Introduction: Metabolism, Life History and Aging

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To an ecologist or evolutionary biologist the notion that the evolution of life history may play an integral role in shaping organismal physiology is elementary; so too the idea that adoption of one life-history strategy over another can have far-reaching effects in terms of aging and life span. For most biomedical researchers, however, this is not so clear. Outside of what they may have gleaned from an introductory ecology course, there is little opportunity (or incentive) for a prototypical biomedical scientist to learn about life-history evolution; rather biomedical scientists are highly proficient in cutting-edge methods in molecular and cellular biology, and “typical” biogerontological research focuses on processes such as cellular senescence using immortalized cell lines or the role of specific signaling pathways via the generation of transgenic animal models. Rarely does it involve the study of free-living organisms under natural conditions.

On the other hand, most organismal biologists often fail to appreciate exactly how much their model system has to offer research on aging or to modern biomedical science in general. Using essentially the same starting material, Mother Nature has provided us with a virtual smorgasbord of species with profound differences in numerous traits including life span. What is even more remarkable is that despite the highly conserved organization and function of tissues/organs among species, the rate at which they deteriorate is markedly different even within closely related species. For example, a process that takes a few years in mice or Japanese quail will take decades in humans or parrots, respectively. If one considers higher-level taxonomic groupings, the magnitude of these differences is considerably greater. For example, mouse-sized birds routinely live 5–10 times longer than their mammalian counterparts, while among all the vertebrates life span can vary by as much as 100-fold or more (Holmes and Martin 2009; Austad 2010).

Currently, the great unknown lies with the identification of key cellular and molecular attributes that contribute to this differential longevity among species, and even more importantly, it remains to be seen whether or not these mechanisms are altered in a manner that is consistent with the change in species’ life spans. Differences in metabolism and its consequences in terms of oxidative stress, a major theme of this symposium, represents just one of many potentially informative applications of the comparative approach to address questions in experimental biogerontology (see Austad, this issue). Utilizing “nontraditional” animal models in modern biogerontological research—meaning species other than the nematode worm Caenorhabditis elegans, the fruit fly Drosophila melanogaster, and inbred laboratory mouse stocks—has much to offer (Harper 2008; Austad 2010; Miller et al., in press).

Unfortunately, despite pleas to the contrary there remains a general lack of enthusiasm to using the comparative approach within biomedical circles. It is largely for this reason that I felt compelled to organize a symposium whose main goal was to bring together individual scientists that are proficient in either the field or at the bench (or both) to discuss the impact of the evolution of life history on metabolism and aging in the unique setting of a meeting about comparative biology. Ultimately, my hope was that this symposium would do much to bridge the gap between laboratory-based and field-based models.
of experimental biogerontology, while introducing SICB participants to collaborative opportunities within the biomedical community.

Very early on, it seemed there was a clear link between the rate of metabolism and the rate of aging within eukaryotes with high metabolism leading to decreased longevity, presumably as a consequence of oxidative metabolism and the production of Reactive Oxygen Species (ROS) (Harman 1956). Early studies using laboratory animal models generally supported this notion; although more recent studies of laboratory models of aging under more controlled conditions have suggested that this model is likely oversimplified (Perez et al. 2009). In addition, studies of exceptionally long-lived rodents and bats have further called the validity of this model into question, but there is still reason to believe that oxidative stress (as well as a suite of other stressors), or more accurately how an organism deals with it, is important to the process of aging (see Austad, this issue).

Moreover, even though it is accepted that the evolution of specific life histories can be driven by metabolic constraints (see Williams et al. this issue; Speakman and Król, this issue), there is actually very little known about how the adoption of specific life-history strategies can shape both the rate of aging and the life span in animals facing different energetic demands. Hence, in my foray toward bridging the gap between comparative biology and biogerontology, the underlying theme of the symposium is an examination of the role of metabolism in shaping the evolution of life history and its resultant effect on organismal aging and on life span. In the following paragraphs, I will provide a brief synopsis of each of the contributed papers, as well as my own thoughts relevant to the topic.

Steve Austad provides us with a wonderful introduction to the topic at large, namely what comparative biology has to offer to biogerontological research in terms of the past, present, and the future. For example, Steve highlights how the comparative approach played a pivotal role in debunking the simplistic rate-of-living theory while stressing the importance of proteome maintenance and resistance to oxidation. More importantly, we are given a plan for the future using the genomic and proteomic resources that are readily available to modern biologists, as well as the potential for creating induced pluripotent stem cell (iPSC) lines from virtually any species of interest. It is the latter that holds the most promise, although I believe there are some important details that remain unresolved—most notably that iPS cells behave differently than embryonic stem cells (Hu et al. 2010; Qiang et al. 2010) and whether or not there will be maintenance of “species identity” in terms of specific phenotypes after transformation. That is, will an iPS cell used to create an epithelial cell line or a neuronal cell line exhibit the same species-specific phenotype as a primary cell line derived from that same organism?

