rate of maturation, exemplified by phagosomes containing apoptotic cells, and a faster "induced" rate triggered by TLR signaling. Curiously, another recent study reported faster disappearance of apoptotic cells in TLR4-deficient macrophages compared with their wild-type counterparts, a finding not replicated in the Blander and Medzhitov study (*11*). Differences in the apoptotic cell and macrophage populations used in the two studies might account for this discrepancy.

How do TLRs accelerate the formation of phagolysosomes? Morphological evidence from the Blander and Medzhitov study suggests that lysosomes dock onto TLR- or MyD88-deficient phagosomes but do not fuse efficiently with them. The increased volume of phagosomes containing yeast cells in wild-type versus TLR2- or MyD88-deficient macrophages is consistent with a block in membrane addition. Because phagosomes can be readily isolated, further dissection of how TLR signaling boosts phagosome maturation should now be possible. In vitro "cell-free" organelle systems have been developed that allow dissection of the complex biochemistry of membrane fusion. Thus, it may be possible to explore further the fusogenic properties of bacterial phagosomes isolated from TLR-deficient and wild-type phagocytic cells.

Blander and Medzhitov found that activation of the p38 mitogen-activated protein (MAP) kinase downstream of TLRs is needed for accelerated phagosome maturation. One p38 substrate that might be relevant is rab guanine nucleotide dissociation inhibitor (GDI), which becomes activated when phosphorylated by p38 (*12*). Rab GDI controls the balance between membrane-bound and soluble pools of prenylated rab proteins such as rab5 and rab7, which are key regulators of the endocytic pathway. However, other studies have found that p38 activation blocks the maturation of phagosomes containing mycobacteria or latex beads by reducing recruitment of the rab5 effector protein, early endosome antigen 1 (*13*). Further investigations using isolated phagosomes harboring different cargo may resolve these issues. Researchers will need to keep in mind the "phagosome autonomous" nature of TLR signaling. As the current authors show, phagosomes containing apoptotic cells do not mature faster in macrophages that also harbor bacterial phagosomes or in macrophages stimulated with LPS. Thus, diffusible cytosolic factors activated by TLR signaling are unlikely to be limiting for phagosome maturation.

Bacterial pathogens have developed diverse ways of avoiding host innate and adaptive immune responses. One such avoidance mechanism is inhibition of phagosomal acidification, maturation, and the consequent presentation of bacterial antigens to host T lymphocytes (*14*). Paradoxically, TLR signaling is also relevant here. For example, the 19-kD lipoprotein of the bacterium *Mycobacterium tuberculosis* signals through TLR2 and inhibits both class I and class II major histocompatibility complex (MHC)–restricted antigen presentation by blocking either antigen degradation or MHC synthesis (*15*). However, such inhibitory effects seem to be the result of chronic rather than acute exposure to *M. tuberculosis* lipoprotein, which, initially at least, promotes bacterial killing by phagocytic cells (*16*).

Although the Blander and Medzhitov study concerns phagosome maturation, the authors also observed a reduced uptake of bacteria in macrophages lacking TLRs or MyD88, particularly in the absence of serum opsonizing factors. Phagocytosis of apoptotic cells and synthetic latex beads proceeds without TLR signaling, but perhaps less efficiently. Because the addition of membrane (from endosomes, the endoplasmic reticulum, or both) at the site of the forming phagosome is usually needed for completion of the overall process (*2*), perhaps membrane fusion events during phagosome formation are also stimulated by TLR signaling. Alternatively, TLR signaling may affect the actin cytoskeleton. Consistent with this idea, recent studies show acute effects of TLR ligands on actin-driven membrane ruffling and macropinocytosis in dendritic cells (*17*). In general, this study adds to the growing evidence that in addition to driving the longer term transcriptional programs associated with macrophage and dendritic cell activation, TLR signaling induces rapid changes that permit new cellular processes to be enacted without delay.

