Is Evolutionary Theory Central to Molecular Cell Biology?

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ABSTRACT

The recent "Happy Birthday, Mr. Darwin" issue of *Science* (6 February 2009) celebrates evolution, the most unifying theory of biology. At the same time, this issue shows that molecular cell biology remains relatively untouched by evolutionary theory. Consider the fascinating studies of the STAT3 protein (Myers, 2009; Wegrzyn et al., 2009). This protein appears to have a dual function, on one hand mediating cytokine signaling at the level of the cell, while on the other regulating mitochondrial respiration. Since mitochondria are remnants of bacterial symbionts, at least two evolutionary hypotheses are suggested by these data. First, STAT3 may have originally been mitochondrial and was co-opted into a new function of manipulating host signaling to the advantage of the symbiont. Second, STAT3 may have originally been cytoplasmic and was co-opted into a new function regulating symbiont respiration to the advantage of the host. Sadly, in these fine articles there is no indication of such evolutionary thinking even though it allows the dual role of STAT3 to be interpreted, and indeed predicted, as a vestige of ancient levels-of-selection conflicts. Changes in the way biology is organized and taught may be necessary for evolutionary thinking to permeate all of biology.

INTRODUCTION

As both the 200th anniversary of Darwin's birth and the 150th anniversary of the *Origin of Species*, the year 2009 saw numerous celebrations of Darwin's life and science. Notable among these was the 6 February issue of *Science*, the journal of the American Association for the Advancement of Science (AAAS). A premier scientific organization in the US, AAAS is the world's largest federation of scientists, with 130,000 members and 262 affiliated societies and academies. AAAS is extensively involved in science-related advocacy to educators, the media, and to

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Congress. As one of the most cited scientific journals in the world, the contents of *Science* thus provide an excellent barometer for the role of evolutionary theory in modern biology. Certainly, first inspection of this celebration of Darwin suggests a large role: the cover, the editorial, book reviews, and a special section of scientific reviews all suggest a congratulatory "Happy Birthday, Mr. Darwin." Closer examination, however, reveals that the articles focusing on evolution primarily deal with only a limited range of the biological hierarchy—particularly organisms and genes. Here as elsewhere, articles that describe the intricate workings of molecular cell biology rarely mention evolution. Two explanations are possible: either evolutionary theory has no relevance to molecular cell biology, or this relevance is being ignored. Both possibilities have important implications for biological education. Here I develop an example from molecular cell biology based on the contents of the "Happy Birthday, Mr. Darwin" issue of *Science*. In the process, I review some of the relevant literature. Additionally, I outline the basic evolutionary context for this particular example. In this way, I suggest that evolutionary theory is highly relevant to molecular cell biology and could indeed provide a predictive and interpretive framework for this field. Molecular cell biologists may not exploit the power of evolutionary thinking largely because the organization of their field does not encourage this. Evolutionary biologists may tend to avoid molecular cell biology because traditionally the evolutionary synthesis focuses on organisms and genes. If evolutionary theory is to be instilled into all of biology, changes in the way biology is organized and taught may ultimately be necessary.

THE CURIOUS CASE OF STAT3

Signal transducer and activator of transcription (STAT) proteins are typically latent in the cytoplasm until activation by extracellular signaling proteins (Levy & Darnell, 2002). The signaling proteins that activate STATs include cytokines, growth factors, and even some simple peptides. These signaling proteins bind to cell-surface receptors and activate tyrosine kinases, which subsequently phosporylate STAT proteins. STAT proteins that are so activated then accumulate in the nucleus and initiate transcription, ultimately affecting the phenotype of the cell. Particularly well studied are the Janus kinases (JAKs) and their STAT targets. The canonical Jak-Stat pathway is an important example of a complex signaling pathway with broad relevance to human health and disease (Schindler, 2002).

