The non-evolution of apoptosis

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The phenomenally complicated programme of cellular 'death', otherwise known as apoptosis, is the chief source of occupation for tens of thousands of scientific researchers. The believer in biblical creation happily ascribes praise to the omniscient Creator for the incredible designed complexity that is apparent. Conversely, the person who subscribes to methodological naturalism faces the significant challenge of accounting for the origin and evolution of apoptosis. The oft-claimed conservation of various apoptotic components, from the very 'earliest' life-forms, does not suffice as an explanation. 'Apoptosis-style' demise is now recognised in unicellular eukaryotes and even bacteria and, in recent years, a handful of evolutionists have published hypotheses in the scientific literature in which they have attempted to explain the simultaneous evolution of apoptosis and endosymbiosis. The latter, itself is an unproven hypothesis for the origin of the first unicellular eukaryotic cells, including the origin of mitochondria. An examination of these evolutionary ideas, for a naturalistic origin of apoptosis, forms the main focus of this paper.

Apoptosis* or 'programmed cell death' is a ubiquitous cellular phenomenon in living organisms. An earlier paper described this process in detail, contrasted it with necrotic cell death and provided a framework in which to understand cell 'death' from a young-earth creationist perspective.[1,2] Readers are advised to familiarise themselves with that paper in order to better appreciate the arguments presented here. Some scientists have recently questioned the distinction between apoptosis and necrosis—since this relates to the author's previous arguments, an appendix includes further discussion. Apoptotic phenomena have been described in several *uni*cellular eukaryotes*. The alleged evolutionary conservation of apoptosis, from the 'earliest' eukaryotic cells, would therefore appear to be problematic on theoretical grounds. Not only must evolutionists explain *how* apoptosis evolved *before* the 'invention' of multicellularity, but they are faced with explaining how *single* cells—that have acquired a functional apoptotic response—pass on this more advantageous, advanced genetic complement to their progeny? In what follows, some evolutionist attempts to grapple with apoptotic origins are reviewed. A major component of these ideas is the hypothesis of endosymbiosis*.

* Items with an asterik, the first time they are mentioned, are defined in a glossary at the end of the article.

Evolutionists on apoptosis—a review

Some examples of the claims by evolutionists, that the widespread occurrence of apoptosis indicates it to be a highly evolutionary-conserved mechanism, have already been documented by this author.[3] The following assertion typifies this approach:

> 'The conservation of transduction* pathways and functional homology of effector molecules [involved in apoptosis and differentiation] clearly bear witness that the principles of life established during prokaryotic and eukaryotic unicellular evolution, although later diversified, have been unshakably cast to persist during metazoan* phylogenesis.'[4]

However, such statements are circular and, by definition, explanation-free. The argument, although not spelled out as such, runs something like this: homology is similarity due to common ancestry; thus the sub-cellular and biochemical homology observed in apoptotic mechanisms is evidence that these multifarious life forms sprang from a common ancestor. As Wells has pointed out, such claims for homology are nonsense.[5]

However, for the purposes of argument, let us allow the possibility that apoptotic mechanisms *have* evolved; that is, that their exquisite design is indeed the product of mutations and natural selection, occurring over millions of years. Have any evolutionists succeeded in their attempts to give substantive explanations for the origin and evolution of apoptosis purely by reference to time, chance and natural processes? The answer is a resounding no; as we shall see, such hypotheses are woefully inadequate. This paper is predominantly a critique of two papers in which the authors speculate on apoptotic origins.[6,7]

Unicellular 'apoptosis'

From an evolutionary view-point, the fact that apoptotic phenomena have been observed in many species of unicellular eukaryotes[8–17] places the origin of apoptosis before that of metazoan life. However, it is conceded that,

> 'The cell death pathways of protozoans…show no homology to those in metazoans, where several death pathways seem to have evolved in parallel.'[18]

One idea is that 'ancient viral infections' transferred key elements of apoptotic pathways to the nuclear DNA of such 'early' cells[17] but it is difficult—if not impossible—to conceptualize the *step-wise* production of highly complex apoptotic cascades in single cells. Nevertheless,

let us imagine that a miraculous combination of the precise information-adding mutations occurred that specified for a complex, fully functioning apoptotic mechanism in a unicellular eukaryote; i.e. hopeful-monster-style! Fitness in evolutionary terms is measured by an organism's survival chances. But, in the case of this unicell, the true test of its apoptotic mechanism is its demise rather than its survival. It is difficult to imagine how natural selection could select 'good' apoptotic genes for their survival value. Therefore, an evolutionary scenario purporting to account for either the *origin* of apoptosis or its *improvement* by natural selection has conceptual difficulties, placing the onus on evolutionists to provide a convincing rationale for these things.

For a long time these issues were ignored, or else were not widely appreciated. In recent years, however, several scientists have put forward hypotheses that attempt to address this conundrum (see later) and there is now discussion of apoptosis in prokaryotes*. One web-article says of bioscientists at the University of Melbourne, Australia,

> '[They] believe apoptosis may have arisen even before the first multi-cellular organisms, possibly in single-celled bacteria, in which virus-infected cells "suicided" to protect their relatives. Multi-cellular life forms later recruited the apoptosis mechanism as a way of discarding unwanted cells during embryogenesis … viruses that can inhibit apoptosis are an obvious hazard, so evolution invented a back-up system to eliminate virus—infected cells—the cytotoxic T-cell.'[19]

The existence of various apoptotic signatures in the developmental processes of several species of extant bacteria has been reported,[20,21] involving gene activation and the interaction of various signal transducers and their regulators. In other words, what has been traditionally termed bacterial autolysis—self-digestion of the cell wall by peptidoglycan hydrolase enzymes, resulting in the cell's disintegration—may represent apoptosis. Programmed death in bacteria also appears to occur in the presence of damaging agents such as antibiotics,[22,23] with some interesting implications for certain types of antibiotic resistance.[24] However, fascinating though the findings of these all research efforts may be, accounting for the evolutionary *origin* of apoptotic mechanisms in 'early' bacteria is quite another matter.

