DOWNLOAD PDF PROTEIN METABOLISM AND HOMEOSTASIS IN AGING

Chapter 1 : The effect of age on protein metabolism â€” Mayo Clinic

DNA metabolism and chromosomal maintenance, together with protein metabolism are critical in the aging process. The focus of this book is on the role of protein metabolism and homeostasis in aging. An overview is provided of the current knowledge in the area, including protein synthesis, accuracy and repair, post-translational modifications.

The book provides a reference for years to come, written by world-renowned expert investigators studying sex differences, the role of sex hormones, the systems biology of sex, and the genetic contribution of sex chromosomes to metabolic homeostasis and diseases. In this volume, leaders of the pharmaceutical industry present their views on sex-specific drug discovery. This book will generate new knowledge and ideas on the importance of gender biology and medicine from a molecular standpoint to the population level and to provide the methods to study them. It is intended to be a catalyst leading to gender-specific treatments of metabolic diseases. There are fundamental aspects of metabolic homeostasis that are regulated differently in males and females, and influence both the development of diabetes and obesity and the response to pharmacological intervention. Still, most preclinical researchers avoid studying female rodents due to the added complexity of research plans. The consequence is a generation of data that risks being relevant to only half of the population. This is a timely moment to publish a book on sex differences in diseases as NIH leadership has asked scientists to consider sex as a biological variable in preclinical research, to ensure that women get the same benefit of medical research as men. Interest in sexuality and reproductive function does not cease when people begin to age. Instead, a new set of questions arises. Women want to know if it is safe to have babies in their late thirties and early forties. They want to know more about hot flashes and other symptoms of menopause-which ones are dangerous and which are merely uncomfortable. They are eager to learn about the relative risks and benefits of estrogen replacement therapy. Men, too, are concerned about age-related changes in their sexual function. Experts in reproductive physiology, gerontology, and genetics met at the National Institutes of Health in June of to discuss these and other concerns about aging and the reproductive system. This volume is based on the proceedings of that confer ence. Cancer, Other Pathologies, Inflammation, Immunity, Infection, and Aging is an eleven volume series that discusses in detail all aspects of autophagy machinery in the context of health, cancer, and other pathologies. Autophagy maintains homeostasis during starvation or stress conditions by balancing the synthesis of cellular components and their deregulation by autophagy. This series discusses the characterization of autophagosome-enriched vaccines and its efficacy in cancer immunotherapy. Autophagy serves to maintain healthy cells, tissues, and organs, but also promotes cancer survival and growth of established tumors. Impaired or deregulated autophagy can also contribute to disease pathogenesis. Understanding the importance and necessity of the role of autophagy in health and disease is vital for the studies of cancer, aging, neurodegeneration, immunology, and infectious diseases. Comprehensive and forward-thinking, these books offer a valuable guide to cellular processes while also inciting researchers to explore their potentially important connections. Presents the most advanced information regarding the role of the autophagic system in life and death Examines whether autophagy acts fundamentally as a cell survivor or cell death pathway or both Introduces new, more effective therapeutic strategies in the development of targeted drugs and programmed cell death, providing information that will aid in preventing detrimental inflammation Features recent advancements in the molecular mechanisms underlying a large number of genetic and epigenetic diseases and abnormalities, including atherosclerosis and CNS tumors, and their development and treatment Includes chapters authored by leaders in the field around the globeâ€”the broadest, most expert coverage available Author by: This work examines recent research in the biochemical basis of aging and offers contributions from an international group of researchers actively engaged in this field. It provides valuable new data on how aging alters protein metabolism and structure, the cell, endocrine and neurobiological functions, and free radicals. The book also explores the effects of dietary restrictions on aging. Specific topics include mechanisms of protein degradation; turnover of plasma membrane proteins in hepatocytes; genetic, biochemical, and molecular studies of cellular senescence; effects of aging and dietary restrictions on protein synthesis; and physiological antioxidant defense and repair systems.

Chapter 2 : Protein Homeostasis, Aging and Alzheimerâ€™s Disease - Europe PMC Article - Europe PMC

Age-associated decline in protein homeostasis, or proteostasis, enables disease-linked proteins to adopt aberrant tertiary structures, accumulate as higher-ordered aggregates, and cause a myriad of cellular dysfunctions and neuronal death.