One of the members of the STAT family, STAT3 was first described for its DNA-binding activity in IL-6 cytokine-stimulated hepatocytes. The protein was found to be structurally similar to other STATs. In response to cytokine stimulation, a Janus kinase mediates tyrosine phosphorylation, which occurs at a single site close to the carboxy terminus (Levy & Lee, 2002). Activated STAT3s dimerize, translocate to the nucleus, and initiate DNA binding. However, STAT3 can also be activated by serine phosphorylation at a site in the transactivation domain. The role of serine phosphorylation in transcriptional activity has remained rather ambiguous (Levy & Lee, 2002). In comparison to other STATs, the function of STAT3 also seems unique, with data suggesting a general role in regulating cellular homeostatsis (Schindler, 2002). At the same time, the diverse roles of STAT3

raised questions of how a single transcription factor could be involved in such seemingly contradictory responses (Levy & Lee, 2002).

Recent work (Gough et al., 2009; Myers, 2009; Wegrzyn et al., 2009) has clarified the ambiguity surrounding the function of STAT3 by showing that it actually has two distinct functions. Early clues were provided by the interaction of STAT3 with GRIM-19, which is a component of complex I of the mitochondrial electron transport chain (Figure 1). Wegrzyn et al. (2009) carry these observations several steps further and show that some of the STAT3 in a cell indeed localizes to mitochondria. Additional evidence indicates that STAT3 is a component of complex I and possibly complex II of the mitochondrial electron transport chain. Using cells deficient in STAT3, Wegrzyn et al. (2009) show that the capacity for oxidative phosphorylation (which is carried out by the mitochondrial electron transport chain) is diminished in these cells as well. A functional role of STAT3 in complex I and II is suggested. Indeed, serine phosphorylation seems to be integral to this mitochondrial function (Figure 2).
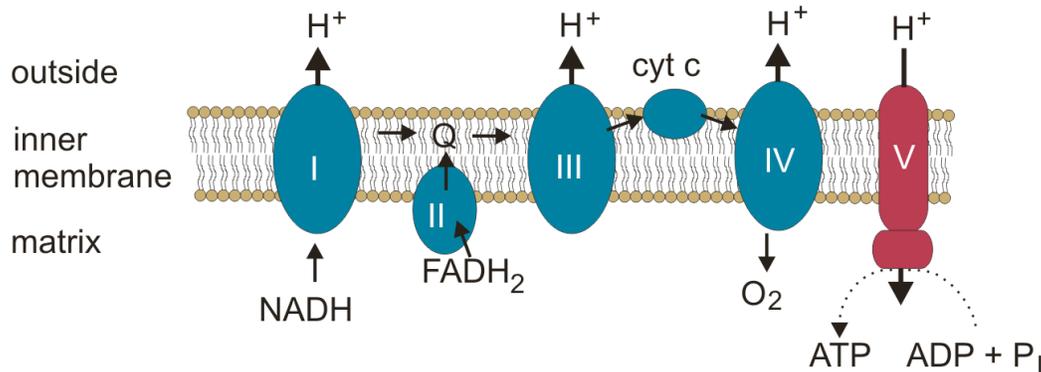
