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VIEWPOINT: PART OF A SPECIAL ISSUE ON FUNCTIONAL–DEVELOPMENTAL PLANT CELL BIOLOGY

Energide–cell body as smallest unit of eukaryotic life

František Baluška[1,*] and Sherrie Lyons[2]

[1]IZMB, University of Bonn, Kirschallee 1, 53115 Bonn, Germany and [2]SUNY Empire State College, 130 N. College Street, Schenectady, NY 12305, USA
**For correspondence. E-mail baluska@uni-bonn.de*

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• **Background** The evolutionary origin of the eukaryotic nucleus is obscure and controversial. Currently preferred are autogenic concepts; ideas of a symbiotic origin are mostly discarded and forgotten. Here we briefly discuss these issues and propose a new version of the symbiotic and archaeal origin of the eukaryotic nucleus.
• **Scope and Conclusions** The nucleus of eukaryotic cells forms via its perinuclear microtubules, the primary eukaryotic unit known also as the Energide–cell body. As for all other endosymbiotic organelles, new Energides are generated only from other Energides. While the Energide cannot be generated *de novo*, it can use its secretory apparatus to generate *de novo* the cell periphery apparatus. We suggest that Virchow's tenet *Omnis cellula e cellula* should be updated as *Omnis Energide e Energide* to reflect the status of the Energide as the primary unit of the eukaryotic cell, and life. In addition, the plasma membrane provides feedback to the Energide and renders it protection via the plasma membrane-derived endosomal network. New discoveries suggest archaeal origins of both the Energide and its host cell.

Key words: Cell body, cell theory, coenocytes, cytoskeleton, endosymbiosis, Energide, eukaryotic cell, evolution, microtubules, nucleus, syncytia.

PETER BARLOW AND PROBLEMS WITH THE CELL THEORY

As documented by papers in this *Annals of Botany* special issue, the interests of Peter Barlow were wide-ranging and profound. These interests touched significantly also on the fundamental problems associated with the current version of the cell theory (Baluška *et al.*, 1997, 1998, 2004*a*, *b*). Multinuclear cells, the supracellular nature of plants and fungi, and the many examples of cells within cells are all exceptions to cell theory. The supracellular nature of higher plants is complemented with the inherent property of animal cells of generating cytoplasmic channels known as tunnelling nanotubes (Wang *et al.*, 2010; Zani and Edelman, 2010; Abounit and Zurzolo, 2012; Wang and Gerdes, 2012; Austefjord *et al.*, 2014). In higher plants, migration of nuclei from cell to cell is known as cytomixis (Heslop-Harrison, 1966; Liu *et al.*, 2007; Lone and Lone, 2013; Mursalimov *et al.*, 2013; Kravets *et al.*, 2017). The individuality of eukaryotic nuclei is apparent from red algal parasites, which transfer whole nuclei in their host cells, and these then redirect the host cell biology and physiology for the parasite's benefit (Goff and Coleman, 1984, 1985, 1987, 1995; Goff and Zuccarello, 1994; Salomaki and Lane 2014).

There are numerous examples of unicellular but multi-Energide coenocytic organisms, including marine algae such as *Caulerpa*, *Cladophora* and *Acetabularia* (Strasburger, 1913; Menzel and Elsner-Menzel, 1990; Menzel, 1994; Mine *et al.*, 2008; Baluška *et al.*, 2012). Probably the most flagrant violation of the current problematic version of the cell theory is provided by Ascomycota (Gladfelter, 2006; Lang *et al.*, 2010; Roper *et al.*, 2011) and Glomeromycota (Kuhn *et al.*, 2001; Bewer and Wang, 2005; Jany and Pawlowska, 2010; Marleau *et al.*, 2011; Boon *et al.*, 2015; Young, 2015). Their fungal mycelia harbour genetically different nuclei in the same cytoplasm. In other words, these coenocytic 'cells' provide shelter for genomically diverse organismal units. For example, one single multinucleate spore of *Glomus irregulare* contains up to 1000 nuclei. In addition, large heterogeneity exists in the number of nuclei (Energides) among sister spores (Marleau *et al.*, 2011). Moreover, non-self vegetative fusions are typical of hyphae of the arbuscular mycorrhizal fungus *Glomus intraradices* (Croll *et al.*, 2009).