References and Notes

1. P. M. Henson *et al.*, *Nature Rev. Mol. Cell Biol.* **2**, 627 (2001).
2. S. Greenberg, S. Grinstein, *Curr. Opin. Immunol.* **14**, 136 (2002).
3. D. M. Underhill, A. Ozinsky, *Annu. Rev. Immunol.* **20**, 825 (2002).
4. J. M. Blander, R. Medzhitov, *Science* **304**, 1014 (2004).
5. R. Medzhitov, C. A. Janeway Jr., *Cell* **91**, 295 (1997).
6. C. A. Janeway Jr., R. Medzhitov, *Annu. Rev. Immunol.* **20**, 197 (2002).
7. S. Akira, *J. Biol. Chem.* **278**, 38105 (2003).
8. D. M. Underhill *et al.*, *Nature* **401**, 811 (1999).
9. H. Hacker *et al.*, *EMBO J.* **17**, 6230 (1998).
10. S. S. Diebold *et al.*, *Science* **303**, 1529 (2004).
11. A. Shiratsuchi *et al.*, *J. Immunol.* **172**, 2039 (2004).
12. V. Cavalli *et al.*, *Mol. Cell* **7**, 421 (2001).
13. R. A. Fratti *et al.*, *J. Biol. Chem.* **278**, 46961 (2003).
14. C. M. Rosenberger, B. B. Finlay, *Nature Rev. Mol. Cell Biol.* **4**, 385 (2003).
15. A. A. Tobian *et al.*, *J. Immunol.* **171**, 1413 (2003).
16. S. Thoma-Uszynski *et al.*, *Science* **291**, 1544 (2001).
17. M. A. West *et al.*, in preparation.
18. I thank R. Wallin for helpful comments.

PLANETARY SCIENCE

The Giant Impact Formation of the Moon

Herbert Palme

During the past 30 years, a scenario in which a giant object collided with Earth has emerged as the leading theory for Moon formation. An off-center collision of a Mars-sized projectile with Earth would produce the present high angular momentum of the Earth-Moon system and would eject enough material into Earth orbit so that the dust could accumulate to form the Moon. The first numerical simulations of this hypothesis nearly 20 years ago (*1*) used about 3000 particles whose trajectories were followed through the entire collision. In a new set of simulations published in *Icarus* (*2*), Canup used up to 120,000 particles and a new equation of state (*3*) that describes the behavior of material at extreme pressures and temperatures. Although the results are not very different from the earlier calculations of similar impacts, they include the most detailed predictions to date of the provenance of the material that makes up the Moon. This is crucial for geochemical arguments relating Earth mantle and Moon.

The most obvious compositional characteristic of the Moon is a deficiency in iron relative to Earth and primitive meteorites. Estimates for the bulk iron content of the Moon range from 8 to 12%, compared to 31% for Earth (*4*). The single-impact hypothesis, first proposed by Hartmann and Davis in 1975 (*5*), explained the iron deficiency by suggesting that the Moon was made of Earth mantle material. According to these authors, "collision of a large body with Earth could eject iron-deficient crust and upper mantle material,

The author is at the Institut für Geologie und Mineralogie, Universität zu Köln, 50674 Köln, Germany. E-mail: palme@gwp-min.min.uni-koeln.de

forming a cloud of refractory, volatile-poor dust that could form the Moon." That the Moon and the mantle of Earth have the same chemical composition is, however, not easy to prove. The chemical composition of Earth's mantle is reasonably well known from the analysis of upper mantle rocks. Such chemically "primitive" rocks are not known from the Moon, making estimates of the chemistry of the Moon very uncertain. Additional complications arise from the lack of water and the low contents of volatile elements in lunar rocks, apparently the result of strong heating of the dust cloud parental to the Moon. Surprisingly, lunar basalts are richer in iron oxide than their terrestrial counterparts, and this is more difficult to accommodate in models where the Moon is made of Earth mantle material.

