Extensive efforts are under way to document the earliest animals in the fossil record (*33*) and test alternative hypotheses about the big mass extinctions (*29*). We must extend these efforts in an organized fashion throughout Earth history if we are to make genuine progress in refining the hypotheses about Phanerozoic paleobiodiversity that Sepkoski laid out for us so brilliantly.

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35. We thank M. Foote for providing data from the Sepkoski database and K. Roy and M. Kirby for helpful discussions and criticism of the manuscript.

PERSPECTIVES: CELL BIOLOGY

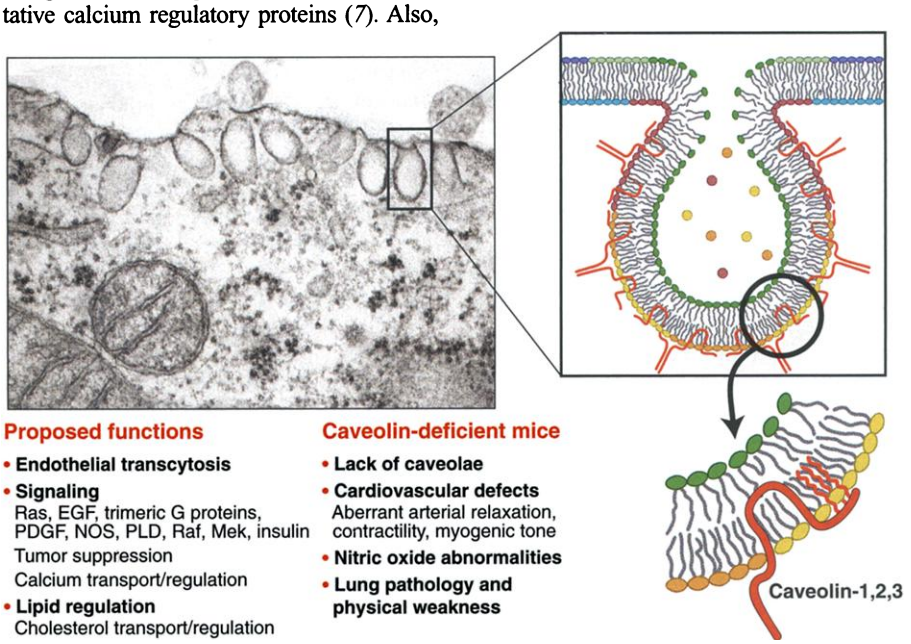
Life Without Caveolae

Robert G. Parton

Discovered by electron microscopists in the 1950s, caveolae—small surface pits in the plasma membrane—remain one of the most abundant yet puzzling features of many mammalian cells. The principal components of caveolae are proteins called caveolins. If caveolin-1, the isoform found in nonmuscle cells, is produced by cells normally lacking caveolae, then caveolae are formed (*1*); if cells that normally produce caveolin-1 become deficient in this protein they lose their caveolae (*2*). On page 2449 of this issue, Drab *et al.* (*3*) provide a thorough characterization of mice deficient in caveolin-1 that apparently have no caveolae.

An electron microscopist scanning the surface of a fat cell (adipocyte) that is covered in caveolae could hardly imagine life without these structures. Yet we do not know exactly what they do or how their characteristic shape is related to their cellular tasks (see the figure). It has been proposed that caveolae are important in signal transduction, forming a platform on which different signaling components can congregate (*4*, *5*). In some cases, signaling components in the caveolae may remain inactive, held in check by caveolins until their activation and release by the appropriate external stimulus. The number of caveolae and amount of caveolin decrease dramatically in immortalized (transformed) cultured cells, hinting that caveolae are important for inhibiting certain signaling pathways that regulate cellular proliferation (*4*). However, it is becoming increasingly apparent that surface microdomains termed "lipid rafts," of which caveolae are a subtype, could account for local concentrations of molecules required for efficient signaling (*6*). In fact, few signaling proteins are exclusively localized to caveolae, although notable exceptions include several putative calcium regulatory proteins (*7*). Also, certain cells with very complex signaling pathways such as lymphocytes and some neurons manage fine without caveolae. Even if these cells have proteins that can take the place of caveolins, they do not seem to need caveolae per se for signaling. Besides signaling, caveolae have been linked to cholesterol regulation: Caveolin binds to cholesterol, its production is controlled by cholesterol, and cells with mutations in caveolin exhibit pertubations in their cholesterol-rich lipid-raft domains (*2*). Again, although definitive evidence is lacking, these studies suggest that caveolae and caveolins may be involved in the regulation of intracellular and surface cholesterol.

Given the variety of possible tasks at-



Caveolae and caveolins. (Left) An electron micrograph of small (65 nm) flask-shaped pits called caveolae in the plasma membrane of a human fibroblast. **(Right)** Caveolae are formed from caveolins, oligomeric integral membrane proteins. Caveolins are thought to have both their carboxyl and amino termini facing the cytoplasm and have palmitoyl groups (red squiggles) attached to carboxyl-terminus amino acids.