EVOLUTION OF THE ENERGIDE–CELL BODY CONCEPT: SACHS, MAZIA AND OTHERS

Discoveries of centrosomes and centrioles organizing both flagella and mitotic spindles of eukaryotic cells (Boveri, 1895; Flemming, 1891; Baltzer, 1967; Paweletz, 2001) strongly suggest that nuclei of eukaryotic cells are closely associated, via perinuclear microtubules (Baluška *et al.*, 1997, 1998, 2004*a, b*), with both centrosomes and centrioles. Daniel Mazia was the first to realize that there is not only structural but also functional unity between all these organelles and he proposed the 'cell body' concept at the end of his scientific career (Mazia, 1987, 1993). Daniel Mazia's cell body concept was preceded by Julius Sachs, who proposed his Energide concept in 1893

(Sachs, 1893; Baluška *et al.*, 2006). But Sachs was not aware of microtubules, centrioles and centrosomes. Under the influence of Theodor Boveri, it was Max Hartmann (1911) followed by Karl Bělař (1926) who further evolved the Energide concept in this respect (discussed in Chen, 2003). It is not known whether Daniel Mazia was aware of the Energide concept (*Energidenlehre* in German; see Chen, 2003) when he proposed the cell body concept in 1993 (Mazia, 1993). However, he had come to think the centrosome was potentially far more than just the organizer and initiator of microtubule synthesis. They were 'bearers of information about cell morphology' and that 'something exists at a level of complexity higher than that of molecules akin to the level of the complexity of chromosomes', and that something was what he called the 'cell body' (Mazia, 1987; Lyons, 2018).

In 1997, 1998 and 2004, together with Peter Barlow, we updated Mazia's hypothesis and proposed that the nucleus with perinuclear microtubules represents the smallest and basic unit of eukaryotic life (Baluška *et al.*, 1997, 1998, 2004*a, b*). This hypothesis solves the problem of syncytia and coenocytes, which are incompatible with the classical cell theory stating that the whole cell is the basic unit of eukaryotic life (Baluška *et al.*, 1997, 1998, 2004*a, b*, 2006). In 2009, we extended the Energide–cell body concept to central nervous systems (Agnati *et al.*, 2009). Later, we discussed the Energide–cell body hypothesis from the perspective of the Neo-Energide concept (Baluška *et al.*, 2006; see also Nicholson, 2010), originally proposed by Julius Sachs (Sachs, 1892*a, b*). Recently, the evolutionary origins of the Energide–cell body complex, as well as its eukaryotic cell, were discussed from evolutionary perspectives (Baluška and Lyons, 2018). Here, we briefly summarize the Energide–cell body concept and highlight the latest evidence of its validity.

The Energide–cell body theory provides a robust explanation as to why there is eukaryotic sex and why male gametes are typically small, flagellated and motile, whereas female gametes are large, not motile and based on the actin cytoskeleton. The flagella of sperm cells are made of microtubules and typically lack any actin cytoskeleton while the larger egg cells are based primarily on the actin cytoskeleton (Baluška *et al.*, 2004*a*, 2006). Importantly, nuclear pores are prototypes of cell–cell channels, resembling plasmodesmata in plants and tunnelling nanotubes in animals. The Energide–cell body concept is useful in explaining such perplexing discoveries as entosis and cannibalism in animal cells (Fais, 2007; Overholtzer *et al.*, 2007; Janssen and Medema, 2011; Sharma and Dey, 2011). Moreover, developing erythroblasts extrude their nuclei, which are then engulfed by macrophages (Yoshida *et al.*, 2005; Klei *et al.*, 2017). Further examples of the independent nature of nuclei from cells include cell–cell transport of nuclei in plants (Lone and Lone, 2013; Mursalimov *et al.*, 2013; Kravets *et al.*, 2017) and infectious transfer of nuclei in parasitic red algae (Goff and Coleman, 1984, 1987). In contradiction to the current version of the cell theory is the unique multigenomic nature of coenocytic (multi-Energidic) Glomeromycota fungi, whose spores contain up to 1000 nuclei (Energides–cell bodies) within one huge single coenocytic cell (Marleau *et al.*, 2011; Boon *et al.*, 2015; Young, 2015).