Endosymbiosis

A handful of evolutionists, pondering unicellular apoptosis, have speculated that endosymbiosis (the hypothesis for the origin of mitochondria* and chloroplasts in eukaryotic cells) and apoptosis evolved simultaneously. Endosymbiosis theory was first popularised by Lynn Margulis in the mid 1970s[25] and, with modifications, is now almost universally accepted by evolutionists. Cellular organisation of eukaryotes is so much more complex than that of prokaryotes—including membrane-bound nucleus, mitochondria, chloroplasts, Golgi body, endoplasmic reticulum, '9+2' flagellum/cilium arrangement, cytoskeleton, diploid stage in life cycle, mitotic and meiotic cell division—that their alleged evolutionary origin is a fundamental question in biology. Of course, from a creationist perspective, each basic kind of prokaryotic and eukaryotic organism (unicellular and multicellular) is the special creation of God and no continuum between these fundamentally different cellular organisations is expected. However, evolutionary theory must account for eukaryotic origins. The basic idea of endosymbiosis is that aerobic, autotrophic bacteria took up residence inside larger prokaryotes and became the forerunners of mitochondria. Likewise, chloroplasts are said to be descended from photosynthesising prokaryotes (e.g. cyanobacteria) that were engulfed by larger prokaryotes (figure 1).

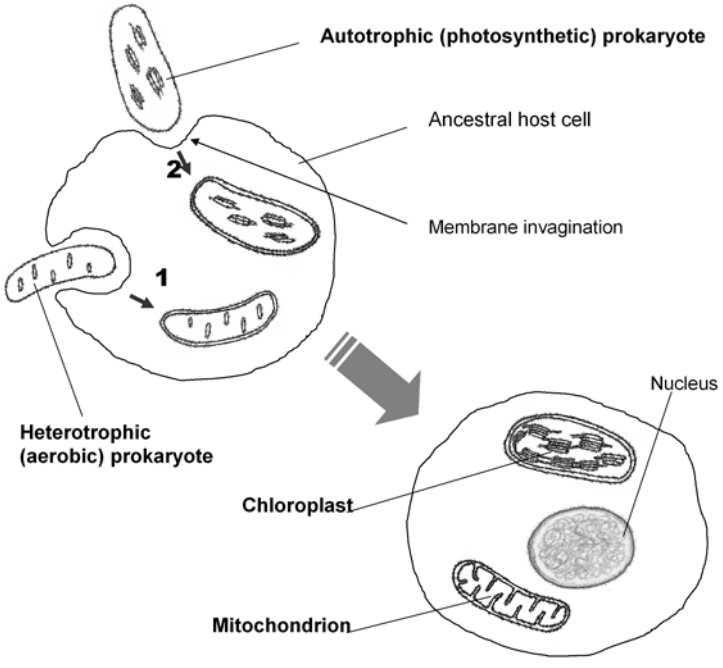

Figure 1. *Diagrammatic representation of the hypothesised events during endosymbiosis. The schematic illustrates the two fundamental events that are envisaged to have contributed to the first eukaryotes. The phagosome (invaginated engulfing membrane) becomes the outer membrane of the endosymbiont. Theorists differ on the order of events; i.e. whether a well-developed nucleus evolved prior to the acquisition of mitochondria (1) and chloroplasts (2) or whether mitochondria predated chloroplasts in serial endosymbiotic episodes.*

Thus, a mutually beneficial arrangement between 'host' and 'endosymbiont' is imagined; e.g. anaerobic cells would have benefited from aerobic endosymbionts in environments where oxygen became available. In time, some of the functions of these precursors of mitochondria and

chloroplasts were allegedly transferred to the nucleus of the 'host' cell. Not surprisingly, there are many problems with such scenarios.[26] In spite of the general acceptance of the basic tenets of endosymbiosis, Jerlström notes that 'current scientific evidence conflicts with the stepwise evolution from prokaryote to primitive eukaryote and then to eukaryote'.[27] Indeed, very recently, a further problem came to light as researchers confirmed the presence of so-called 'mitochondrial remnants' in the gut parasite *Giardia intestinalis*.[28] This nucleated unicell (a protozoan) has long been thought to lack mitochondria and, therefore, has been said to be an intermediate between prokaryotes and eukaryotes; as such it has been the standard textbook example of a key player in eukaryotic history.[29] It was argued that the nucleus developed *prior* to the acquisition of mitochondria. Evolutionists now recognise that the finding of 'mitosomes' in *Giardia* argues strongly *against* it being an intermediate in the endosymbiotic evolution of eukaryotes.[30]

In spite of these problems with endosymbiosis, many evolutionists will undoubtedly continue to contend for a *simultaneous origin* of endosymbiosis and apoptosis. Ideas of a 'coupled' endosymbiosis/apoptosis origin will now be examined in some detail to see how they stand up to close scrutiny.

