ENERGY METABOLISM AND LIFESPAN DETERMINATION

VOLUME 14

Mark P. Mattson

ADVANCES IN CELL AGING AND GERONTOLOGY

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PREFACE

This volume of *Advances and Cell Aging in Gerontology* presents a collection of articles aimed at reviewing and synthesizing information concerning the roles of energy metabolism and systems that regulate and respond to changes in energy metabolism in aging and age-related disease. The first chapter sets the stage by presenting a viewpoint on the importance of energy sensing, acquisition and utilization in the evolution of all organisms from single cells to complex multicellular organisms. The case is made for competition for a limited supply of energy sources in the development of nervous systems and the importance of these master-regulating systems in not only evolution, but the aging process itself. Francesco Facchini reviews the roles of insulin-signaling, glucose metabolism and oxidative stress in the aging process and the inter-relationships between energy metabolism and oxyradical production in the kinds of damage to cells and consequent organ dysfunction that occur during aging. John Speakman then provides a detailed description of mitochondrial electron transport complexes and their roles in energy production and oxyradical production. This chapter highlights the importance of mitochondria in processes that are fundamental to the aging process in all eukaryotic organisms. Alterations in protein turnover occur during aging. Stephen Spindler and colleagues describe the relationships between energy metabolism and protein turnover during aging and consider how caloric restriction modifies the age-related alterations. My colleagues and I then review the evidence that many of the anti-aging and disease preventing effects of dietary restriction are mediated through mild cellular stress responses. The ability of dietary restriction to protect against cellular damage and dysfunction in disease models has been correlated with upregulation of genes that encode proteins that protect cells against stress and promote plasticity and recovery following injury. The mechanisms whereby caloric restriction suppresses the aging process are further explored in a chapter by Ricardo Gredilla and Gustavo Barja which focuses on the effects of caloric restriction on mitochondrial function and oxidative stress. The remaining four chapters of this volume present intriguing data from studies of experimental models of aging including *Drosophila*, *C. elegans* and yeast. Fanis Missirlis presents an integrated view of the genes that regulate lifespan in Drosophila in the context of a complex inter-relationship between energy balance, stress resistance and reproduction. Koen Houthoofd et al. then describe the genes known to regulate lifespan in *C. elegans* and how these genes impact on pathways involved in production and removal of reactive oxygen species. Naoaki Ishii and Philip Hartman then focus on electron transport changes in *C. elegans* and their possible roles in lifespan determination in this worm. Finally, Stephen Lin and colleagues review the intriguing advances that have been made in understanding the roles of energy acquisition and metabolism in the aging process using

Saccharomyces cervisiae as a model system. Collectively the chapters in this volume provide an integrated view of the importance of energy in determining lifespan and in modifying susceptibility to age-related disease.

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Advances in
Cell Aging and
Gerontology

The search for energy: a driving force in evolution and aging

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1. Evolutionary aspects of cellular and organismal energy requirements

In this chapter a view of the importance of energy acquisition and utilization in evolution and aging is presented. Portions of this chapter were modified from a previous article (Mattson, 2002). Life revolves around the acquisition of energy and its use in the multitude of cellular processes required for animals and plants to survive and reproduce. Many of the structural and functional systems of all cells and organisms are therefore concerned with seeking, ingesting, and utilizing energy (Fig. 1). The multitude of molecular interactions necessary to sustain cells and allow them to carry out their various functions within an organism are fueled by the high-energy bonds of adenosine trisphosphate (ATP). ATP is produced mainly from the metabolism of glucose in glycolytic and mitochondrial respiratory chain pathways, and organisms must therefore obtain or produce sufficient supplies of glucose and more complex glucose-containing molecules to sustain their functions. Single-celled organisms and small multicellular organisms have developed cell-surface receptors that sense glucose or molecules specifically associated with the energy source (Knowles and Carlile, 1978). In most cases organisms compete for a

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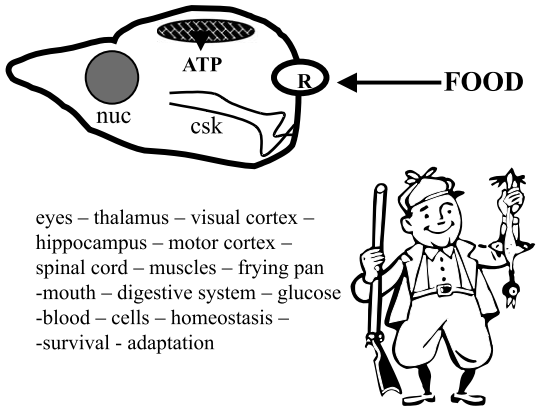