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tributed to caveolae, the generation of knockout mice deficient in caveolin-1 has been eagerly awaited. Drab and colleagues (*3*) report that their knockout mice are fertile and at first sight healthy, but, as they had hoped, the mice do show a remarkable lack of caveolae, at least in the tissues that they examined. This confirms the importance of caveolin-1 in caveolae formation but also shows that if compensatory pathways do exist (and one presumes that they do), then they do not involve caveolae or similar structures. So why are caveolae required at all?

Drab *et al.* question whether caveolae are involved in transcellular transport across endothelial cells. They find that their knockout mice have normal concentrations of the protein albumin in the cerebrospinal fluid, an indication that transendothelial transport is unaffected. Does this indicate that other noncaveolar pathways compensate for caveolae when they are absent, or are caveolae of little importance in transendothelial transport? The authors do see extensive changes in the cardiovascular system of their knockout animals. Using isolated aortic preparations, they detect defects in vascular relaxation, contractility, and myogenic tone due to impaired nitric oxide and calcium signaling. Previous studies have implicated caveolae in various calcium-dependent processes, including the local release of pulses of calcium from internal stores ("calcium sparks") in muscle cells (*8*) and the generation of calcium waves in endothelia (*9*). The effects on nitric oxide generation are also intriguing and strongly implicate caveolae in the regulation of nitric oxide synthases, either directly or through the control of calcium ions. Supporting these findings, a synthetic caveolin-derived peptide specifically inhibited acetylcholine-induced vasodilation and nitric oxide generation in endothelia (*10*). Although the Drab *et al.* mice generally appeared healthy, subsequent tests showed that they were physically weak and that their lungs displayed severe abnormalities, with increased cell numbers and a disorganized architecture. The causes of these abnormalities are hard to discern but are at least consistent with hyperproliferation due to loss of the normal control of cell proliferation (*4*). If this turns out to be the case, it is not yet clear why hyperproliferation abnormalities are found in the lungs but not in other tissues that are normally caveolae-rich.

So, life goes on without caveolae. The phenotype of the knockout mice appears to be relatively mild in view of the loss of such an abundant structure, but the Drab *et al.* work is only the beginning of a more extensive investigation seeking subtle defects in these animals. With the linking of caveolins and caveolae to tumor suppression, chemotherapeutic drug resistance, and cholesterol regulation, it will be interesting to examine the response of caveolin-1–deficient mice to specific challenges. Perhaps most intriguingly, we still do not understand the importance of the characteristic shape of caveolae. The caveolae-deficient mice provide researchers with a tremendous new resource and surely have many more secrets to divulge.

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PERSPECTIVES: NEUROSCIENCE

The Face of Controversy

Jonathan D. Cohen and Frank Tong

Neuroscientists have long puzzled over whether the brain represents and processes information in a modular or a distributed fashion. According to modular theories, the brain is organized into subcomponents, or "modules," each dedicated to processing and representing a particular type of information (*1*). This well-structured view of brain organization is intuitively appealing. In contrast, distributed theories argue that any information regardless of type is processed by many different parts of the brain, and that any brain region is likely to represent many classes of information. Despite the complexity of distributed representation, computational modeling demonstrates that it can be an efficient, robust, and flexible method of neural coding (*2–4*). Reports in this issue by Downing *et al.* (*5*) (page 2470) and Haxby *et al.* (*6*) (page 2425) about the areas of the human brain involved in perception of the face and other human body parts illustrate that the modular versus distributed controversy is still very much alive.

The study by Downing *et al.* (*5*) provides new evidence in favor of the modular view. Using functional magnetic resonance imaging (fMRI), the authors offer an impressive demonstration that a circumscribed region of the lateral occipital cortex in the human brain responds preferentially to pictures of the human body. This region, which they call the extrastriate body area (EBA), showed stronger visual responses to pictures of the human body than to pictures of common objects, animals, or cars. Line drawings, silhouettes, and even stick figures of the human body also evoked much stronger responses than scrambled versions of the same visual stimuli. The authors suggest that the EBA is a specialized system for processing the visual appearance of the human body.

This finding follows on from similar work by the same group investigating a region in the medial temporal lobe called the parahippocampal place area (PPA) that responds selectively to spatial layout (*7*), and a region near the occipital-temporal junction called the fusiform face area (FFA) that responds selectively to faces (*8–10*). Damage to the FFA of the human brain is associated with severe deficits in face recognition, a syndrome called prosopagnosia (*11–13*). Subdural electrode recordings in human patients with epilepsy have also revealed face-selective responses in this region, and moreover, electrical stimulation of these regions can disrupt face identification (*14*). Pioneering work by Gross and colleagues (*15*) has also revealed face-selective neurons in the temporal cortex of the monkey. Subsequent studies have shown that these "face cells" can be tuned to specific facial attributes such as the identity (*16*), expression (*17*), viewpoint (*18*), or parts of a face (*16*, *19*). This collection of findings presents persuasive evidence for a brain module dedicated to face processing. Furthermore, it raises the possibility that similar modules may exist for other visual categories, including spatial layout and, as suggested by Downing *et al.*'s findings, the appearance of the human body.

Establishing evidence in favor of distributed theories is a more challenging undertaking. Computational models have convincingly demonstrated the plausibility and power of distributed representation [for example, see (*2–4*)]. However, empirical evidence has been harder to come by. A distributed representation, by its very

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