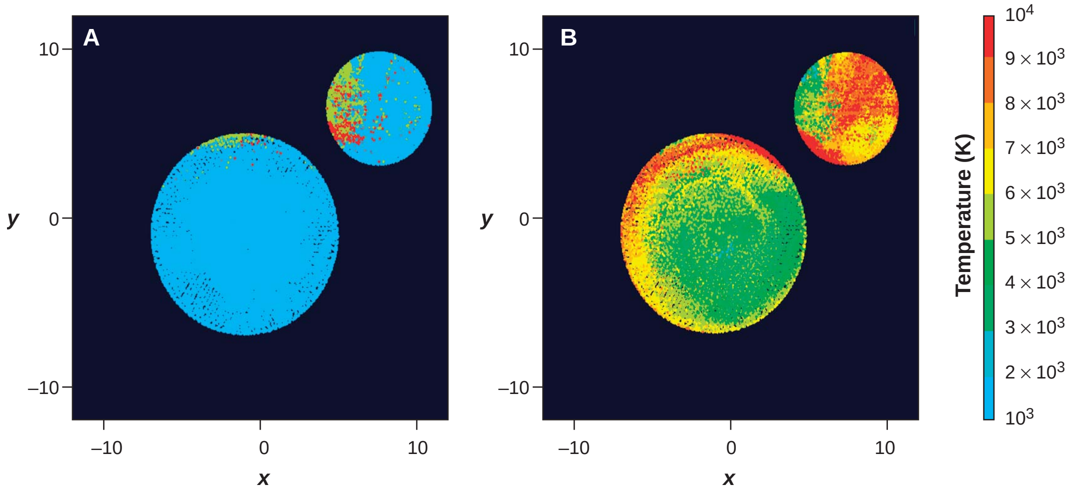
The situation changed completely when Benz *et al*. (*1*) performed the first detailed numerical simulations of the collision of a 1/10 Earth mass planetesimal with Earth and concluded that "the Moon is formed almost exclusively by material coming from the impactor" (*6*). Initially the authors had assumed compositional uniformity of Earth and projectile. Later simulations where a core-mantle structure was assumed for Earth and the impactor led to the conclusion that the Moon was predominantly produced from material of the mantle of the impactor. This result was ignored by many geochemists, one reason being the small number of particles that were used in these simulations. Given a total of 3000 particles of the Earth-Moon system, only 37 were required to make the Moon and one particle represented the core of the Moon.

According to the new simulations by Canup, there is no doubt, given the assumptions of the calculations, that on average more than 80% of the Moon's composition comes from impactor mantle material. The material that ends up in orbit around Earth and from which the Moon is made comes predominantly from the leading, outer regions of the projectile. These regions do not collide directly with Earth, and after the initial impact they expand to distances of several Earth radii where they are placed into stable Earth orbits by gravitational torque. The impactor core loses energy by its more direct collision with Earth, is thus more strongly decelerated, and (after distortion by gravitational forces) largely collides again with Earth. In the figures, reprinted from the paper by Canup, the final positions and the highest temperatures of individual particles are plotted into the their positions in the original bodies. The red particles in panel A escape the system, the yellow-green particles end up in the orbiting disk from which the Moon is made, and the blue particles accrete to Earth. As shown in panel B, the highest temperatures are reached for material at the location of the first collision. Canup found the most favorable conditions for making the Moon by assuming that Earth is accreted to more than 95% of its present mass, the mass of the impactor is 11 to 14% that of Earth, and both impactor and Earth have an iron core occupying 30% of the planet and an overlying mantle of forsterite.

If the Moon was indeed made by a single impact and if the results are appropriately described by this kind of model, then a number of consequences for the geochemistry of Moon and Earth follow that are normally not considered.

