Immune recovery after hibernation and HIV infection

At first blush, the idea that hibernation and treatment of HIV infection have common characteristics seems unconventional at best. But a collaboration between scientists Carol Meteyer from the US Geological Survey (Madison, WI) and Daniel Barber and Judith Mandl of the US National Institute of Allergy and Infectious Diseases (Bethesda, MD) has produced evidence that both phenomena can result in a type of immune hyperactivity called immune reconstitution inflammatory syndrome (IRIS).

People with HIV may be treated with anti-retroviral medications to suppress replication of the virus. This also results in immune suppression, which may leave the patient vulnerable to opportunistic bacterial or fungal infections. Once anti-retroviral therapy is complete, the immune system is slowly restored and may over-react to an existing infection, triggering severe tissue damage and even death. This over-reaction and its clinical consequences—IRIS—can also occur after recovery from other forms of immune suppression in humans.

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Hibernation is a strategy by which homeothermic mammals can reduce their energy requirements during the cold season when food is scarce. During hibernation, body temperature is substantially reduced and the animal enters a state of torpor characterized by reductions in physical activity and in metabolic, heart and respiratory rates. Immune function may also be downregulated during hibernation, as it is energy-intensive and temperature-sensitive.

In the past few years, mortality among several species of cave-hibernating bats in the US has climbed steadily. An estimated 5–7 million bats in North America have died from white nose syndrome, an infectious disease that is now known to be caused by the cave-dwelling fungus *Geomyces destructans*. The optimal temperature range for its growth closely corresponds with the body temperature of hibernating bats, and the fungus rapidly colonizes the skin of their wings, ears and muzzles. Despite extensive fungal colonization, however, affected bats show minor gross pathology and minimal immune response. Upon emergence from hibernation, however, the bats' immune systems mount an aggressive response to the fungal infection, causing serious tissue damage that can lead to death. Meteyer, Barber and Mandl propose that this process is a form of IRIS (*Virulence* **3**, 1–7; 2012). A better understanding of this immune response is crucial both for people with IRIS and for bats with white nose syndrome. Bats have essential roles in the ecosystem as pollinators and as controllers of insect populations. Hence, declines in bat populations have serious economic and environmental implications for crop production and pesticide use.

Monica Harrington

THE HEART BEATS ANEW

Pacemaker cells account for fewer than 10,000 of the approximately 10 billion cells in the adult mammalian heart, yet the initiation of the heartbeat depends critically upon this small subpopulation of cardiac cells situated in the sinoatrial node (SAN). When the native pacemaker fails, the cardiac rhythm is disrupted, resulting in bradyarrhythmia, a disturbance characterized by an abnormally slow heartbeat. Current treatments for pacemaker failure are costly electronic devices.

After a decade of searching for a biological alternative to electronic SAN therapy, researchers at The Cedars-Sinai Heart Institute (Los Angeles, CA) believe they have found success. The team, led by Eduardo Marbán and Hee Cheol Cho, has successfully converted rodent cardiomyocytes into pacemaker cells both *in vitro* and *in vivo* using transduction (*Nat. Biotechnol.* published online 16 December 2012; doi:10.1038/nbt.2465).

The researchers expressed *Tbx18*, a gene required for embryonic development of the SAN area, in rodent heart muscle cells. As early as two days after *Tbx18* transduction, these reprogrammed cardiomyocytes or 'induced-SAN' (iSAN) cells exhibited all of the key features of native pacemaker cells, including spontaneous automaticity and SAN cell morphology. Furthermore, iSAN cells retained their phenotype even after the expression of *Tbx18* had faded, indicating a permanent conversion to a pacemaker phenotype.

Previous efforts to create heart muscle cells that could beat on their own have been partially successful; the modified cells acquired spontaneous automaticity but retained their muscle cell morphology. Other approaches using embryonic stem cells to derive pacemaker cells have shown promise but are burdened by challenges such as heterogeneity of the resultant heart cells and the persistent risk of cancer cell formation.

Marbán and Cho's work demonstrates that a single transcription factor suffices for the direct conversion to iSAN cells. "Although we and others have created primitive biological pacemakers before, this study is the first to show that a single gene can direct the conversion of heart muscle cells to genuine pacemaker cells. The new cells generated electrical impulses spontaneously and were indistinguishable from native pacemaker cells," Cho notes in a press release.

The results of this study are extremely promising for the development of specific and highly effective alternatives to electronic pacing devices. The authors now plan to conduct longer-term experiments using large-animal models to assess safety and efficacy with the hope of one day being able to use this technology to treat human patients with bradycardia.

Thomas Rowley

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