temperature increase of the past 100 years must be small, and climate models must be much more sensitive to this small difference if they are to agree with past observations. The future, then, might be more at the upper range of climate projections. But if aerosols do not increase low-level cloud brightness as much as some models have it, then greenhouse gases may be only slightly masked by aerosol-induced cloud changes, and projections of future climate might follow the more benign path.

How fast the world needs to address the issue of greenhouse-gas warming still depends on which of these two paths is correct. We still have the conundrum. But it is now less daunting than it was, given that the results of Ackerman *et al.* mean we can rule out some of the large effects of aerosols on cloud water content. ■

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Developmental biology

Survival by self-digestion

Nathaniel Heintz

Mammals face a problem just after birth: they are no longer nourished through the placenta, but suckling has not yet begun. How do they survive? Digestion of the animal's own cells could be the answer.

All organisms must adapt to environmental stresses. One of the most beautiful examples of a response to stress is autophagy — a process first described in electron microscopic studies in the kidneys of newborn mice[1], and now known to be one of the major pathways for the degradation of long-lived proteins and cellular organelles[2,3]. It has become clear that autophagy is activated in a variety of circumstances in multicellular organisms, and thus must be regulated by diverse stimuli in different cell types. But our knowledge of the biological roles of autophagy in mammals is quite primitive. On page 1032 of this issue, however, Kuma *et al.*[4] provide a fascinating insight into the mammalian response to birth and the biological benefits of autophagy.

In cells, nutrient deprivation and other stresses elicit a complex series of orchestrated steps that result in the cells enveloping portions of their cytoplasm, delivering them to enzyme-packed organelles known as lysosomes for degradation and recycling (hence the name autophagy, or self-eating)[2,3]. Over the past decade, genetic analysis in yeasts and morphological studies in a wide variety of species have defined the molecular mechanisms of autophagy and shown its induction under many developmental and pathological situations. The logic for the pathway that has been revealed by the genetic and molecular dissection is very pleasing — in response to nutrient deprivation, the autophagy pathway scavenges intracellular substituents to supply vital components until conditions improve.

To investigate the importance of this pathway in mammals, the Mizushima laboratory has previously[5] made use of a fusion of green fluorescent protein (GFP) and LC3, the mammalian equivalent of Atg8 — an essential protein in the yeast autophagy pathway. With this fusion protein they could reveal the formation of autophagosomes, vesicular structures that are hallmarks of autophagy. Having introduced GFP–LC3 into young mice, the authors were able to map the induction of autophagy in response to food withdrawal in many tissues, by studying the formation of small fluorescent vesicles carrying the fluorescent fusion protein.

Now, the same group (Kuma *et al.*[4]) have turned their attention to the developmental roles of autophagy. To do so, they first used GFP–LC3 to study the formation of autophagosomes in newborn mice. They observed massive induction of autophagy in the heart muscle, the diaphragm, the lungs and the skin — all tissues that undergo sudden increases in energy expenditure or environmental exposure immediately following birth. The induction of autophagy was immediate and transient, reaching maximal levels only 3 to 6 hours after birth and declining to basal levels within a day or two. To explain this phenomenon, Kuma *et al.* postulated that the induction of autophagy following birth is required to provide energy before nursing begins.

To test this attractive idea, the authors generated mice that lack Atg5 — another protein required during an early step in the autophagy programme[6]. The Atg5-knockout animals were born in normal mendelian ratios but died during the first day after birth. Measurements of autophagy with the GFP–LC3 assay demonstrated that, as expected, the formation of autophagosomes was blocked in the mutant mice. The Atg5-deficient mice also died earlier than wild-type mice when not being suckled; their survival could be extended by hand feeding; and plasma and tissue amino-acid concentrations in non-suckling mutant mice were normal at birth but very much reduced relative to controls 10 hours after delivery. Furthermore, measurements of energy status in the knockout pups indicated that energy production was severely depressed but could be restored by re-feeding.

These data show that autophagy is required to produce amino acids and to maintain energy levels in neonatal mice. Taken together with the severely low glucose and lipid levels that are generally evident in newborn mice, the death of the Atg5-knockout mice after birth provides strong support for the hypothesis that autophagy is essential for survival during the unique period experienced by mammals as they make the transition from transplacental nutrition to milk.

The idea that autophagy is important to provide nutrients for neonatal survival is very attractive. It provides a genetic link between the incisive studies of mechanisms of autophagy in individual cells, and studies documenting the induction of autophagy in tissues of fasting animals[2,3]. It demonstrates that our understanding of the biological roles of autophagy in mammals will ultimately require precise genetic dissection of this pathway *in vivo*. And it raises several issues for further investigation.

For instance, under what other conditions can autophagy contribute to viability in mammals and other vertebrates? What is the mechanism through which autophagy, which is understood as an intracellular catabolic pathway (one that breaks complex molecules down), contributes to the maintenance of plasma amino-acid levels? Which tissues contribute to this process? How important is this mechanism in other organisms in maintaining energy levels during development or fasting? What is the anatomical basis for the suckling defect seen in Atg5-knockout mice, and how does that contribute to neonatal death? In the studies presented here, Kuma *et al.*[4] make a powerful case that our understanding of the unique features of mammalian development can be enriched by genetic dissection of this beautiful and fundamental biological pathway. ■

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