An undifferentiated projectile could not have produced an iron-poor Moon, even if it were a metal-containing ordinary chondrite. Therefore, the present bulk iron content of the Moon is almost entirely derived from the mantle of the impactor, as are other siderophile elements. Most of the tungsten now in the Moon must be derived from that of the impactor's mantle and could, in principle, thus have a substantial ^{182}W excess. Mixing or equilibration of the tungsten in the mantle and core of the impactor seems impossible. Similarities in the chemistry of the Moon and Earth (*7*, *8*) would then require alternative explanations (*4*); geochemical constraints imposed by niobium/tantalum ratios are not consistent with 80% of impactor material in the Moon (*9*). Chondritic meteorites, however, display a range in niobium/tantalum ratios (*10*), making the initial niobium/tantalum ratios of Earth and projectile uncertain. The similarity in oxygen and chromium isotopes of the Moon and Earth is often cited as evidence for a close relationship of Earth and Moon. The importance of oxygen isotopes is unclear. Differences among Earth, Mars, and Vesta are very small relative to the huge variations in individual phases of single unequilibrated chondritic meteorites. Chromium isotopes reflect primarily bulk manganese/chromium ratios, and similarities between Earth and Moon indicate similar manganese/chromium ratios of Earth and impactor (*11*). Another intriguing feature of the present calculations are the extremely high temperatures, at which many elements would be partly or fully ionized; perhaps this would explain the complex behavior of the alkali elements in the Moon (*4*).

However, some caution is appropriate. All of the simulations performed to date tracking the formation of a protolunar disk have used a single numerical method, smooth particle hydrodynamics, in which the trajectories of a large number of spherical particles with similar masses are calculated. Simplifications are unavoidable; even in the recent work, the spatial resolution (a few hundred kilometers) is not sufficient to describe early jetting processes or



Origin of Moon material. Mapping of results of a giant impact simulation onto the original configuration of Earth and impactor; *x* and *y* axes are in units of 1000 km. (**A**) The red particles escape the system, the yellow-green particles end up in the orbiting disk from which the Moon is made, and the blue particles accrete to Earth. (**B**) The highest temperatures are reached for material at the location of the first collision. [Reprinted from (*2*), figure 3, with permission from Elsevier.]

the behavior of the small amount of iron in the protolunar disk. Ideally, the results should be verified with complementary simulations using different hydrodynamic methods (*12*).

Nonetheless, the detailed predictions now possible with the new calculations and further improvements, together with the refinement in analytical tools and the corresponding progress in stable and radiogenic isotope analyses, offer a wealth of new possibilities for testing models of lunar origin.

References

1. W. Benz *et al.*, *Icarus* **66**, 515 (1986).
2. R. Canup, *Icarus* **168**, 433 (2004).
3. H. J. Melosh, *Lunar Planet. Sci.* **XXXI**, 1903 (2000).
4. J. Jones, H. Palme, in *Origin of the Earth and Moon*, R. M. Canup, K. Righter, Eds. (Univ. of Arizona Press, Tucson, AZ, 2000), pp. 197–216.
5. W. K. Hartmann, D. R. Davis, *Icarus* **24**, 504 (1975).
6. W. Benz *et al.*, *Icarus* **71**, 30 (1987).
7. H. Wänke, G. Dreibus, in *Origin of the Moon,* W. K Hartmann, R. J. Phillips, G. J. Taylor, Eds. (Lunar and Planetary Institute, Houston, 1986), pp. 649–672.
8. A. E. Ringwood, in *Origin of the Moon,* W. K. Hartmann, R. J. Phillips, G. J. Taylor, Eds. (Lunar and Planetary Institute, Houston, 1986), pp. 673–698.
9. C. Münker *et al.*, *Science* **301**, 84 (2003).
10. S. Weyer *et al.*, *Chem. Geol.* **187**, 295 (2002).
11. H. Palme, *Philos. Trans. R. Soc. London* Ser. *A* **359**, 2061 (2001).
12. H. J. Melosh, personal communication.

RETROSPECTIVE: EVOLUTION

In Memory of John Maynard Smith (1920–2004)

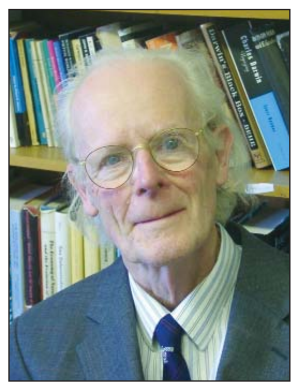
Richard Lewontin

When John Maynard Smith died on 19 April at the age of 84, one of the last grand evolutionary theorists of the 20th century passed. The example of Charles Darwin has induced intellectually ambitious biologists, many of them in Britain, to search for general formulations by which evolution as a whole, or large domains of evolutionary phenomena, can be understood and explained. One thinks of R. A. Fisher's self-consciously named "Fundamental Theorem of Natural Selection" (which turned out not to be quite so fundamental or general as Fisher thought), or W. D. Hamilton's theory of kin selection, the chief theoretical tool used to explain the origin of cooperative, social, and apparently altruistic behavior in a world supposedly dominated by the struggle for existence.