Kroemer's hypothesis—role of mitochondrial permeability transition

A French scientist, Guido Kroemer, published the first major attempt at a hypothesis for apoptosis evolution.[6] In spite of the huge diversity of apoptosis pathways, some features are usually the same in the majority of species/tissues/cell types; e.g. DNA fragmentation, externalization of the membrane phospholipid, phosphatidylserine, cell shrinkage, production of ROS* (reactive oxygen species), and activation of proteases.[31] Seemingly, a common 'pathway' exists at the point of no return, the 'executioner' stage. Kroemer argues therefore, that mitochondria play a key role at this stage and he speculates on their evolutionary origins.

He initially gives a detailed review of the various requirements for the *'central executioner'* of apoptosis, which may be summarized as follows:

- It must become activated at the effector stage (i.e. at point of no return);
- Its presence should be sufficient to cause apoptosis but vital if apoptosis is to occur at all;
- Many triggering pathways should converge onto it;
- It should coordinate all nuclear, cytoplasmic and membrane apoptotic manifestations;
- It should be ubiquitous as diverse cell types undergo apoptosis;
- It must include a function(s) that is(are) essential for cell survival, otherwise mutations could potentially result in a supremely apoptosis-resistant cell;
- It should act like a switch (on/off) so that cells either 'die' or survive.

Apoptosis 'executioner' revealed

Kroemer convincingly argues that the mitochondrial permeability transition step (hereafter MPT) fulfils these criteria. MPT* involves the movement of solutes across the inner mitochondrial membrane, disrupting the potential of the trans-membrane proton pump and resulting in the *efflux* of soluble proteins from the matrix and inter-membrane space of the mitochondrion to the cytoplasm.[32] This occurs via permeability transition (PT) pores (or 'mitochondrial megachannels').[33,34] Evidence that MPT constitutes the apoptosis executioner step includes the following: many triggering pathways *do* converge on MPT;[35] MPT *is* manifest by *disparate* cellular effects (nuclear apoptotic changes, production of ROS—which themselves can trigger MPT, altering cellular redox potentials—and oxidation of membrane lipids); molecular components of the PT pore and MPT events *are* ubiquitous.[36] The caspases (ICE/proteases) have been previously mentioned as 'executioners' as well as their activation by mitochondria;[37] ongoing research is helping to clarify the role of protease cascades and MPT at this crucial juncture of apoptosis.

What seems to be important is the release, via these pores, of (a) Apoptosis Inducing Factor (AIF)—a potent inducer of the nuclear apoptotic changes, culminating in oligonucleosomal DNA fragmentation, and (b) cytochrome c*—an activator of one of the key apoptotic-signature protease (caspase) enzymes.[38] Proteins in the Bcl-2 family, such as Bcl-2 and Bcl-xl, reside in the outer mitochondrial membrane[2,37] and research suggests that they can stop liberation of AIF[39] and cytochrome c[40,41] by controlling the MPT, thereby suppressing apoptosis. Conversely, the Bcl-2 antagonist, Bax, has been shown to promote MPT by disrupting the trans-membrane potential.[42]

Apoptosis/endosymbiosis hypothesis and axioms

Refreshingly, Kroemer admits that he takes as a given the 'widely accepted' endosymbiosis hypothesis.[25] He states that this is one of his 'premises' and describes his subsequent hypothesis as 'speculation'.[43] Additionally, because of his evolutionary world-view, the existence of apoptotic phenomena in *uni*cellular eukaryotes as well as all metazoa (animal, plant and fungal cells) constrains him to believe that apoptosis evolved *before* multicellular life appeared[44]—indeed he plumps for its *simultaneous* origin with endosymbiosis (discussed below). From this alone, we see that no matter how plausible his ideas might seem, they are not the inescapable conclusion of data from operational science. In other words, providing a possible evolutionary scenario does not equate to proof for the origin and alleged conservation of apoptosis. One can equally choose to regard the ubiquity of apoptotic machinery in living cells as testimony to a common design plan.

As evidence for the apoptosis/endosymbiosis hypothe-

sis, Kroemer mentions that certain MPT-like phenomena and associated molecules (or their homologues; or analogues) have been found in widely disparate cell types, including the yeast, *Saccharomyces cerevisiae*, and various bacteria. He states,

> ' … it *appears possible* that many of the constituents of the PT pore and several apoptogenic mitochondrial proteins were already present in the aerobic bacterium from which the mitochondrion evolved' [emphasis added].[45]

However, although certain *mitochondrial* cell-death events in eukaryotic cells seem to have *some* parallels in bacteria, it has been reported elsewhere that the specifics of MPT-mediated mitochondrial destruction are not thought to be related to autolysis of bacterial cells.[21] Furthermore, the characteristic *nuclear* apoptotic events of multi-cellular eukaryotes are absent from unicellular eukaryotes like yeast. Needless to say, many evolutionists interpret this to mean that mitochondrial apoptotic phenomena are ancient and phylogenetically conserved, whereas the nuclear events are a later innovation.

Having discussed several *additional* premises (themselves based on another author's hypothesis for bacterial apoptosis![20]), Kroemer states:

> ' … it is conceivable that the basic mechanism of apoptosis became fixed during evolution *in the very moment* in which endosymbiosis became established' [emphasis added].[46]

Of course, implicit within this statement is the admission that the 'basic mechanism of apoptosis' is irreducibly complex. However, if one considers the extraordinary complexity of apoptosis,[1,2] this statement is seen to be a tremendous leap of faith, little short of belief in miracles.

