecol. Evol.* **19**, 385 (2004).
6. A. Strauss, A. White, M. Boots, *Funct. Ecol.* **26**, 1249 (2012).
7. J. C. Dunn, H. E. McClymont, M. Christmas, A. M. Dunn, *Biol. Invasions* **11**, 315 (2009).
8. A. Katsanis, D. Babendreier, W. Nentwig, M. Kenis, *BioControl* **58**, 73 (2013).
9. K. A. Lee, K. C. Klasing, *Trends Ecol. Evol.* **19**, 523 (2004).

10.1126/science.1238998

CELL BIOLOGY

Insulin Finds Its Niche

Localized insulin signaling allows organ-specific rather than organism-level responses to the environmental conditions.

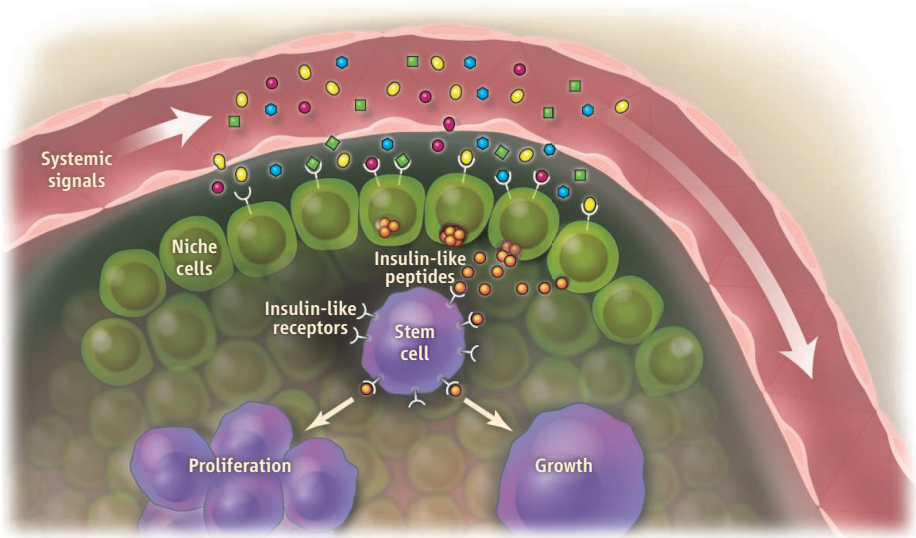
Seth W. Cheetham and Andrea H. Brand

Coordination of organ growth and metabolism in response to changing environmental conditions is essential for physiological homeostasis. A central metabolic control mechanism in multicellular organisms is insulin signaling. Under conditions of elevated blood sugar, insulin promotes the storage of glucose in tissues such as muscle, fat, and liver. Classically, the role of insulin signaling is systemic. In mammals, insulin is produced by pancreatic beta cells and released into the bloodstream in response to increased concentrations of blood glucose, inducing global changes in growth and metabolism. Intriguingly, recent studies have demonstrated that insulin signaling can also occur locally, over a short range. Why have local insulin signaling? Local signals allow organ-specific, rather than organismal responses to changing environmental conditions (see the figure). This allows the modulation of the growth and development of individual tissues to be separately controlled, and raises the question of whether this phenomenon could be exploited for therapeutic strategies. Many of these recent findings have arisen from research in invertebrates; however, there are striking parallels in mammals.

The dynamic control of stem cell populations in response to a variety of stimuli is critical to organismal adaptation to environmental conditions. Local insulin signaling has emerged as playing a critical role in regulating stem cell behavior. In the fruit fly *Drosophila melanogaster*, reactivation of neural stem cells from a period of quiescence is critically dependent on the availability of dietary protein (*1*). Amino acids are sensed by the fat body, the *Drosophila* equivalent of the mammalian liver and adipose tissue. In the presence of nutrients, the fat body signals to neuroendocrine cells in the brain to secrete insulin-like peptides (dILPs). Circulating dILPs reach target cells in various organs and tissues where they bind to the insulin receptor and activate the conserved phosphatidylinositol 3-kinase (PI3-kinase)–Akt signaling cascade, triggering cell growth and proliferation (*2*). It was initially speculated that this systemic insulin signaling was responsible for neural stem cell reactivation (*3*). Surprisingly, however, neural stem cells respond only to locally produced insulin provided by neighboring glial cells that comprise a stem cell niche. The glia secrete the insulin-like peptide dILP6, which stimulates neural stem cells to exit from quiescence. Blocking this insulin release impairs stem cell reactivation. Conversely, forced expression of dILP6 in glial cells rescues neural stem cell reactivation under starvation conditions (*4*, *5*). Thus, the stem cell niche acts as a buffer that insulates stem cells from systemic signals and restricts their response to local signals.

Interestingly, local insulin signaling is not a unique feature of the nervous system but is also found in the intestine. Upon feeding, *Drosophila* intestinal stem cells proliferate extensively within their niches. This increase in the stem cell population is induced by dILP3, which is secreted in a nutrient-dependent manner by the visceral muscle that underlies intestinal stem cells. Depletion of dILP3 in this muscle greatly reduces feeding-dependent proliferation (*6*). The distinct roles for dILP3 and dILP6 and their differential expression patterns suggest that other dILPs may also have defined roles in specific tissues (*3*).

The modulation of stem cell function by insulin signaling appears to be an evolutionarily conserved mechanism. Mammalian pluripotent stem cells rely on local signals from support cells to maintain self-renewal



CREDIT: K. SUTLIFF/*SCIENCE*

Local effects. Diverse systemic signals stimulate niche cells to secrete insulin-like peptides. These peptides bind to cognate receptors expressed by stem cells and change their behavior, triggering growth and proliferation.

The Gurdon Institute and Department of Physiology, Development, and Neuroscience, University of Cambridge, Tennis Court Road, Cambridge CB2 1QN, UK. E-mail: a.brand@gurdon.cam.ac.uk

Published by AAAS