Maynard Smith saw that a major remaining problem in evolutionary theory was to explain the evolution of characteristics whose reproductive advantage or disadvantage to an individual depended on the response of other individuals. So, for example, is it reproductively advantageous for an animal to engage in threatening aggressive behavior toward another animal when they are competing for a bit of food or space? If the response of the second animal is to back down, then the aggressive behavior has paid off, but if the opponent meets aggression with aggression, then an escalating conflict may leave both of them dead. Maynard Smith realized that this class of evolutionary problem could be approached through game theory. His invention of the concept of an Evolutionary Stable Strategy created a new and lively branch of theoretical studies of evolution.

The author is at the Museum of Comparative Zoology, Harvard University, Cambridge, MA 02138, USA.

Although the concept of the evolutionary game has considerably enriched the way in which evolutionists think about the history of life, what remains unclear is the extent to which it will be possible to measure in nature the quantities that are required to turn the theory into a predictive device. It is very difficult to measure fitnesses in nature and especially the kinds of contingent fitnesses of genotypes that depend on what other interacting individuals are doing. Moreover, Evolutionary Stable Strategies only tell us whether, if a particular strategy is adopted by the entire population, an alternative strategy can invade at low frequency. They tell us nothing about the stability of the strategy after massive invasion by alternatives, as might occur from mixtures of populations with different strategies. It may turn out that game theory will serve only as a rough heuristic rather than as a precise mode of evolutionary prediction.



CREDIT: UNIVERSITY OF SUSSEX

The impact of evolutionary game theory has been such that Maynard Smith's earlier, largely experimental work has been unduly neglected. His demonstration that there is a trade-off between female fertility and longevity in *Drosophila* is of general importance to our understanding of the evolution of life histories. His marvelous experiments with K. C. Sondhi on changing invariant characteristics by selection is one of the best demonstrations of Waddington's claim that there is considerable hidden genetic variation underlying such constant features, variation that can be made manifest when development is disrupted. Most extraordinary was their ability to produce heritable asymmetry in a normally bilaterally symmetrical organism such as *Drosophila.* Such experiments are as important to our understanding of evolutionary processes as Maynard Smith's more seductive work on game theory.

John Maynard Smith was the child of a Harley Street surgeon, spent much of his youth on Dartmoor, attended Eton College, and went on to Trinity College, Cambridge. Like so many of his upper-middle class contemporaries at Cambridge in the 1930s, he became enamored of Marxism and joined the Communist Party. He told me he was recruited into the party by Harry Harris (who later achieved fame as a human biochemical geneticist), and that Harry was the first urban Jew he, a boy from Dartmoor, had ever laid eyes on. Like so many others he became disillusioned by Stalinism and left the Communist Party after the Hungarian uprising. This was a common pattern. I once sat in the Staff Club at the University of Sussex with Maynard Smith and a number of other faculty members trying to recall whether a particular person had been a member of the Communist Party. John said he couldn't remember and asked the man on his right, who couldn't remember either but asked the man on *his* right, and so on around the whole circle. Unlike so many Americans of a similar history, neither Maynard Smith nor his colleagues became hardened rightists, but held on to their socialist sympathies, so much so that when I told a British immigration officer that I was to spend a year at Sussex he remarked, "Ah, that Bolshie University!"

John Maynard Smith was a humane, humorous, and sensible person who did not take himself or other people more seriously than they deserved. He had a sensibly skeptical view of science and its claims, which is best encapsulated in the famous dictum of his teacher, J. B. S. Haldane, who said that a scientific idea ought to be interesting even if it is not true.