John Speakman and Elżbieta Król then introduce us to the notion that body size, and its consequent effect on an organism’s ability to lose heat, is a driving force in life-history evolution as a result of increased heat load reducing the net reproductive investment of large endothermic animals. Ultimately, they assert that these constraints favor longevity-assurance mechanisms (e.g., increased stress defense, improved DNA-repair capacity) and increased longevity in habitats with low extrinsic mortality. I find this heat-dissipation-limit theory, as it is called, rather refreshing, as it represents a novel take on the mechanistic basis for the evolution of increased life span in conjunction with slowed development, delayed reproduction, and reduced reproductive output. More importantly, John and Elżbieta go so far as to outline a series of testable hypotheses that should stimulate fruitful lines of research of interest to evolutionary ecologists and biogerontologists alike. Indeed, this is one line of inquiry that simply begs to go beyond the limitations of laboratory-based models to see how it stacks up under “real world” conditions.

The role of lipids in shaping organismal aging has been largely ignored in biogerontology, which is why I am pleased that the next contributor agreed to participate in this symposium. Tony Hulbert has long argued that lipids, particularly membrane fatty acids, are key cogs in the cellular machinery that drives metabolism, oxidative stress, and aging in eukaryotes, and his paper will provide readers with a thorough and compelling argument for why we should pay more attention to lipids when thinking about modulators of aging. For example, Tony demonstrates that fatty-acid composition has repeatedly been shown to vary in a systematic manner with body size in birds and mammals, and that it is inversely related to species’ maximum life spans; even within species there are significant differences in fatty-acid composition between long-lived versus short-lived populations. At the heart of this “membrane pacemaker” theory lays the fact that the degree of unsaturation present in fatty-acid chains has a profound influence on susceptibility to oxidation damage, and it is presumed, but I would argue still unproven, that differences in the phospholipid composition of membranes are ultimately responsible for
differential susceptibility to oxidation damage at the cellular level. Although there are clearly differences in the fatty-acid composition of whole extracts of some organs from species of differing longevity, whether this is true at the level of the plasma membrane remains to be seen; however, substantial differences in mitochondrial membranes that have been linked to species’ longevity. Another important unknown is the influence of subtle differences in phospholipid structure on susceptibility to oxidation, such as the interaction of each of the fatty-acid chains with one another, or exactly how the head group is joined (e.g., whether or not it is an ester linkage).

The next contribution represents a departure from the more traditional realm of invertebrate biogerontologists. In their contribution, the members of John Hatle’s laboratory use lubber grasshoppers to examine allocation of nutrients in individuals with differing reproductive demands as a test of the disposable soma theory. It has already been argued by Speakman and Król that the disposable soma theory is dead on the basis of reproductive output and its impact on organismal heat load, at least in endotherms, but clearly there is more to be learned. Thus, it is noteworthy that John and his colleagues pioneered the use of stable isotopes in tracking the allocation of nutrients in their model. In a nutshell, they developed diets with distinct isotopic signatures that allowed direct tracking of specific nutrients to multiple tissue compartments in grasshoppers with differential reproductive demands. In general, it would appear that the results of this study broadly support the notion that altering reproductive demand has no appreciable effect on the amount of resources made available to maintaining the soma; although, as noted by John, there are model-specific caveats that need to be considered. We cannot overlook the fact that these methods should be broadly adaptable to other model systems thereby providing us with an excellent tool for testing hypotheses that hinge on differential nutrient allocation in the future.

While enhanced oxidative stress resistance and/or a reduced oxidative burden have been postulated to act as key determinants in the modulation of life span, we have already seen that this view is likely too simplistic and that no clear cause-and-effect between the degree of oxidative stress and aging has been identified. However, it is entirely possible that protection against oxidative insults represents just a single component of a multi-factorial defense network that protects against cellular stressors beyond oxidation such as protein misfolding and DNA damage. Indeed, a constitutive upregulation of multiple defense mechanisms is commonly observed in naturally long-lived species, as well as in genetic and dietary models of life span extension in rodents.

In the contribution from Shelly Buffenstein’s group, we are provided with an extensive review of the putative role of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcription factor as a master regulator of cellular and organismal defense mechanisms in a diverse array of species. In addition, they provide compelling evidence that increased Nrf2 activity is critical to the evolution of long life within vertebrates. Clearly, there is more to be learned about species-specific regulation of Nrf2 activity, and more importantly, whether or not the same effector molecules are involved among taxa.