Received Dec 29; Accepted Feb 5. The two main hypotheses of AD, the amyloid cascade hypothesis and the Tau hypothesis, are still in the focus of AD research. With aging as the accepted main risk factor of the most important non familial and late onset sporadic forms of AD, it is now mandatory to discuss more intensively aspects of cellular aging and aging biochemistry and its impact on neurodegeneration. Since aging is accompanied by changes in cellular protein homeostasis and an increasing demand for protein degradation, aspects of protein folding, misfolding, refolding and, importantly, protein degradation need to be linked to AD pathogenesis. This is the purpose of this short review. Sporadic late-onset AD is the most common form of dementia in the elderly and is strongly associated with age. One genetic risk factor for late-onset AD that has been reported throughout many studies is Apolipoprotein E ApoE which physiologically functions as a ligand in receptor-mediated endocytosis of lipoprotein particles [2 , 3]. Several single nucleotide polymorphisms in apoE lead to alterations in the coding sequence and result in three common isoforms called apoE2, apoE3 and apoE4 with the E4 allele being an AD risk factor and E2 being protective [4 â€” 6]. This challenges the amyloid hypothesis of AD and up to date the nature of the disease-relevant alteration in aged neurons remains unclear. Although Alois Alzheimer already described protein deposits in the brain of demented patients, the question why distinct proteins that are potentially causative for the disease accumulate in discrete brain regions in the course of aging remains unanswered. Recently, it has been proposed that the accumulation of disease-relevant proteins in aggregates might actually even be considered as a protective mechanism to dispose these proteins and remove them from the cellular metabolism [13 , 14]. Generally, within the crowded cellular environment, proteins are always at risk for denaturation. Changing genetic and environmental factors, as during pathology or aging, challenge the integrity of the cellular protein homeostasis proteostasis. Therefore, the stability and metabolism of the proteome needs to be controlled carefully and is carried out by a complex network of several hundred evolutionarily conserved proteins. This network, including molecular chaperones, the ubiquitinâ€”proteasome system UPS and the autophagy system is stringently regulated and indispensable for the maintenance of proteostasis. All main players of this network are ubiquitously expressed and consequently also present in neuronal tissue. Molecular chaperones, most be prominently represented by the heat shock protein 70 HSP70 family and their regulators, are responsible for correct folding and refolding of proteins as well as for the transport of misfolded proteins to the protein-degradation systems [15]. The chaperone network is controlled by the activity of transcription factors, e. The UPS is the major protein-degradation machinery of the cell and controls the metabolism of cytosolic proteins and the degradation of misfolded proteins. Proteins that are destined for proteasomal degradation become specifically tagged with the protein ubiquitin in a well-organized enzymatic cascade [16]. Interestingly, also a ubiquitin-independent way of proteasomal degradation has been described recently that mostly involves small and misfolded proteins [17]. As an additional mechanism for protein degradation the term autophagy summarizes degradation pathways that deliver their substrates to the lysosome [18]. The major autophagic systems described so far are macroautophagy and chaperone-mediated autophagy CMA. Macroautophagy is a complex process that involves the formation of a membrane structure, the autophagosome, which engulfs bulk cellular material proteins and organelles and subsequently fuses with the lysosome. CMA involves the constitutively expressed heat shock cognate 70 HSC70 that targets client proteins with a specific consensus motif directly to the lysosome [19]. In fact, HSP70 is also an important factor to assure selectivity of macroautophagy of degradation-prone proteins in a distinct pathway, mediated via the co-chaperone BCL2-associated athanogene 3 BAG3 [20]. Aging and disease challenge the proteostasis network and the accumulation of instable proteins results in wide-spread protein aggregation [21 , 22]. Our discussion presented here attempts to integrate two major factors that are associated with

