in the functional separation of metabolism. Importantly, the demonstration of divergent NAD^+ metabolism in the nucleus and cytosol during adipocyte differentiation shows not only that the two pools are distinct but that their separation represents a point of regulation in control of a physiological process.

Analogous regulation likely applies to other metabolites such as acetyl–coenzyme A (CoA) and *S*-adenosylmethionine (SAM), which are needed in the nucleus for histone acetylation and histone and DNA methylation, respectively. Both acetyl-CoA and SAM are thought to be present in the cell at levels that can limit acetyltransferase and methyltransferase activity (*9*); yet, definitive measurements of these metabolites specifically within the nucleus are lacking. Nevertheless, enzymes that produce acetyl-CoA and SAM are present and distinctly regulated within the nucleus (*1*, *2*), and recent metabolic evidence also supports the notion of functional separation between nuclear and cytosolic pools of acetyl-CoA (*10*, *11*).

In addition to prompting further investigation into the nuclear and cytosolic compartmentalization of metabolism, the Ryu *et al.* study raises a number of intriguing questions about NAD^+ metabolism in adipocytes and other cell types. NAD^+ rises with calorie restriction and exercise and is proposed as a mediator of their beneficial effects through regulation of sirtuin activity (*12*). SIRT1 in particular could be affected by variations in nuclear NAD^+ levels, raising questions about the potential role of NAD^+ compartmentalization in regulating the myriad processes controlled by SIRT1 (*13*). Furthermore, how might compartmentalized NAD^+ metabolism integrate with other stimuli that affect NAD^+ levels, such as aging, caloric restriction, and circadian oscillations (*13*)? How does nuclear NAD^+ affect other cellular differentiation processes or responses to stimuli that are regulated by PARPs or sirtuins, and how might dysregulation of compartmentalized NAD^+ production contribute to disease states or present therapeutic opportunities? Notably, *NMNAT-1* is deleted in some cancers (*14*). The findings of Ryu *et al.* will surely prompt numerous important avenues of investigation. ■

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CONSERVATION

The hidden biodiversity of amphibian pathogens

Discovery of additional amphibian chytrid pathogens increases conservation concerns

By **Karen Lips**

Since the discovery of the salamander chytrid pathogen [*Batrachochytrium salamandrivorans* (*Bsal*)] (*1*), the world has been preoccupied with determining where it does and does not occur (*2*) so that policies can be implemented to prevent introduction into unaffected areas (*3*). Pathogenic chytrids cause chytridiomycosis, a disease of the skin that can cause mortality and die-offs, including population declines and species extinctions. In the United States—the world's biodiversity hot spot for salamanders and currently free of *Bsal*—a multinational scientific task force has been created to test the susceptibility of native species and to prepare an emergency response should *Bsal* be detected (*4*). Meanwhile, attention to *Bsal*'s better-known cousin *B. dendrobatidis* (*Bd*), another chytrid pathogen that has decimated amphibian populations around the world, has faded, in part because of perceptions that once *Bd* is present, conservation actions and policy options are limited. On page 621 of this issue, O'Hanlon *et al.* (*5*) remind us that *Bd* remains a serious threat to global amphibian biodiversity and clarify where and when *Bd* came from and how it spread.

The Brazilian pumpkin toadlet (*Brachycephalus pitanga*) is host to *Bd*Brazil.

PHOTO: ALBERTO LOPEZ TORRES

O'Hanlon *et al.* use whole-genome sequencing of 234 *Bd* cultures taken from around the globe to identify East Asia as the site of origin of *Bd*, including the Global Panzootic Lineage (*Bd*GPL), the invasive, hypervirulent form of chytrid that has been implicated in losses of amphibians from six regions (*5*, *6*). The authors date the emergence of *Bd*GPL to the second half of the 20th century, consistent with the period of high commercial trade in amphibians. The authors describe phylogenetic patterns of *Bd* as clustering into five main lineages—four of which were previously identified (*6*) and one entirely new, genetically distinct, hyperdiverse lineage from the Korean peninsula. The high genetic diversity of this new Asian lineage differs from that of the other four lineages, all of which exhibit a pattern of genetic diversity typical of population fluctuations and/or natural selection and consistent with increases in spatial distribution or in the number of host species. This suggests that East Asia is the most likely source of origin for amphibian chytrid pathogens. O'Hanlon *et al.* also identify two new kinds of hybrid lineages, raising the possibility that introductions of new lineages might produce more hybrid chytrids. Finally, the authors show that all *Bd* variants are present in the commercial trade of amphibians (including food, pets, and scientific specimens), demonstrating contemporary intercontinental transmission and the failure of international biosecurity measures to control the spread of this pathogen.