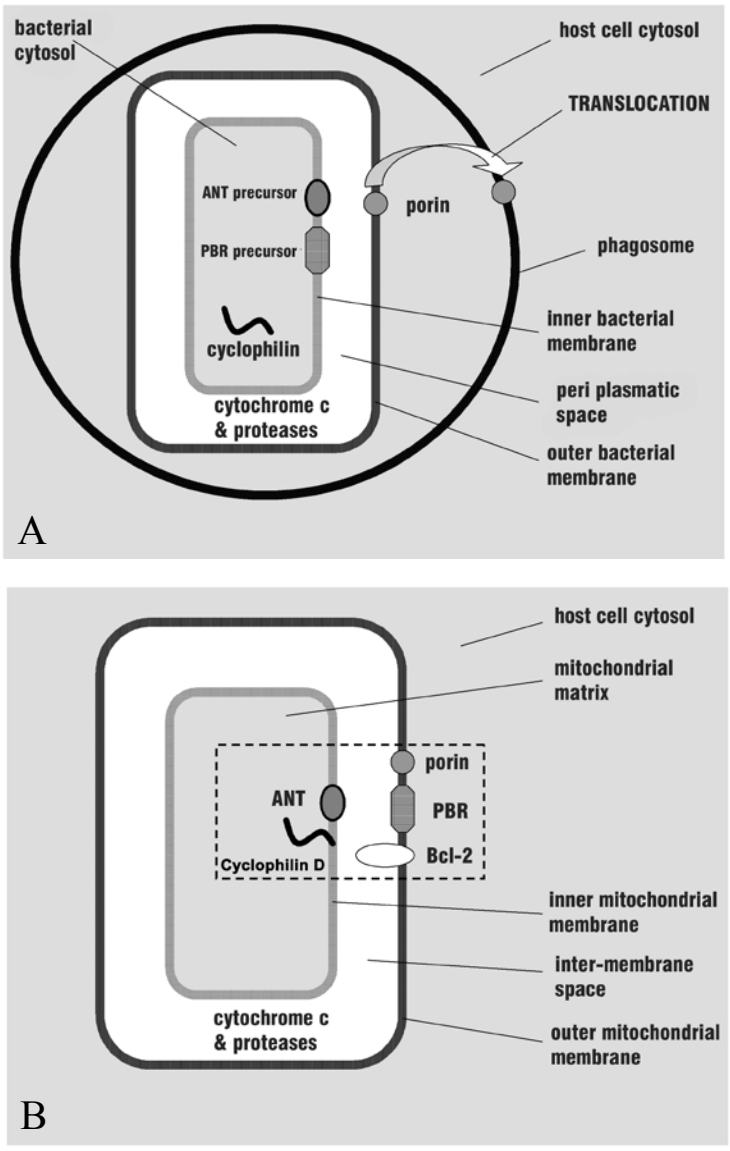

Figure 2. *Kroemer's 'Highly speculative model' for the endosymbiotic evolution of mitochondrial permeability transition (adapted and redrawn from figure 5 of the author's paper; see ref. 6). (A) The hypothetical moment of accommodation of the aerobic bacterial endosymbiont (possessing both an inner and outer membrane) into the host cell. Bacterial molecules such as perforins translocate to the host cell phagosome, allowing diffusion of small molecules such as ATP. Precursors of ANT (adenine nucleotide translocator), PBR (peripheral benzodiazepine receptor) and cyclophilin D are also envisaged to be present, though not in their contemporary locations. (B) Later in evolution, a true PT pore complex arises (enclosed by the dashed box). The PT-dependent release of molecules such as cytochrome c and protease enzymes may then cause apoptosis.*

Multiplied speculation

Kroemer goes on to detail his 'Highly speculative model for the molecular evolution of mitochondrial permeability transition (PT)'[47] which is summarised as follows: The aerobic bacterium (precursor of the 'protomitochondrion') that invaded or was ingested by the potential host cell (itself a bacterium) is envisaged to possess toxins, which may or may not have been host-specific. In order to avoid releasing these harmful chemicals into the host cytoplasm (thereby killing the host cell) the host's bactericidal enzymes (precursors of apoptotic proteases) had to be sequestered in sub-cellular organelles (e.g. a lysosome; though how this evolved is not explained)[48] or else maintained as inactive precursors. Thus, a sort of stand-off was established, where any attempt by the protomitochondrion to kill the host, or vice versa, was inhibited—obligating both parties to accept a symbiotic relationship.

> '*From this moment*, the two initially independent organisms are forced to co-evolve. During this co-evolution, large parts of the bacterial genome are gradually incorporated into the nuclear genome' [emphasis added].[49]

How did MPT simultaneously evolve during this endosymbiosis event? The author describes a

scenario whereby certain bacterial molecules (e.g. porins) are imagined to be precursors of the PT pore complex that forms across the mitochondrial membranes. A basic PT pore was formed at the moment of endosymbiosis, with porins and other molecules hopping across from bacterial membrane to the phagosome*—later on, other molecules 'evolved' to produce the PT pores seen in mitochondria today (figure 2). After yet more speculation—the text is littered with words like 'may', 'possibly', 'conceivable', 'speculative'—the reader is told,

> 'The essential role of the PT pore (or its components) in the host-parastie [*sic*; parasite] coordination, for instance at the level of ATP* metabolism or respiratory control, would then account for the fixation of PT throughout eukaryotic evolution. In other words, the interaction of a few proteins at the host/parasite interface would be neuralgic [painful] for endosymbiosis but would also lay the evolutionary grounds of apoptotic cell death.'[49]