Figure 1. *Mitochondrial electron transport chain*. A schematic of the mitochondrial electron transport chain shows complexes I – V, coenzyme Q (Q), and cytochrome *c* (cyt c). Small arrows trace the flow of electrons from NADH and $FADH_2$ to oxygen. Large arrows show the extrusion of protons (H^+) by complexes I, III, and IV and the return of protons to the mitochondrial matrix via ATP synthase (complex V), triggering the assembly of ATP (dashed arrow). Oxidation of substrate (i.e., food) generates NADH and $FADH_2$ which are the source of electrons that flow between complexes, generating a transmembrane proton gradient. This proton gradient triggers the formation of ATP. Several points of environmental regulation are apparent: (i) lack of substrate (starvation), which results in minimal amounts of NADH and $FADH_2$, minimal electron flow, complexes that are relatively free of electrons (oxidized), a minimal proton gradient, and little ATP formation, (ii) lack of metabolic demand, which results in minimal amounts of ADP, complexes saturated with electrons (reduced), a maximal proton gradient, and little ATP formation, (iii) lack of oxygen (O_2), which results in complexes saturated with electrons (reduced), a maximal proton gradient, and little ATP formation. The "Goldilocks" metabolic state is intermediate: sufficient substrate is matched by metabolic demand and availability of oxygen. In this metabolic state, complexes are transferring electrons at maximal rates, a moderate proton gradient forms, and ATP is produced at maximal rates. The electron transport chain was likely a key functional difference between symbiotic mitochondria and their hosts early in the history of the eukaryotic cell (modified from Blackstone, 2003).
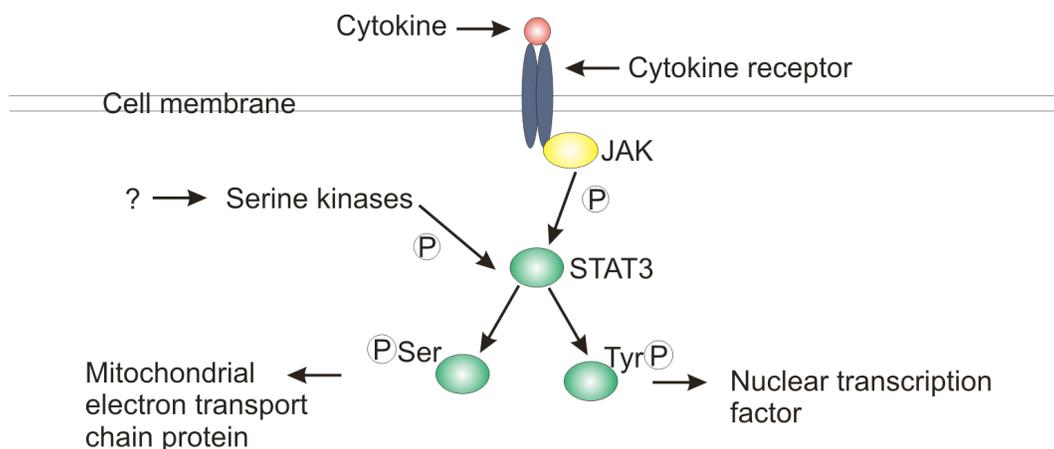
Figure 2. *Two functions of STAT3*. The activation of a cytokine receptor on the cell membrane triggers the tyrosine phosporylation of STAT3 by a Janus kinase (JAK). Tyrosine phosphorylated STAT3s dimerize and move to the nucleus where they function as transcription factors. On the other hand, serine phosphorylation results in STAT3s moving to the mitochondrion where they function as integral proteins of electron transport chains (Figure 1). Presently, it is not known what signals activate serine phosphorylation (modified from Myers, 2009).