neurodegeneration, protein homeostasis and aging. Most importantly, we focus on the role of specific pathways which are needed to restore and maintain proteostasis during aging and their interplay with a special focus on impaired proteostasis in AD, which may add to a novel view and understanding of AD pathogenesis. Since recently many excellent reviews on various aspects providing in depth discussions have been presented, we are concentrating here on the integration of these different aspects. Therefore, we frequently refer to review work with the recommendation of further reading rather than trying to fully cover the discussed issues by their original publications. Maintenance of Proteostasis via Molecular Chaperones: Within the crowded cellular environment, the correct conformation of proteins must be controlled and misfolded and irreversibly damaged proteins must be efficiently refolded or removed. Central players of the protein homeostasis system are molecular chaperones that sense misfolded proteins and, when refolding fails, direct them to the protein-degradation pathways. Molecular chaperones are specified as proteins that interact with and participate in folding or refolding of non-native proteins. Therefore, chaperones help unfolded proteins to achieve their functional conformation without being present in the final structure [15 , 23 â€” 27]. They exert a multitude of activities, including de novo folding, refolding of denatured proteins, transport to subcellular compartments, oligomeric assembly and disposal by proteolytic degradation [28 , 29]. Different classes of chaperones work together to form co-operative networks and are often termed heat shock proteins HSPs , because they are sensitively up-regulated under stress conditions in which the amount of misfolded proteins is increased [30]. They recognize short hydrophobic amino acid stretches of misfolded proteins and can co-operate with ATP-independent chaperones, e. HSP70 proteins are central players in proteostasis control and increasing HSP70 levels prevent protein aggregation in various disease models that are based on the expression of aggregation-prone proteins [32 , 33]. Thus, chaperone binding to the hydrophobic region of misfolded proteins transiently blocks aggregation and the subsequent ATP-dependent release allows controlled folding of the client protein. Recently, it has been shown that BAG3 interacts with HSP70 and directs the chaperone and its substrates into the autophagic pathway, providing an association of HSP70, co-chaperones and autophagy [40]. An extensive description of the HSP70 machinery, the exact structure-function relationship between HSP70 and its various cofactors, has been excellently reviewed elsewhere [34]. The functional variability of the chaperone system that is exerted by a multitude of single proteins highlights the complexity of this proteostasis network. However, limited knowledge exists on the exact composition and capacity of the chaperone system within a cell or a certain tissue. A general view assumes that total levels of cellular chaperones exceed the actual requirements and that a sufficient amount of chaperones is free of clients. Thus, the network has excess capacity to initially deal with sudden additional chaperone requirements, as exhibited during stress conditions [41]. An opposite view proposes that the capacity of the chaperone network is always closely titrated to the actual demand of chaperone activity and that the system is otherwise rapidly adapted to conditions of increased requirements [41]. The analysis of the chaperone capacity of neuronal and muscular tissue of Caenorhabditis elegans C. However, the adaptation of the chaperone network during aging is critical as it is well acknowledged that protein aggregation and disruption of proteostasis are characteristic for aged cells [21]. Several studies have clearly implicated a role of chaperones in aging. The periodical application of mild heat stress decreases mortality in Drosophila melanogaster and C. Several reports have analyzed chaperone protein or mRNA levels in aged cells and found increased or basal amounts, whereas the stress-mediated induction of chaperone expression is impaired. The transcription of chaperone genes in response to stress conditions is controlled by the transcription factor HSF1, which shows an impaired DNA-binding potential in aged cells [46]. A reduced activity of HSF1 in C. Thus, HSF1 and chaperone activity can promote longevity, demonstrating a clear association of chaperones, proteostasis and aging. Molecular Chaperones Get in Touch with the Protein Degradation Machineries Some of the factors mentioned so far are involved in linking chaperone functions with cellular protein-degradation pathways, the UPS and autophagy, for the removal of misfolded proteins. Besides protein aggregation, one factor that induces ubiquitination is protein damage caused by free radical oxygen species ROS and oxidative stress. Most likely, irreversible oxidation may activate chaperones and the UPS to induce protein repair of misfolded proteins and lead to ubiquitination and protein degradation. During aging, mitochondria are affected and produce increasing