The significant possibility of 'host cell' rejection of foreign proteins and nucleic acid is envisaged by Kroemer to be the very *facilitator* for simultaneously establishing both apoptosis and endosymbiosis! But, one does not need to be an expert biochemist or cell biologist to realise that this is a case of story-telling; another example of turning contrary evidence into evidence *for* evolution, revealing a considerable faith in veritable biochemical and cellular miracles. With a few crude brush strokes, the on-looker is expected to visualize a picture in which exquisitely fine detail has also suddenly appeared on the canvas, without questioning where it came from! Is the admirer of the work to conclude that these intricacies are somehow a property of the paint pigments? Yet evolutionists must similarly suspend disbelief each time they indulge in these origin scenarios (choosing to overlook the stupendous biochemical complexity that really exists). Unfortunately for them, even to peep beneath the lid of the 'Black Box' of the cell is to be confronted with a world of astonishing complexity, the simplest of whose apoptotic molecular machines (proteins)—not to mention their interactions—demands an explanation, yet whose existence is simply ignored.[50] To say that the evidence of apoptosis points to the creation of a supremely intelligent God is the most rational—and this author would add, honest—conclusion to which one could come.

Kroemer realises that the piece-meal (slow and gradual) evolution of apoptosis in unicells is conceptually—even theoretically—very difficult, to say the least:

> '…the existence of PCD* [in unicellular eukaryotes] obviously cannot constitute a direct advantage for Darwinian selection.'[51]

This is precisely why he argues that his endosymbiont hypothesis helps explain why these cells already have apoptotic capabilities; i.e. apoptosis developed 'in the very moment' that endosymbiosis occurred.

Blackstone and Green hypothesis—Host cell manipulation by ATP and ROS

Blackstone and Green, who acknowledge the ideas of Kroemer's paper, begin the introduction to their article thus,

> 'Biological and biochemical mechanisms often seem dauntingly complex, suggesting to some that such mechanisms could not have evolved. While this conclusion need not follow, the complexity nonetheless remains.'[52]

It is highly significant that the first sentence is referenced to Michael Behe's book in which he discussed the irreducible complexity of several biochemical systems.[50] Blackstone himself wrote a scathing review of Behe's thesis in a popular biology journal, charging him with committing the basic logical error of *argumentium ad ignorantium*—i.e. arguing for the truth of a proposition on the basis that it has not been proven false, or vice versa.[53] Therefore, it is transparent that this paper by Blackstone and Green is a case of taking up the gauntlet that Behe threw down when his book was published. By commencing their paper in this way, the authors are tacitly confirming that the phenomenon of irreducible complexity applies to apoptosis—one of the major conclusions drawn in an earlier paper by this author[1]—although they attempt to provide a rationale for how this might have been circumvented. Incidentally, Behe has ably responded to Blackstone's criticisms in some detail and the interested reader is referred to his paper.[54]

Axioms

As with Kroemer, these two authors uncritically *assume* endosymbiosis as fact.[55] Hence, mitochondria are *presumed* to be descendants of the eubacteria (protomitochondria)[56] that were engulfed by 'primitive host cells'. The authors also assume that,

> 'Caspases may … be a relatively recent evolutionary addition to an older signalling pathway.'[57]

The protomitochondria are assumed to have been aerobes; as such, it is supposed that their oxidative phosphorylation (using an electron transport chain) would have given them a survival advantage relative to the host cell (discussed below). In contrast, the 'primitive host cell' is said to have been *an*aerobic, this despite the overwhelming evidence for an oxygen-rich atmosphere from the earliest times of Earth history,[58–63] incorporating the 'Precambrian era' during which the putative first eukaryotes arrived on the scene. It is left to the reader to speculate as to *where*, exactly, endosymbiosis occurred.

Endosymbiotic role for ATP and ROS

In the presence of oxygen, such protomitochondria were

allegedly better equipped to survive than the incipient host cell due to a more rapid ATP synthesis and a more sophisticated defence against ROS. The endosymbiont theory requires that, at some point in time, these protomitochondria became dependant for their survival on the 'host cells'; *why* this should have been necessary is not explained but one presumes that the author would lean towards Kroemer's obligative endosymbiosis event, described above. Again, the crucial questions surrounding *how* this endosymbiosis event occurred are avoided. Instead, all of the authors' subsequent ideas (discussed below) are focussed on the stage just afterwards: the putative new eukaryote. They argue that from this point on,

> 'Natural selectionwould favor those protomitochondria that influenced the host's phenotype to enhance their own rate of replication.'[57]

These protomitochondria achieved this by supposedly using their ATP and ROS to 'manipulate' the host!

Readers are invited to imagine a *rapidly dividing* host cell (i.e. oxygen is present) with protomitochondria inside it:

> 'The large metabolic demands of the dividing host cells would trigger a maximal rate of phosphorylation in the protomitochondria as long as supplies of substrate remained adequate, thus shifting the redox state of the mitochondrial matrix in the direction of oxidation.'[57]

The idea is that the consequent production of ATP satisfies the host cell's energy requirements, and the host also benefits from the fact that little/no harmful ROS are produced (figure 3A). Thus, the host cells can divide unhindered which also provides more living space for the protomitochondria.

Conversely, *low rates* of host cell division would mean much less demand for ATP and would cause the protomitochondria to enter a sort of 'resting state' with oxidative phosphorylation just ticking over. However, the protomitochondria would produce more ROS, causing lots of genetic mutations in the host cells, followed by their sexual recombination (figure 3B). This is another example of evolutionists' imagining advantageous mutations that protomitochondrial cells is thought to have generated genetically novel hosts that thereby enhance the survival of the protomitochondria!

Apoptosis as a vestige of host/endosymbiont conflicts?