ARCHAEAL ORIGINS OF SYMBIOTIC ENERGIDES–CELL BODIES AND THEIR HOST CELLS (CHRONOCYTES)

In the contemporary literature, diverse versions of autogenous theories for the origin of the eukaryotic cell predominate. However, it is very important to consider that, although initially treated with scepticism, the symbiotic origin of mitochondria and plastids turned out to be true. Viewing the nucleus as the primary eukaryotic endosymbiosis event would solve problems with the sudden appearance on the evolutionary scene of the complex eukaryotic cell, with its nucleus inherently associated with an endoplasmic reticulum and microtubular cytoskeleton. The various autogenous theories also are not able to explain why the last eukaryotic ancestors (LECAs; Woese, 1998, 2002) were complex organisms having almost all the eukaryotic features, including centrosomes, nuclei with lamina and nuclear pores, as well as the flagellar apparatus based on microtubules (Gräf *et al.*, 2015; Grau-Bové *et al.*, 2015; Vicente and Wordeman, 2015). All this provides evidence for the parasitic–symbiotic concept of a small motile cell, using its microtubular flagella, invading a large non-motile host cell based on the actin cytoskeleton (Baluška *et al.*, 2004*a*). Recent advances in our understanding of these elusive issues reveal archaeal origins of this eukaryotic complexity (Guy and Ettema, 2011; Guy *et al.*, 2014; Koonin and Yutin, 2014; Koonin, 2015; Eme *et al.*, 2017; Zaremba-Niedzwiedzka *et al.*, 2017). All these data point to the archaeal nature of both the host and guest cells that generated the LECA (Eme *et al.*, 2017; Baluška and Lyons, 2018). Archaeal host cells [termed 'chronocytes' by Hartman and Fedorov (2002)] were proposed to acquire microtubule-based guest cells endosymbiotically (Baluška and Lyons, 2018), and these cells transformed into eukaryotic nuclei associated with the microtubule-based cytoskeleton. Thus, both the discovery of critical eukaryotic signature proteins (ESPs; Hartman and Fedorov, 2002) in Archaea of the 'TACK' superphylum (Guy and Ettema, 2011; Eme *et al.*, 2017; Spang *et al.*, 2017; Zaremba-Niedzwiedzka *et al.*, 2017) and new discoveries in cell biology (summarized by Baluška and Lyons, 2018) suggest archaeal origins of both the Energides–cell bodies and their host cells.

THE ENERGIDE–CELL BODY COMPLEX AS THE SMALLEST UNIT OF EUKARYOTIC LIFE

Autogenous evolution is a kind of self-generated evolution (O'Malley and Müller-Wille, 2010); whereas the parasitic–symbiotic scenarios for the evolutionary origin of complex eukaryotic cells are examples of evolution by associations imposed on cells from outside (Baluška *et al.*, 2004*a, b*, 2006; Klepzig *et al.*, 2009; Sapp, 2010; Gilbert *et al.*, 2012; Baluška and Lyons, 2018). The symbiotic origin of the nucleus as an Energide–cell body complex, as proposed in the latest version of the Neo-Energide theory (Baluška and Lyons, 2018), is supported by several unique features of eukaryotic cells that are not compatible with the diverse autogenous theories. First of all, the eukaryotic cilia and flagellar apparatus share their basal bodies with the perinuclear centrioles and centrosomes (Baluška and Lyons, 2018). Importantly, SYNE proteins, which anchor nuclei to neuromuscular synaptic junctions (Grady *et al.*, 2005) and centre nuclear positions within eukaryotic cells (Zhu *et al.*, 2017), are also integral proteins of ciliary rootlets (Potter *et al.*, 2017). Relevant in this respect are algae such as *Chlamydomonas* and the protozoan *Giardia*, which have flagellar basal bodies connected to the nuclear surfaces via centrin-based contractile fibres (Salisbury, 1988; Wright *et al.*, 1989; Koblenz *et al.*, 2003; Dawson and House, 2010). The flagellar apparatus is an ancient eukaryotic organelle that is based on basal bodies acting as the primary microtubule-organizing centres (MTOCs) of the eukaryotic cell (Azimzadeh, 2014; Gräf *et al.*, 2015). Nuclear pores resemble and act like classical cell–cell channels (Lee *et al.*, 2000; Baluška *et al.*, 2006; Bloemendal and Kück, 2013). There are also similarities between nuclear pores and flagellar entry domains (McClure-Begley and Klymkowsky, 2017; Rout and Field, 2017). Intriguingly in this respect, flagellar centrins (Salisbury, 1988; Salisbury *et al.*, 1988) are components of plant-specific cell–cell channels (plasmodesmata; Blackman *et al.*, 1999) and nuclear pores (Resendes *et al.*, 2008); and also connect centrioles/centrosomes to the nuclei (Gräf *et al.*, 2015). The symbiotic origin not only of nuclei (Baluška and Lyons, 2018) but also of cilia and flagella is strongly supported by numerous similarities between cilia/flagella and immunological synapses (Stinchcombe and Griffiths, 2014; Stinchcombe *et al.*, 2015). There are strong parallels between ciliogenesis and the formation of immunological and cytotoxic synapses (Stinchcombe *et al.*, 2015; Dieckmann *et al.*, 2016).