Gough et al. (2009) follow up on this work. Augmented STAT3 activity is associated with numerous human tumors, yet such an observation seems inconsistent with STAT3 acting solely as a transcription factor. Using Ras-dependent oncogenic transformation as an exemplar, the authors show that this transformation was dependent on STAT3. While tyrosine phosphorylation is not required, serine phosphorylation of STAT3 is critical for this transformation. Further data support the hypothesis that Ras transformation requires non-transcriptional and non-nuclear STAT3. This suggests a mitochondrial role for STAT3, raising the possibility of a connection between STAT3 activity and the abnormal mitochondrial metabolism that characterizes cancer cells (Garber, 2006). Indeed, mitochondrial STAT3 appears to contribute to Ras-dependent cellular transformation by altering the activity of complexes of the electron transport chain as well as somehow upregulating glycolysis.

All of this groundbreaking work on STAT3 was apparently carried out and reported without any reference to the evolutionary history of eukaryotic cells. One might surmise from reading this literature that such an evolutionary view could not possibly add any insight to the still on-going investigation of the curious case of STAT3. As an evolutionary biologist, I would minimally suggest that such a judgment would be premature without at least a consideration of this evolutionary history and what perspective it could add to the STAT3 story.

THE EVOLUTIONARY CONTEXT

Our understanding of the evolutionary context for the function of STAT3 begins with the now widely accepted mitochondrial endosymbiosis. Based on structural features, some biologists have long suggested that mitochondria were

symbiotic bacteria (Margulis, 1981). More recently, nucleotide sequence data have strongly supported this view (Gray et al., 1999). A wide variety of hypotheses have been proposed regarding the nature of the initial association and the capabilities of the original host and symbiont (e.g., Lane, 2005; Embley & Martin, 2006). Some areas of broad agreement nevertheless have emerged.   The mitochondrial symbiosis is generally viewed as a seminal event in the origin of eukaryotes, which is one of the major evolutionary transitions in the history of life (Maynard Smith & Szathmáry 1999). This symbiosis created the principle compartment for eukaryotic metabolism, but as always the lunch is never free.   The early stages of this symbiosis were likely very different from the relative harmony seen in modern eukaryotic cells. Because mitochondria were evolutionary units capable of heritable variation, levels-of-selection synergies and antagonisms no doubt ruled the emerging features of the eukaryotic cell. Much of the cooperation and conflict that occurred related to a functional difference between the symbiont and the host: at the onset of the symbiosis, the symbiont possessed a functional electron transport chain while the host lacked this feature (Blackstone, 1995).

When analyzing any feature of modern eukaryotes, this evolutionary history should be kept in mind. Mitochondrial signaling pathways may remain as vestiges of ancient levels-of-selection conflicts (Blackstone & Green, 1999). Consider the case of STAT3. Two evolutionary interpretations are possible and each will be discussed at length. First, STAT3 may have originally been a mitochondrial protein that was co-opted into a new function of manipulating the host to the advantage of the symbiont. Once mitochondria became obligate symbionts and thus part of a new higher-level evolutionary unit (the eukaryotic cell), they would no longer directly interact with the environment. Selection would favor symbionts that could trigger particular host responses to stimuli if those responses subsequently increased symbiont fitness. (Think of small children riding in the back seat of a car during a long trip: a well-timed "Daddy, I'm hungry!" leads to Daddy stopping the car and feeding them.)   In this context, a mitochondrial protein that could act as a transcription factor for host DNA would be an invaluable tool. When symbionts detected certain metabolic signals that were ultimately environmental, this transcription factor could be activated, perhaps by phosphorylation, and could move to the nucleus where appropriate gene activity would be initiated. In this case, "appropriate gene activity" would benefit the symbionts; it might also benefit the host under a certain range of conditions or have no effect on the host at all. If this gene activity was detrimental to the host, i.e., if there is a conflict between what selection favors at the level of the symbiont and at the level of the host, the evolutionary calculus would then become more complex.

Electron transport chains are typically the locus of not just energy conversion, but environmental sensing as well. Bacteria illustrate this point particularly well (Allen, 1993; Georgellis et al., 2001). The Arc system of *Escherichia coli* provides a well-studied example of the sort of two-component signal-transduction systems that are often used in adapting bacterial metabolism to environmental conditions. Two proteins, ArcA and ArcB, are involved. ArcB is a transmembrane sensor kinase with a loop exposed to the cytoplasm. This cytoplasmic loop contains a conserved histidine residue that can be autophosporylated in response to metabolic conditions. This phosphorylation