Having sought to establish their case for a manipulative role of ATP and ROS, the connection of all the foregoing to apoptosis is made:

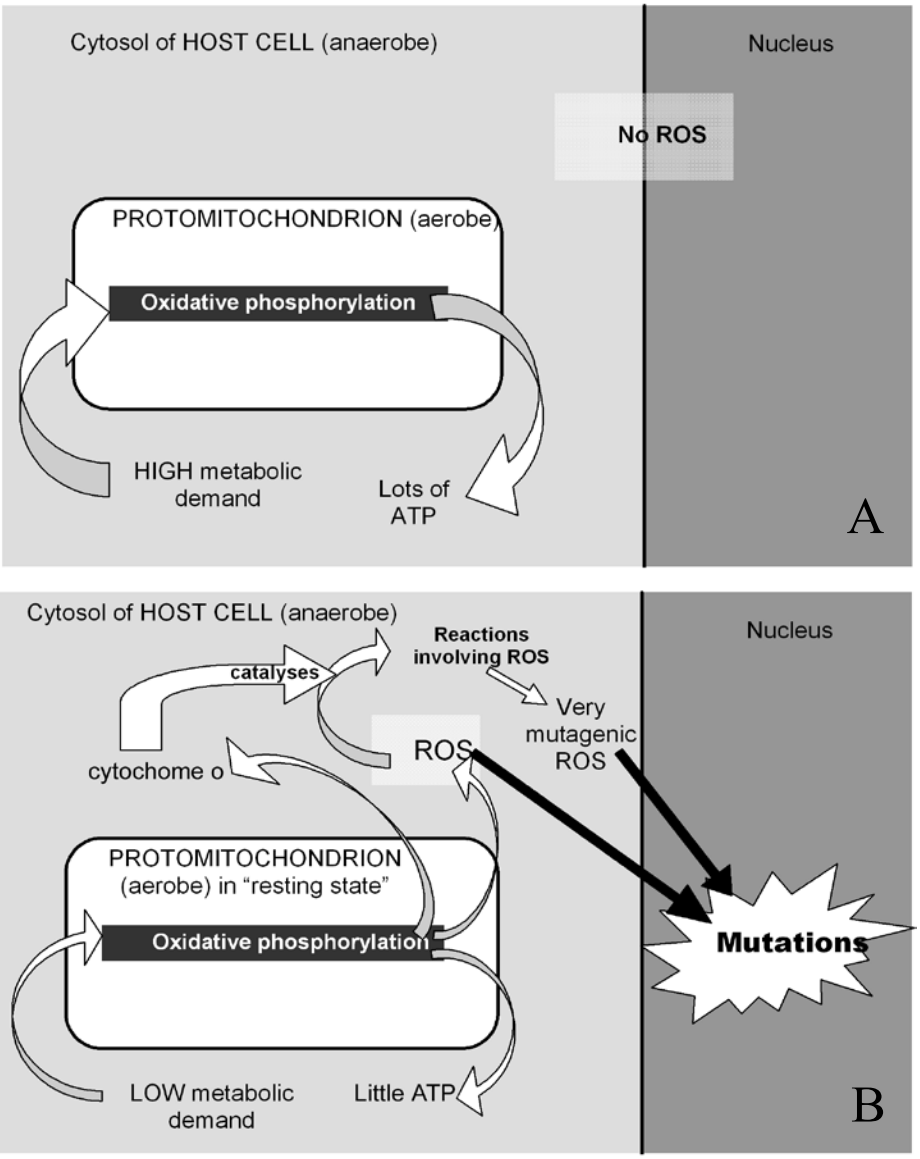

Figure 3. *Schematic depiction of the key elements of the endosymbiosis/apoptosis hypothesis of Blackstone and Green. This is alleged 'ancient signalling pathway' is said to be the precursor of apoptosis. (A) A rapidly dividing anaerobic host cell with its newly acquired aerobic endosymbiont—protection from ROS is afforded by the relationship. (B) Under conditions of low metabolic demand, host cell division is much reduced, resulting in the release of ROS and cytochrome c from the protomitochondria. Cytochrome c acts synergistically with ROS formation to produce highly reactive free radicals (the most mutagenic ROS) and a consequent high mutation rate in the host. This, in turn, is assumed to trigger sexual recombination, generating novel host cells.*

> 'The unexpected role of mitochondrial cytochrome c in programmed cell death *may be* an evolutionary *vestige* of levels-of-selection conflicts between protomitochondria and their hosts [emphasis added].'[65]

The over-used term 'vestige', by evolutionists, immediately sets the alarm bells ringing.[66] However, let us critically examine this idea. In eukaryotic cells, inhibition of the mitochondrial electron transport chain is known to enhance production of harmful ROS (e.g. superoxide and hydrogen peroxide). If cytochrome c is released into the cytoplasm from mitochondria (as occurs in mammalian cells, prior to the caspase activation stage of apoptosis) it catalyses further reactions involving these ROS, forming particularly mutagenic ROS. Therefore, Blackstone and Green surmise that when protomitochondria were stressed they released cytochrome c, thereby enhancing ROS formation, which, in turn, led to the mutation and 'genetic recombination' of host cells. They further speculate that this benefited the protomitochondria by creating 'a less stressful environment' inside the host! How or why such an outcome logically follows is not explained and is hardly self-evident.