amounts of ROS. In particular, the mitochondrial respiratory chain is strongly linked to the production of ROS and as one consequence may cause protein dysfunction, apoptosis, necrosis, aging and disease [49 , 50]. Protein oxidation leads to a change in protein conformation and function and chaperones may sense such changes and in turn activate the UPS as a quality control system. The UPS is a complex enzymatic pathway that starts with the ligation of ubiquitin, a amino-acid-long and highly conserved protein, to other cellular proteins and thus labels them for degradation. This process consists of three steps. Initially the C-terminal end of ubiquitin is activated by ATP-dependent phosphorylation and formation of a thiol ester via an activating enzyme, E1. It is then transferred to a thiol group of an ubiquitin-carrier protein, E2. The C-terminus of an additional ubiquitin protein can be ligated onto one of the seven lysine residues within the attached ubiquitin molecule. For degradation via the proteasome, target proteins need to be polyubiquitinated. Ubiquitinâ€”ubiquitin linkages between either the C-terminus and lysine residues K48 or K63 are the major recognition signals for proteasomal degradation. Ubiquitin chains also occur among other lysine residues, whereas ubiquitin extension via K6 is associated with DNA repair, K11 with endoplasmatic reticulum-associated protein degradation and cell cycle regulation, K27 with ubiquitin fusion degradation, K29 with lysosomal degradation and K33 with kinase modification [55]. Monoubiquitination can modify the activity of the protein transport machinery and when attached to transmembrane proteins can serve as a sorting signal to direct their movement between different cellular compartments [56 â€” 59]. The polyubiquitinated proteins destined for degradation are processed by the multienzymatic proteasome complex: The eukaryotic 20S proteasome core complex consists of four heptameric rings comprising two classes of seven non-identical but homologous subunits. The outer rings contain alpha-type subunits with gating function for substrate entrance and product release, while the beta-subunits exhibit peptide hydrolyzing activity. The 19S regulatory complex binds to the 20S catalytic core in a flexible manner and consists of six ATPases, forming a ring at the entrance of the core and exerting chaperone-like activity [60]. The UPS is the major degradation system in the cell for the degradation of short-lived, misfolded and defective proteins. An accumulation of polyubiquitinated proteins is reported for numerous neurological disorders [61], which suggests that UPS dysfunction plays a prominent role in the pathogenesis of neurodegenerative diseases and moreover in aging [62]. Since proteasomal activity decreases during aging over all, the degradation demand of the cell increases, which results in an age-associated induction of the autophagy pathway that delivers substrates for degradation ultimately to lysosomes [20 , 63]. Autophagy is negatively regulated via the evolutionarily conserved enzymatic mammalian target of rapamycin complex 1 mTORC1. In turn, if mTOR activity is inhibited by rapamycin, the autophagy pathway is switched on. Rapamycin exerts its stimulatory effect on autophagy by preventing mTOR phosphorylation at Ser and thereby subsequently blocks mTOR signaling [64]. So far, many different autophagic systems have been described including macroautophagy and CMA that form the main pathways. Macroautophagy is a multi-step process by which cytosolic material is sequestered into a double-layered membrane structure, the autophagosome, and is delivered to the lysosome for degradation. It is a highly orchestrated process and involves autophagy-related ATG proteins. More than 30 genes have been identified in genetic analyses of yeast mutants which have defects in autophagic function [65]. A subset of ATG proteins is required for autophagosome formation: These so-called autophagy receptors can simultaneously bind to ubiquitinated proteins and LC3, employing their LC3-interacting motif and ubiquitin-associated domain. These inclusions are then specifically engulfed by the autophagosome membrane by recruiting LC3 [69 , 70]. While macroautophagy is considered as a rather unspecific robust degradation process, CMA is a highly selective lysosomal pathway that removes a distinct subset of proteins containing a pentapeptide lysosome-targeting motif. These co-chaperones provide a direct link to the UPS and the folding and refolding activity of molecular chaperones. In the course of aging, a variety of proteins tend to aggregate and impair the UPS directly [71]. Therefore, these proteins, most of which are ubiquitinated, cannot be handled by the proteasome and have to be degraded by different protein clearance pathways. Proteasome activity decreases in an age-dependent manner in a cell model of replicative senescent human fibroblasts and is associated with an increased autophagic activity in aged cells. The BAG3-mediated selective pathways have been shown to be involved in a variety of disease causing processes. Additionally, the transport of target

proteins to the aggresome, a compartment with high autophagic activity, has been shown to be mediated by BAG3. This aggresome-targeting pathway involving BAG3 and HSP70 is distinct from other before-described mechanisms as it does not depend on substrate ubiquitination [75]. Taken together the molecular chaperone machinery, the UPS and the autophagy system are involved in PQC and maintaining proteostasis within aging and disease to prevent protein misfolding and aggregation. A summary of the main routes for protein degradation is shown in Fig. As aggregated proteins are found in AD patients and aging is a prevailing risk factor for AD it is important to further characterize how these pathways are regulated and how misregulation possibly contributes to the pathology of AD.

Chapter 3 : Protein homeostasis and aging in neurodegeneration.

Protein metabolism and lifespan in Caenorhabditis elegans / Geert Depuydt, Jacques R. Vanfleteren, and Bart P. Braeckman Mitochondrial protein quality control systems in aging and disease / Karin Luce, Andrea C. Weil, and Heinz D. Osiewacz.