occurs in response to the oxidation state of quinone electron carriers (i.e., if they are saturated with elections or not). Quinones are part of the electron-transport chain, comparable to CoQ in Figure 1 (note that the electron transport chain of *E. coli* is similar to, but not entirely the same as the mitochondrial one that is illustrated). Oxidized forms of quinone inhibit autophosphorylation (Georgellis et al., 2001). On the other hand, if quinones are reduced this inhibition is removed. As with the complexes of the electron transport chain (Figure 1), the oxidation state of quinones is sensitive to environmental conditions. In the presence of substrate and ADP, quinones remain relatively oxidized and autophosphorylation is inhibited as long as electron transport to the terminal electron acceptor (oxygen) is possible. If oxygen is not available, electrons "back up" on the electron carriers of the electron-transport chain and these carriers become reduced. Autophosphorylation then ensues. Subsequent to autophosphorylation, ArcB transphosphorylates the second component, ArcA, which is a global regulator of transcription. When phosphorylated, ArcA represses the expression of many genes whose products are involved in aerobic respiration and activates many of the genes whose products are involved in anaerobic fermentation. In this way, the bacterium adapts its metabolism to the environmental conditions.

Mitochondria are descended from bacteria not unlike *E. coli*. Primitively, they are expected to have employed similar environmental sensing mechanisms. Consider STAT3 in this context. Evidence suggests that if it is activated by serine phosphorylation, it is a component of mitochondrial complexes I and II. On the other hand, if it is activated by tyrosine phosporylation, it is a nuclear transcription factor. Such a juxtaposition of functional roles suggests that it may have originally been an environmental sensor for the mitochondrial electron transport chain. Under the appropriate metabolic conditions, it could quickly be converted into a nuclear transcription factor, modifying gene activity to suit the metabolic circumstances of the mitochondria. While initially there may have been exploitative aspects to this interaction (i.e., favored by selection on mitochondria, but possibly disadvantageous to the host), simultaneously there would have been strong selection on a host to maintain mitochondria in good functional condition. Put another way, a host responsive to signals that facilitate mitochondrial metabolism would reap an energy dividend in the form of ATP generation. This energy dividend could then be used in faster host replication and higher host fitness. Thus the system of a STAT3 mitochondrial sensor/nuclear transcription factor could have quickly evolved into a mutually beneficial signaling pathway.

The second evolutionary interpretation of STAT3 signaling begins with the alternative hypothesis that it was originally derived from the host. Given that the principle functional difference between the host and the symbiont was the presence of the electron transport chain, products and by-products of this chain could be used by the symbiont population within a single host to manipulate their host (Blackstone, 1995). For instance, reactive oxygen species, a by-product of respiration, could be used to trigger recombination and whole cell fusion in the host, thus providing the symbionts with new habitat (Blackstone & Kirkwood, 2003). Ultimately, such manipulation would destabilize the symbiosis because new and "selfish" variant symbionts would continuously evolve, sacrificing the group-level benefits of cooperation for short-term gains in individual-level fitness. For a stable symbiosis to

emerge, the higher level unit (which includes the host as well as the entire population of symbionts) must evolve mechanisms to hold such selfish variant mitochondria in check (Michod & Nedelcu, 2004). In modern mitochondria, these mechanisms are many and various, perhaps most notably shifting the bulk of the mitochondrial genome to the nucleus. Moving these genomes to the nucleus diminishes the amount of heritable variation available to produce selfish lower-level units. The mitochondrial electron transport chain in particular has seen most of the genes coding for components of the complexes I – V moved to the nucleus. With some important exceptions (Allen et al., 2005), regulation of respiration is too critical to be left to the control of individual symbionts. Nevertheless, this gene transfer may have taken a relatively long period of time to accomplish. Early in the symbiosis, inserting a host protein into the electron transport chain to allow host regulation of respiration may have been critical and strongly selected for. STAT3 is a plausible candidate for such a regulatory protein. Ultimately, eukaryotic cells with this regulatory protein established a stable symbiosis, while those without it succumbed to the selfish manipulation of mitochondrial variants.

Since the canonical Jak/Stat signaling pathway is involved in signaling between cells of the same multicellular organism, this pathway is expected to have evolved later in the history of eukaryotes, perhaps as animals themselves evolved. Increasingly, at least some of the proteins involved in complex signaling pathways in multicellular eukaryotes are found in unicellular eukaryotes performing other tasks (Nedulcu, 2009). In this context, host-symbiont signaling may provide a plausible functional origin of the STAT family of proteins.