As with Kroemer's hypothesis, that of Blackstone and Green lacks pertinent details and barely mentions any of the complex apoptosis machinery. They skip over these things (as well they might) and simply assert that:

> 'Later in the history of symbiosis, with conflicts between mitochondria and the host cell largely resolved by the transfer of all but a fragment of the mitochondrial genome to the nucleus, this ancient signaling [sic] pathway may have been co-opted into a new function, that of programmed cell death in metazoans.'[65]

No attempt is made to suggest *how* the DNA instructions for this 'signalling pathway' passed from the mitochondrial matrix to the host cell's genome (in spite of the many obstacles to their doing so), or *why* this should have occurred. More importantly, although this paper purports to present a hypothesis for the evolution of apoptosis, it is merely *stated* that this hypothetical metabolic 'signalling' between host cell and protomitochondria was possibly 'co-opted' as a programme of cell death (Figure 3). Considering the bewildering array of tightly interwoven components that constitute the apoptotic machinery,[67] it seems almost farcical to postulate the interplay of these few bio-molecules of protomitochondria and host cell as being the precursor of apoptosis!

Moreover, the authors fail to give any reasons, let alone offer a plausible scenario, for how their hypothetical mechanism for generating sexual recombination in host unicells (the alleged novel habitats for endosymbionts) became fundamentally involved in the apoptosis of *multi*cellular organisms. The fact is that all such ideas remain essentially untestable, concerned as they are with events that are imagined to have happened in deep time, as the authors themselves admit. Since cytochrome c production is a key part of their hypothesis, it is pertinent that it does *not* appear to play a role in apoptosis signalling in the nematode worm, *Caenorhabditis elegans*,[68] unlike the situation in mammals and in yeast.[69]

Discussion and conclusions

Unicellular 'apoptosis'—evolved or designed?

It seems clear that 'death-programs' do exist in unicellular organisms, both prokaryotes and eukaryotes, although even evolutionists admit that these pathways show little or no homology with true apoptotic cascades described in multicellular organisms.[18] Bacteria are known to be able to take up naked DNA and (if this foreign DNA can be 'recognized' by the host cell DNA polymerase enzymes) replicate this together with their own DNA; this is a known mechanism for acquiring antibiotic resistance, for example. Could this possibly explain the origin of apoptotic functionality? The author has been unable to locate any papers where this case is argued but even a 'basic' apoptosis-type mechanism (being irreducibly complex[70]) would involve too many components to make this a plausible idea. The host of apoptotic molecular machines involved in even the simplest *euk*aryotes (not to mention their pleiotropic interactions) renders any idea of piece-by-piece addition of components by DNA uptake and transformation extremely improbable. Incorporating just a few of the components of an irreducibly complex system into the cell would give it no survival benefit. Rather, it would be less fit because resources would be wasted; natural selection operates to maintain genetic integrity and such transformed cells would likely be 'weeded out'. In addition, since there would be no selection against mutation in these acquired but unused, apoptosis-component genes, their DNA sequences would almost certainly become scrambled over time.

From a creationist perspective, just as apoptosis is known to have numerous roles in multicellular creatures, including humans,[71] so the programmed deletion of unicells must be of functional benefit—if not to the unicell itself, then to its surviving clonal siblings. In bacteria at least, since stretches of DNA from damaged cells could conceivably be hazardous (due to uptake and transformation), bacterial demise might better serve the population as a whole; i.e. such altruism by the few, benefits the many by preventing potential genetic conflict between genes in the remaining bacteria. When altruistic behaviour of the minority increases the inclusive fitness of the general population of closely related individuals, this is termed kin selection. Accepting that 'apoptotic-style' cell-deletion of unicellular organisms (including eukaryotes) might be an example of

kin selection makes perfectly good sense *without* giving any ground to evolution. An example of natural selection, it may be, but support for the evolution of apoptosis, it certainly is not—rather the implied *pre*-programming necessary for such 'apoptotic altruism' in unicells is compelling evidence for a teleological view of these organisms. It might be argued that the persistence phenomenon in bacteria[24] is a form of kin selection in this context, potentially allowing gradually accrued death-program genes (by uptake and transfection) to be passed on to clonal siblings even though the majority of cells die. However, unless these had survival value at *every* one of the dozens of intermediate steps (towards a fully fledged apoptosis program), maintaining their sequence integrity and place in the genome would be highly implausible for the reasons given at the end of the previous paragraph.

There is even the intriguing possibility that, from a design perspective, God has incorporated carefully regulated 'death-programs' into certain unicellular organisms in order to facilitate their symbiosis with the host. For instance, in cultured *Fibrobacter succinogenes* (bacterial members of the gut flora of ruminant mammals), the lysis rate has been found to be influenced by extracellular sugar concentration.[72] When the sugar level is depleted, the bacteria produce an extracellular proteinase enzyme which inactivates autolysins, thereby preventing bacterial death. However, in the presence of high sugar concentration, despite the fact that *F. succinogenes* exhibit a logarithmic growth rate, many of the ruminal bacteria lyse, akin to apoptosis. While the impact of bacterial lysis in ruminants is not entirely clear, this autolytic regulation (when sugar levels are low) seems to decrease the turnover of stationary cells, increasing the availability of microbial protein in the animal's lower gut and thus, benefiting the host. This example of symbiosis, involving an 'apoptosis-style' response and a switching mechanism to boot, again supports a purposeful design explanation rather than one of random, gradualistic processes.

Apoptosis falsifies evolution

Two hypotheses for the concurrent evolution of apoptosis and endosymbiosis have been critically reviewed and found wanting. In a more recent paper, other evolutionists instead argued that 'the endosymbiotic bacterial ancestors of mitochondria are unlikely to have contributed to the recent mitochondrial death machinery … .'[18] However, rather than provide a rational alternative, they merely speculate that this complex mitochondrial apoptotic machinery derives from 'mutated eukaryotic precursors' for which they admit that there is 'no direct evidence'! This lack of any direct evidence for either idea leads to the unavoidable—and for the creationist, unsurprising—conclusion that apoptosis evolution is a *belief* that ignores empirical science. Rather, the challenge of the irreducibly complex nature of the apoptosis machinery still stands in defiance of the keenest attempts of scientists to demonstrate otherwise. The very existence of apoptosis effectively falsifies evolution.