Cologne is a vibrant city with a highly international academic research environment. CECAD forms a focal point of ageing research in Europe bringing together researchers and clinicians at the University of Cologne with researchers at the new Max Planck Institute for Biology of Aging in a unique research venture. Protein homeostasis proteostasis is achieved via conserved quality control pathways that support the maintenance of correctly folded proteins. Unfortunately, the proteostasis network has a limited capacity and its impairment causes protein aggregation that deteriorates both cellular and organismal viability. Our research particularly aims to understand the dynamic regulation of proteolytic pathways that integrate environmental and physiological changes. The detailed analysis of both cellular and tissue-related coordination of proteostasis will allow us to assemble a global picture of conserved quality control mechanisms important to safeguard the organismal proteome in health and disease. The assembly and maintenance of striated muscles require a tightly balanced proteostasis network. The integrity of sarcomeric structures is permanently challenged upon muscle growth and mechanical stress. In response to eccentric exercise or damage to the myofiber, the conserved myosin-specific co-chaperone UNC shuttles between the Z-disk and myosin containing areas of the muscle sarcomere. The long-term objective of this project is to define proteostasis networks essential for myosin assembly and muscle integrity. A combination of optogenetics, biochemical and in vivo imaging techniques will allow us to examine stress-induced changes of protein folding and degradation pathways. The conserved regulation of proteostasis networks will be studied in C. The proposed project will have broad implications for the understanding of muscle regeneration mechanisms and human myopathies. We are seeking a highly motivated PhD student to join our enthusiastic and collaborative group. Candidates should have demonstrated outstanding performance through their undergraduate studies. Besides creativity, a strong ability for problem solving through analytical thinking combined with an enthusiasm for scientific research is highly desirable. Additionally, we expect good communication skills, fluent English and the ability for teamwork. The successful applicant will join an enthusiastic and collaborative group where a multidisciplinary approach is pursued. Please send your CV, letter of intent, names and addresses of three references to office-hoppe uni-koeln. The ubiquitin ligase CHIP integrates proteostasis and aging by regulation of insulin receptor turnover. E4 ligase specific ubiquitylation hubs coordinate DNA double strand break repair and apoptosis. Challenging muscle homeostasis uncovers novel chaperone interactions in C. Protein quality control gets muscle into shape. Activities and responsibilities - Studying proteostasis with in vitro and in vivo bioechemical assays and determine the response mechanisms upon mechanostress and aging - Combine state of the arte optogenetis, biochemical and in vivo imaging techniques Qualification profile - Master of science e.

Chapter 4 : The effect of age on protein metabolism â€" Mayo Clinic

metabolism are critical in the aging process. the focus of this book is on the role of protein metabolism and homeostasis in aging. an overview is provided of the current knowledge in the area, including protein synthesis, accuracy and repair.

Advanced Search Abstract The demographic shift of the average age in the United States and worldwide mandates that careful attention be paid to the nutritional and health needs of all segments of our older adult population. Well-defined changes in body composition occur in aging animals and humans. Characteristic of this change is the age-associated decline in skeletal muscle mass, sarcopenia. Data from observational studies of dietary intake and body composition suggest that a substantial proportion of adults over the age of 60 y consume less than the U. Studies of acute ingestion of high-quality dietary protein in healthy older adults suggest that the age-related blunting of protein synthetic capacity can be overcome with increased dietary protein intake. However, studies on chronic administration of high-quality protein supplements in cohorts of older adults are more equivocal with respect to improving or preserving muscle mass. This review highlights selective aspects of protein supplementation in older adults. Between one-fifth and one-quarter of the world would fall into this category by this time. Increasingly, older adults continue to lead productive lives that involve active roles in caregiving, volunteerism, and many other integral social facets. Despite this, older adults are susceptible to disease and accompanying disability. Taken together, these circumstances highlight the importance of understanding the etiology of the aging process and the underlying metabolic alterations that occur consequent to advancing age. A characteristic hallmark of aging in humans is the well-described loss of muscle mass and function, which has been shown to contribute to functional limitations and disability 2 , 3 see Fig. Recent estimates have shown that sarcopenia incurs a substantial cost to the U. The underlying understanding of the pathogenesis of sarcopenia has evolved over the past 15 y. Preferential loss of type 2 muscle fibers is characteristic and seen in individuals as early as the age of 25 y, but the loss of muscle function to actual tissue loss seems disproportionate: Recently, studies have implicated a derangement of the equilibrium between muscle protein synthesis MPS 4 and muscle protein breakdown as a major contributor to this phenomenon. In particular, alterations in MPS during anabolic conditions in aged populations have been implicated as a substantial contributor to this imbalance 6 , 8 , 9. What remains unclear is the influence of aging and these age-related changes in muscle mass on the dynamics of protein turnover and their resultant effects on the requirements for dietary protein intake in this population. In addition, the role of supplemental protein intake has yet to be fully clarified with respect to promoting skeletal muscle growth or attenuating the rate of skeletal muscle atrophy. Although the mean age of active duty and reserve military personnel in all branches of the armed services is between 25 and 30 y, an increasing number of active-duty and reserve personnel are remaining until the mandatory retirement age of 60 y In addition, it is clear that many of the age-related declines in muscle mass and performance begin in early to late middle age and thus can have substantial effects on military readiness of some personnel. Finally, changes in muscle mass during active service may have latent health effects on the increasing population of retired former active military personnel. The purposes of the present review are to highlight our current understanding of the age-associated loss of skeletal muscle mass, sarcopenia; discuss the role of dietary protein intake on this process; and finally review the potential for supplemental protein ingestion to attenuate this process. Robust skeletal muscle mass is essential for maintaining homeostasis and whole-body health Aging is associated with the loss of skeletal muscle and can lead to declines in physical functioning The causes of sarcopenia like many complex geriatric syndromes are believed to be multifactorial but include decreased physical activity, increased cytokine activity, increased disruption of muscle motor unit firing, and a decrease in circulating anabolic hormones The loss of muscle mass and strength, and the concurrent increase in joint dysfunction and arthritis that occurs with aging, results in a decrease in physical function and an increased risk of disability see Fig. Disability is associated with the limitations to perform regular activities of daily living, including rising from a chair, climbing flights of stairs, or performing tasks such as bathing and food preparation. Studies have shown that the inability to perform these tasks increases with age in both men and women 16 , although others have

