How did complex life evolve? The answer could be inside out

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A new idea about the origin of complex life turns current theories inside out. In the open access journal *BMC Biology*, cousins Buzz and David Baum explain their 'inside-out' theory of how eukaryotic cells, which all multicellular life - including us - are formed of, might have evolved.

Scientists have long pondered the question of how simple "prokaryotic" cells, like bacteria, which are little more than a membrane-bound sack, evolved into more complex eukaryotic cells, which contain numerous internal membrane compartments. These compartments include the nucleus, which holds genetic information in the form of DNA; the endoplasmic reticulum, which shunts proteins and lipids around the cell; and mitochondria which act as the cell's powerhouse. The mitochondria also contain their own distinct DNA, which is one good indicator of their once having been separate organisms. The trouble is that no one has identified eukaryotic cells that are intermediate in complexity, making it much harder to know how they evolved.

At present, the most widely accepted theory is that mitochondria derive from a bacterium that was engulfed by an archaeon (plural = archaea), a kind of prokaryote that looks similar to a bacterium but has many molecular differences. The eukaryotic membrane systems, including the nuclear envelope, then formed within the boundaries of this archaeal cell through the invagination of the outer membrane. This fits with much current data, but a few problems remain. Most significantly, no archaeal cells are known that invaginate membranes.

Furthermore, it seems unlikely that mitochondria were engulfed since engulfing food requires a lot of energy, which in eukaryotes is provided by mitochondria, and engulfment likely also requires mitochondrial-derived lipids.

David Baum, University of Wisconsin, says: "All agree that eukaryotes arose from a symbiotic relationship between two cell types: bacteria that became mitochondria and a host cell, archaea, or a close relative of archaea, that became the cytoplasm and nucleus. This symbiosis explains the origin of mitochondria, but what about other eukaryotic structures, most notably the nucleus?"

The Baums' inside-out theory provides a gradual path by which eukaryotic cells could have evolved. The first stage began with a bacterial cell whose outer membrane forms protrusions, which the Baums call 'blebs', that reached out from the cell. These protrusions trapped free-living mitochondria-like bacteria between them. Using the energy gained from being in close contact with bacteria (and using bacterial-derived lipids), cells were able to get bigger and expand the size of their blebs.

The sides of the blebs formed the endoplasmic reticulum and their inner surfaces formed the outer membrane of the nucleus, with the original outer membrane of the archaeon becoming what we now call the inner nuclear membrane. Finally, the fusion of blebs with one another led to the formation of the plasma membrane. The result was the eukaryotic cell as we now know it. This inside-out theory is explained in more detail using a diagram in the research article (see notes to editors).

David Baum explains the differences between the outside-in and inside-out theories using a metaphor: "A prokaryotic cell can be thought of as a factory composed of one large, open building in which managers, machinists, mail clerks, janitors, etc. all work side by side. In contrast, a

eukaryotic cell is like a factory complex, composed of a several connected work spaces: a single control room and specialize rooms for receiving, manufacturing, shipping, waste disposal, etc. The traditional theories propose that the factory complex arose when partitions were built within a single hangar-like building. The inside-out theory, in contrast, imagines that a series of extensions were added around an original core building - now the control room - while others functions moved out into new, specialized quarters."

The inside-out theory is radically different from all existing theories because the action in building the eukaryotic cell is outside the boundaries of the ancestral cell. As David Baum, who came up with an outline of the model 30 years ago, when still an undergraduate, noted: "The inside-out model ought to be an obvious alternative to the outside-in models, but maybe you have to be a naive undergraduate to consider such an inverted perspective."

We can't know how these very early evolutionary steps occurred, but we can look at current processes for inspiration. The Baums use some examples of modern archaea that produce bleb-like protrusions to support the credibility of their ideas, and draw on many common features of eukaryotes that are easily explained by the inside-out model.

Like any good scientific theory, the inside-out model leads to predictions that can be tested in modern cells. The Baums hope, therefore, that their theory will stimulate empirical research, since there is still a lot that it not known about the biology of prokaryotic and eukaryotic cells.

Commenting on the inside-out theory Miranda Robertson, Editor of *BMC Biology*, says: "Not everyone is going to be convinced by this theory – any reconstruction of events in a past as far distant as the origin of eukaryotes is going to have areas of uncertainty which it would be futile to try and fill in. But a theory doesn't have to be right to be useful,

if it provokes people to think. And to test it."

Buzz Baum, University College London, says: "Even if the hypothesis or parts of it are refuted, we are optimistic that the effort to evaluate it will spawn new cell biological discoveries and, in so doing, will improve our understanding of biology of eukaryotic cells as they grow and divide. Although students studying cell biology may come to think that it's too late for them to contribute to a field where almost everything is known, this simply isn't the case. As the model helps to make clear, there is still much to be discovered about the basic logic of eukaryotic cell organisation."

More information: *BMC Biology*, www.biomedcentral.com/1741-7007/12/76

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