As with the many other examples of biochemical machines, the engineering and design of this programmed complexity in living cells is a striking testimony to the Creator: 'O Lord, how manifold are Your works! In wisdom you have made them all.'[73] Indeed, 'The works of the Lord are great, *studied by all who have pleasure in them* [emphasis added].'[74] How sad that, while many scientists do gaze at God's works in wonderment (in this case, elegant apoptotic machinery), they fail to give glory to the Master Engineer behind them all. May we be able to say with the psalmist, 'I will meditate on … Your wondrous works'[75] for, 'All Your works shall praise You, O Lord, and Your saints shall bless You.'[76]

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Glossary

apoptosis – an active, non-inflammatory process (requiring energy) involving the programmed deletion of scattered cells by fragmentation into membrane-bound bodies which are ingested by other cells.

ATP – Adenosine triphosphate is the predominant high-energy phosphate compound in all living organisms. It plays a pivotal role in metabolic reactions and is basically the energy currency of cells.

cytochrome c – An iron-containing protein (with similarities to haemoglobin) that evolutionists consider to be one of the most ancient biological molecules in living organisms. Cytochromes generally, are components of electron transport chains in both mitochondria and chloroplasts.

endosymbiosis – Refers to the hypothetical origin of the first eukaryote. It is believed that aerobic bacteria and photosynthesising bacteria were taken in by another bacterial cell (becoming the precursors of today's mitochondria and chloroplasts) and established a mutually beneficial relationship.

eukaryote – A cell with a true, membrane-bound nucleus and subcellular, membrane-bound organelles.

metazoa – an old taxonomic word which is still used generically, as in this paper, to describe multi-celled organisms; i.e. as opposed to prokaryotes and unicellular eukaryotes (including yeasts, protozoa and others).

mitochondria – Organelles, found in all eukaryotic cells, which are the cell's powerhouses. They are bound by a double membrane, the inner of which is folded into plate-like structures called cristae. Mitochondria house the machinery of the terminal electron transport chain including the cytochrome enzymes. They also contain enzymes involved in oxidative phosphorylation.

MPT – Acronym for mitochondrial permeability transition (see text for explanation).

PCD – Programmed cell death; a synonym for apoptosis.

phagosome – the name given to the membrane that forms around any material that is engulfed by a cell (by a process termed phagocytosis).

prokaryote – Any cell which does not have the diagnostic features of a eukaryote, principally the bacteria, but also unicellular blue-green algae and other, more obscure unicellular organisms. Instead of a nucleus, there is a circular duplex of DNA.

ROS – Reactive oxygen species. Also termed reactive oxygen intermediates (ROIs). These are short lived, energetic and potentially toxic; e.g. the superoxide anion, $\cdot O_2^-$, is harmful and tends to generate other ROS.

transduction – in the context of biochemical pathways involved in cellular apoptosis or differentiation, this means the conversion of a signal from one form into another.

Appendix—Cellular fate: apoptosis or necrosis? Is the distinction valid?

Kroemer's paper[6] gives examples of *pathologies* (i.e. not healthy situations) where the distinction between apoptosis and necrosis is not always clear cut. It is known, for example, that Bcl-2 expression inhibits *necrotic* death in several experimental models by inhibiting disruption of the mitochondrial trans-membrane potential. Consequently, the fate of a stressed cell might depend on whether there is time for proteases to be activated (downstream of MPT) and to target nuclear and cytoplasmic effectors of apoptosis. If the injurious agent results in very rapid ATP depletion, necrosis is the outcome. This is compatible with this author's published observations that certain cytotoxic drugs that are used in cancer chemotherapy induce apoptosis at low concentration but necrosis at higher concentration.[77] A recent article by Tavernarakis in *New Scientist* re-examined the distinction between apoptosis and necrosis,[78] suggesting that there might actually be,

> '… a core "necrosis program" that is activated upon injury and ravages the cell.'

However, as the article reveals, investigations into necrosis at the molecular level have not revealed any specific genes or gene-products in contrast to what we know of apoptosis.[79] The author states that the necrosis-trigger 'culprits' are the lysosomes (the oft-described 'suicide bag' organelles of the cell) and implies that this fact has emerged recently; rather, this has been known for many years. Nevertheless, new research has revealed that increased levels of Ca^{2+} ions are what cause the lysosomes to release their lethal enzyme cocktail and this obviously calls into question the *entirely* passive image of necrosis.

This and several other lines of evidence are causing researchers to consider whether the long-standing distinction between apoptosis and necrosis might be too simplistic—they argue that the cell's fate should be viewed as on a continuum between *programmed* cell 'death' and necrosis (catastrophic) cell death. However, the research findings that have inspired this rethink have all involved cellular response to *damaging* chemicals, heat shock etc. There may sometimes be a continuum between these modes of cell demise (e.g. morphologically), but as Tavernarakis states in the *New Scientist* article, concerning necrosis,

> 'Unlike programmed cell death, no biochemical processes have evolved specifically to carry it out.'

Necrosis is never a good thing and is a consequence of a fallen world.[80] The blurring of apoptosis and necrosis comes from studying the morphology of cell attrition *as a result of injurious agents*—not present in the once-perfect, pre-Fall world.

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