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The implications of these new findings are wide ranging. For example, although *Bd*GPL is globally distributed, other lineages are geographically restricted. This identifies areas that might be susceptible to new invasions by these endemic lineages and may explain variation in species responses to infection (*7*, *8*). Despite decades of research, quantitative studies of the impacts of chytridiomycosis on amphibian populations are lacking from most areas, especially Asia (*8*). Demographic analyses are critical in providing robust estimates of demographic parameters such as species or population-specific survival and mortality rates and population growth rates. In addition, mark-recapture studies that follow the fate of infected individuals are needed to identify mechanisms underlying the causes of population decline, persistence, or recovery and to identify effective conservation measures.

To control emerging infectious diseases (EIDs), we also need a better understanding of the relative contributions of global change (for example, changes in climate, land use, and trade) on the emergence and spread of pathogens. Knowing that all chytrid lineages are circulating in trade routes, but not all are globally distributed (*5*), highlights the need for coinfection experiments to predict responses to future invasions. Knowledge of how the trade ecosystem might amplify disease by promoting hybridization events among lineages or by facilitating the spread of lineages into naïve populations could be useful to mitigate and manage disease within the live-animal trade.

Many areas of the world lack chytrid cultures, disease surveillance programs, or amphibian population studies necessary to study or conserve amphibian biodiversity. Developing collaborative partnerships between investigators from these regions and established research groups could increase the global capacity to understand the emergence of *Bd* and responses of amphibian populations. Even more important is the need to expand veterinary capacity for wildlife diseases. Many national veterinary authorities lack sufficient resources, staff, or bandwidth to respond effectively to the rapidly increasing numbers of wildlife pathogens that threaten global biodiversity.

Proactive measures to address EIDs will be possible when we can predict future outbreaks, species susceptibility, and disease spread, perhaps through analyses to model disease outbreaks from genomics, Google search histories, or social media data (*9*, *10*). Advanced detection technologies would improve the ability to address new introductions. Alternatively, coordination of citizen science programs might serve as an early warning system in some regions.

Successful mitigation of the impacts of chytridiomycosis is also lacking. No effective treatments exist for wild populations, and policies restricting imports are only as strong as enforcement efforts (*7*). One of the most important advances in the global response to *Bsal* was the development of an emergency response plan (*11*, *12*), including the establishment of a *Bsal* task force (*4*); such a coordinated effort is lacking for *Bd* and could speed discovery and identify effective interventions.

Both *Bd* and *Bsal* are notifiable diseases under the World Organisation for Animal Health (OIE) standards, but, despite global support, this agreement has lacked strong, consistent enforcement. Strengthening application of the OIE standards should be a first step. In the United States, new laws are needed to improve the ability of the U.S. Fish and Wildlife Service to monitor and control invasive species and diseases (*13*). New policies developed in collaboration with trade organizations, lobbyists, and national and international organizations to implement quarantine measures, testing procedures, and clean-trade programs could minimize the risk of pathogen introductions. The European Union has recently approved such a law (*14*).

The work of O'Hanlon *et al.* serves as a case study for studying and addressing EIDs. With accelerating global change in a more connected world, we can expect to see more EIDs, so international collaborations such as this one will be increasingly necessary to address global pathogens of wildlife, agriculture, and humans. ■

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NUCLEAR PHYSICS

Resolving the neutron lifetime puzzle

A measurement of trapped neutrons dramatically improves control of systematic uncertainties

By **Pieter Mumm**

Free electrons and protons are stable, but outside atomic nuclei, free neutrons decay into a proton, electron, and antineutrino through the weak interaction, with a lifetime of ~880 s (see the figure). The most precise measurements have stated uncertainties below 1 s (0.1%), but different techniques, although internally consistent, disagree by 4 standard deviations given the quoted uncertainties. Resolving this "neutron lifetime puzzle" has spawned much experimental effort as well as exotic theoretical mechanisms, thus far without a clear explanation. On page 627 of this issue, Pattie *et al.* (*1*) present the most precise measurement of the neutron lifetime to date. A new method of measuring trapped neutrons in situ allows a more detailed exploration of one of the more pernicious systematic effects in neutron traps, neutron phase-space evolution (the changing orbits of neutrons in the trap), than do previous methods. The precision achieved, combined with a very different set of systematic uncertainties, gives hope that experiments such as this one can help resolve the current situation with the neutron lifetime.

"Researchers have primarily used two techniques to measure the neutron lifetime, typically referred to as 'beam' and 'bottle' measurements."

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