The above narrative can be further developed to make specific, testable predictions. The goal here is somewhat more modest: merely to point out that there is a robust evolutionary context for the molecular crosstalk between modern mitochondria and the cell nucleus. Rather than being ignored by molecular cell biology, this context can and should be the starting point of any investigation.

COMPLETING THE SYNTHESIS IN MOLECULAR CELL BIOLOGY

As suggested by Wilson et al. (2009), the evolutionary synthesis is strong but in some ways incomplete. Biology departments are often divided (e.g., ecology and evolutionary biology [EEB] and molecular cell biology [MCB]). Members of EEB and MCB typically apply for support to different funding agencies, publish in different journals, and teach different courses. Evolutionary biology is typically taught by EEB faculty, and such a course tends to reflect evolutionary research, i.e., organisms and genes. Most other biology courses might never mention the possibility of using evolutionary theory as a predictive tool to explore the particular subject matter. While probably most biologists would agree that all biology courses should be evolutionary, the question remains as to how to accomplish this goal.

Certainly, the situation is not entirely bleak. The advent of genomics has injected some degree of comparative and evolutionary thinking into all levels of biology. Intelligent design advocates have challenged evolutionary biologists to move beyond a focus on organisms and genes and to consider biochemical mechanisms. Even the coveted pages of *Science* have recently included some

notable studies of protein evolution (Holt et al., 2009; Tan et al., 2009; Matsuno et al., 2009). Nevertheless, further steps need to be taken to hasten this synthesis and to bring it more fully into the classroom.

An additional important step is for evolutionary and molecular cell biologists to acquire some appreciation for each others' work. From the point of view of evolutionary theory, molecular cell biology is a rich descriptive natural history literally begging for evolutionary explanations. With a little terminological familiarity, evolutionary biologists could use their expertise in countless ways to illuminate this natural history, just as evolutionary biologists since Darwin have illuminated organismal natural histories. From the point of view of molecular biology, evolutionary theory can be used to rationalize what otherwise may seem to be baroque results. More broadly, evolutionary theory can provide a predictive framework that otherwise is largely lacking in molecular cell biology. In his overview of the beginnings of molecular biology, Stent (1968: p. 393) writes: "though immediate conclusions drawn from the results of experiments…were almost always right, the more general and really interesting speculations built upon these first-order conclusions were mostly wrong." Indeed, one only has to consider the number of genes in the human genome to be reminded of molecular biology's lack of predictive success. Nevertheless, the great strengths of molecular biology are also apparent by this missed prediction: no sooner was it clear that humans had no more genes than "worms, flies, and mice" that whole new fields of the regulation of hereditary information blossomed, e.g., alternative splicing and micro RNAs. What modern molecular cell biology lacks in predictive direction it makes up for in its depth and relentless power. This is also clear from the STAT3 story: no sooner had the mitochondrial function been elucidated (Wegrzyn et al., 2009) than efforts began to link this new function to human disease and to suggest therapeutics (Gough et al., 2009).

One might thus conclude—"if it ain't broke, don't fix it." Certainly, the goal here is not to criticize the many outstanding successes of molecular cell biology. Yet it is not impossible that some direction from evolutionary theory might improve an already enormously successful field. For instance, a simple-minded evolutionary approach to genes and genomes might have made useful predictions: humans are animals, animals have about 20,000 genes in their genomes, and therefore humans have about 20,000 genes in their genomes. In the case of the STAT3 example, if molecular cell biologists reflected on the possible evolutionary roots of the Jak/Stat pathway, they might have actively searched for a STAT family member that was involved in mitochondrial signaling. The early ambiguity of the function of STAT3 would have made this protein a likely candidate, and its dual function might have been resolved sooner rather than later. So too might this thinking lead to useful predictions as to what may be the effectors of serine phosphorylation. Ultimately, a complete evolutionary synthesis will balance the value of both holistic evolutionary thinking and reductionist molecular approaches.

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