As we are well aware, the life sciences are rapidly moving beyond taking a reductionist approach and looking at a single, or at most a few, levels of organization and into a new realm whereby all the data collected from multiple organizational levels are coalesced into vast data networks (i.e., systems biology). This approach is particularly well-suited for complex, multifaceted processes such as aging and in the next contribution Daniel Promislow and his colleagues do an excellent job of highlighting the power of network analysis for the examination of metabolomic data sets. In addition, they provide details on constructing networks and give a brief overview of previous research on networks that focused on higher (i.e., genomic, proteomic) organizational levels. A rather comprehensive view of the methodologies currently in use in metabolomic studies is also provided. Most importantly, however, they clearly outline why analysis of the metabolome versus other levels of organization is likely to be the most informative in gleaning information about organismal status. Simply stated, the metabolome represents the furthest level down the line from gene to function. They go on to show that, in the context of aging, an alteration in the metabolome provides a comprehensive picture of characteristic declines in function with age using data generated from aging populations of multiple species with an emphasis on their own work on common marmosets. After reading this paper the power of network analysis, regardless of organizational level, should be apparent, and it should be doubly apparent that analysis of the metabolome might be critical to understanding what happens with aging at the organismal level. Nevertheless, I do not believe that Daniel and his colleagues would argue that the wholesale exclusion of data from other levels, such as the genome, is warranted and, in fact, I suspect that
incorporating data from all levels into a single vast network is not too distant on the horizon.

In the next contribution, Joe Williams and myself, as well Rich Miller and Popko Wiersma, argue that learning more about the link between metabolism and life history is critical to improving our understanding of how natural selection can shape species’ life spans. As our model we use data collected from phylogenetically paired groupings of birds: one from the tropics and another from a temperate region. The expectation is that tropical species have a slower pace of life concomitant with an increase in longevity. Although it remains to be seen whether tropical species are indeed longer lived, we show that tropical birds have reduced metabolism compared with their temperate counterparts and that mass-adjusted metabolic rate is associated with survival. In addition, we see that relative organ mass and oxidative stress resistance in the modulation of life span—this comes through. It should also have been apparent that the final contribution from Anne Bronikowski and David Vleck employs a reptilian model for biogerontological research. In particular, garter snakes were sampled from populations harboring long- versus short-lived ecotypes and raised under controlled laboratory conditions prior to measuring O2 consumption as a proxy for metabolic rate. In the broadest sense, the data are not surprising; there is a clear link between body size and O2 consumption and between ambient temperature and O2 consumption, with O2 consumption increasing as a function of both increasing size and higher ambient temperatures. What is interesting, however, is that there are consistent differences in the long-versus short-lived snakes under standardized test conditions with short-lived snakes using far more O2 than their long-lived counterparts. The short-lived snakes in this study differ from long-lived snakes in a number of other physiological measures as well; including stress-induced H2O2 production and DNA repair efficiency. Taken together Anne and David’s data suggest that differential O2 consumption (and hence metabolic rate) has evolved in concert with, and perhaps is causal to, population-level differences in longevity within garter snakes, although the mechanistic bases for these differences remain unknown. Epigenetic regulation of gene expression during early development may well be at work, as there is no difference in resting metabolic rate between ecotypes at birth, while the consequences of the dramatic increase in O2 consumption are also unknown.

At times, the symposium may have deviated a bit from trying to tie in differences in metabolism with specific life-history traits (i.e., longevity), but I hope that a prevalent theme of applying “modern” techniques to the study of aging in a comparative setting comes through. It should also have been apparent that there is an acknowledged role of differential stress resistance in the modulation of life span—this is certainly the case for C. elegans, D. melanogaster...
and laboratory mouse stocks, but it is more likely that this is a generalization extendable to all vertebrates (Miller et al., in press)—and that comparative studies have already done much to either debunk or support certain aspects of this thinking. Finally, it should be clear that there is a paucity of thinking on the specific topic of “Metabolism, Life History and Aging”; hence the tendency to stray off-topic. As I alluded earlier, my thought has been a general lack of inquiry into this area is largely the result of unfamiliarity with blending these concepts on the part of field biologists and biogerontologists alike. Perhaps new new research relationships will be forged and these ideas will be brought to the forefront of biogerontological research where they belong.

Lastly, I would like to take a moment to thank all of the speakers and acknowledge the Society of Integrative and Comparative Biology, especially the Division of Comparative Physiology and Biochemistry (DCPB) and the Division of Ecology and Evolution (DEE), for making this symposium a success. Special thanks go to Kathy Dickson, the current program officer for DCPB.

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References