Fig. 1. From the simplest cells to the most complex organisms many different signaling mechanisms have evolved for the purpose of seeking, acquiring, storing, and efficiently utilizing energy. Single cells sense a food source, move toward it, ingest the food, convert it to ATP and then use the ATP to survive, find more food and reproduce. Complex multicellular organisms have evolved very sophisticated ways of obtaining food that are mediated, in large part, by complex nervous systems as illustrated by the duck hunter.

limited supply of food, and the development of novel mechanisms for sensing and ingesting the food were therefore favored by evolutionary pressure. One example of such adaptations is genes that encode proteins that couple a signal from a food source to an intracellular machinery that controls cell motility (i.e., the cytoskeletal microtubules and actin filaments). Indeed, there are many such examples of ligands in various food sources that act as chemotactic stimuli (Moulton and Montie, 1979). Additional mechanisms evolved that enhance the ability of cells and organisms to ingest food, once sensed; an example of a simple mechanism is the movement of glucose transporters to the cell surface (Olson et al., 2001) and an example of a complex mechanism is the development of appendages such as the hands of primates (Bloch and Boyer, 2002). Of course humans have evolved even more elaborate means of acquiring specific types of food (Fig. 1).

The inability of an organism to successfully compete for a limited food supply would obviously place it an evolutionary disadvantage. Such a disadvantage might be due to an inferior ability to sense the food source, to rapidly move to and ingest the food, or to a limited ability to store energy as glycogen or fat molecules. It may therefore be the case that adaptations that enhance the ability of individuals to survive on lesser amounts of food would increase the likelihood of the species surviving. In this view, phenotypes that promote a long life span would be selected for. However, it is likely that in many cases a long post-reproductive life span is selected against because such aged individuals consume resources while not contributing further to the gene pool as the species evolves.

2. Energy in aging and age-related disease

Other chapters in this issue of ACAG consider how differences in cellular and organismal energy metabolism might contribute to different life spans among organisms, and to determining the life span of individuals within a species. There are several lines of evidence that support an important role for energy metabolism in regulating life span. Examples include: among mammals, there is a strong, but not absolute, inverse relationship between metabolic rate and life span (Speakman et al., 2002); caloric restriction extends life span in a range of organisms (Weindruch and Sohal, 1997); mitochondrial ATP production and free radical production are linked, and there is reason to believe that free radicals mediate/promote aging (Sohal, 2002). Diseases that make major contributions to mortality, and hence life span, often involve abnormalities in cellular and organismal energy metabolism. Examples in mammals include: type 2 diabetes in which insulin resistance is the hallmark (Groop, 1999); myocardial infarction and stroke in which heart and brain cells die because of reduced glucose and oxygen availability (Mattson et al., 2000; Wang et al., 2002); and neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases in which impaired mitochondrial energy production is thought to compromise neurones and contribute to their death (Mattson et al., 1999; Duan et al., 2003a).

How might competition for a limited supply of food influence the life span of a species? Among mammals the longest-lived species are, in general, those that are the most highly evolved and therefore possess the most sophisticated mechanisms for competing for food. Thus, a species is more likely to avoid extinction if its individuals are able to (on average) live longer, and individuals are able to live longer if they eat less. Of course when individuals eat less there should be more food available to support a larger population of that species. Living longer allows individuals to acquire more knowledge and make greater contributions to the development of novel strategies for competing against other species, as well as against other populations within a species. One area of debate in the field of aging research concerns the interrelationships of reproduction and aging in the context of competition for limited resources (food). In order for the phenotype of an individual to contribute to the evolution of a species, its genome must be passed on to future generations in the process of reproduction. Obviously, this requires that the individual survive at least until a reproductive age. The ''disposable soma'' theory of aging proposes that longevity requires investments in somatic maintenance that reduce the resources available for reproduction or, conversely, that senescence is the result of the allocation of energy resources toward reproduction at the expense of repair and maintenance functions that would otherwise extend life (Westendorp and Kirkwood, 1998). By delaying reproduction life span is increased. This is also consistent, at least in part, with data from studies of dietary restriction in that dietary restriction reduces reproductive fitness (age of onset of sexual maturation, fertility, litter size) and extends life span. However, we have found that disease resistance and longevity can be increased in C57BL/6 mice by an intermittent fasting regiment that does not decrease caloric intake (Anson et al., 2003).