In the recently proposed updated version of the Energide–cell body theory, the endoplasmic reticulum membranes represent an outgrowth of the outer part of the nuclear envelope (Baluška and Lyons, 2018) and membranes of the Golgi apparatus represent specialized extensions of the endoplasmic reticulum (Chapman and Alliegro, 2012; Baluška and Lyons, 2018). Finally, the Energide–cell body complex is proposed to represent the primary and smallest unit of eukaryotes that can generate a complete cell, whereas de-nucleated eukaryotic cells can never generate a new Energide–cell body *de novo* (Baluška *et al.*, 2006; Baluška and Lyons, 2018). This primacy of the Energide–cell body unit over the rest of the eukaryotic cell can also be seen during cell division, which invariably starts with the division of the centriole/centrosome, is followed by nuclear division and completed by cytoplasmic/cell periphery division, known as cytokinesis. The latter is instructed by the newly emerged daughter Energides–cell bodies of early cytokinetic cells. In conclusion, Rudolf Virchow's famous tenet *Omnis cellula e cellula* should be updated to *Omnis Energide e Energide* (Baluška and Lyons, 2018).

DANIEL MAZIA VERSUS LYNN MARGULIS: ENERGIDE–CELL BODY VERSUS KARYOMASTIGONT

In their karyomastigont hypothesis, Lynn Margulis and her co-authors proposed the origin of the nucleus via the karyomastigont, which consisted of a nucleus and flagellar apparatus (Margulis, 1996; Margulis *et al.*, 2000, 2005, 2006, 2007). The problematic part of the karyomastigont concept is the spirochaete origin of the tubulin-based flagellum, which should be descended from putatively *Mixotricha*-like ectosymbionts (Margulis, 1996; Margulis *et al.*, 2000, 2006; König *et al.*, 2006; Radek and Nitsch, 2007). In our recent Energide–cell body concept (Baluška and Lyons, 2018), the microtubule-based putative flagellated Archaea are proposed to invade the actin-based host cell Archaea and be transformed into the Energide–cell body. This Archaea–Archaea concept of eukaryotic origin explains why the eukaryotic nucleus is inherently associated with microtubule-based flagella via centrin-based and contractile rootlet/rhizoplast structures in evolutionarily ancient protists, including *Naegleria*, *Giardia* and *Breviata* (Walker *et al.*, 2006; Minge *et al.*, 2009; Dawson and House 2010; Fritz-Laylin and Fulton, 2016) and in flagellated algae, including *Chlamydomonas reinhardtii* (Salisbury, 1988; Salisbury *et al.*, 1988; Dutcher, 2003). Later in eukaryotic evolution, the nucleus was liberated from the flagellar apparatus (*sensu* the akaryomastigont of Margulis and colleagues) but remained functionally coupled to cilia via basal bodies, centrioles and centrosomes (Dolan *et al.*, 2000*a, b*). Moreover, higher plant cells accomplished further liberation when their Energides–cell bodies lost corpuscular centrioles/centrosomes during land plant evolution (Mazia, 1987, 1993; Baluška *et al.*, 1997, 1998, 2004*a, b*). The Energide–cell body concept provides answers as to why centrioles and basal bodies share not only the same centrin-based architecture (Dutcher, 2003; Koblenz *et al.*, 2003; Ruiz *et al.*, 2005), but also why their duplication is typically linked to the nucleus, accomplished only once per cell cycle (Salisbury, 1995, 2007), and why there are similarities between cilia/flagella and immunological synapses (Stinchcombe and Griffiths, 2014; Stinchcombe *et al.*, 2015).

OUTLOOK

The main reason the Energide–cell body concept has essentially been ignored is because researchers have been reluctant to accept the endosymbiotic origin of the nucleus (Baluška and Lyons, 2018). A better understanding of the true nature of the eukaryotic cell is not only important for understanding the development of multicellular organisms but is also essential for our ability to cure cancer (Boveri, 1929; Mazia, 1987; Lingle *et al.*, 2005; Cosenza and Krämer, 2016). Our understanding of the true nature of the eukaryotic cell as a symbiotic consortium organized via Energide–cell body activities is essential for our ability to comprehend life based on eukaryotic cells and their nucleus-based Energides–cell bodies. The archaeal nature of both the Energide–cell body and its host cell supports the two-domain Tree of Life (Eme *et al.*, 2017; Spang *et al.*, 2017). This is a real archaeal revolution in our understanding of the evolutionary origins of eukaryotic cells and their nuclei.

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