shown a higher risk of disability in women than in men Despite the high prevalence and major health implications, sarcopenia still has no broadly accepted clinical definition or diagnostic criteria. This definition has been endorsed as a component of the objective determination of sarcopenia, but other measures are used to assess reductions in physical functioning and the risk of future disability. These include cumulative score on the short physical performance battery 19 , the m walk 20 , stair climb 21 , and grip strength Protein requirements for older adults. The average daily RDA for protein in all adults has remained at 0. Dietary Guidelines for Americans This recommendation has been derived from small, carefully controlled studies of nitrogen balance that have determined the Estimated Average Requirement for protein to be 0. Although many older adults consume an adequate amount of protein on the basis of these standards, there is a subset of older individuals who routinely have protein intakes below the current RDA In addition, there has been some suggestion that the current RDA for protein is inadequate for older adults 25 , However, consensus from the available data on protein requirements for older adults is lacking Not surprisingly, evidence from large epidemiologic cohort studies suggests that the loss of lean mass with advancing age is in part mediated by dietary consumption of protein. Despite the conflicting reports from carefully controlled nitrogen-balance studies, it appears that observational studies in older people suggest a relation between lower dietary protein intake and loss of muscle mass. This apparent discrepancy may be related to limitations in the ability of the nitrogen-balance technique to detect subtle alterations in whole-body protein metabolism and the selection of generally healthy participants in these intensive metabolic studies. In addition, observational cohort studies may capture exacerbations of disease or comorbid conditions that can substantially alter protein homeostasis and exert long-term cumulative effects on whole-body lean mass that are not manifest in carefully controlled short-term nitrogen-balance studies in healthy older adults. Future studies will need to carefully consider target populations and other outcomes beyond nitrogen balance to fully understand the impact of aging on the control of skeletal muscle protein turnover. Whole-body lean mass is tightly controlled and a product of the difference between MPS and degradation and is directly associated with the net activation of signaling pathways regulating anabolism and catabolism in skeletal muscle. During muscle atrophy, total protein degradation is increased 31 and protein synthesis is reduced Muscle growth or hypertrophy occurs when protein synthesis exceeds degradation cumulatively over time. Muscle loss or atrophy occurs when cumulative degradation exceeds synthesis. There is a selective degradation of white muscle type 2 fibers during skeletal muscle atrophy with resultant sparing of tonically active red muscle type 1 fibers 33 , Similar changes occur with aging based on studies of whole thigh muscle obtained at autopsy, which reported a loss in the total number and size of muscle fibers, particularly the white type 2 fibers It appears likely that these age-related changes are driven by declines in protein synthesis and an increase in protein degradation. Interestingly, aging appears to have no effect on basal rates of skeletal muscle protein synthesis but does seem to be reduced in response to anabolic stimulation after feeding or contraction 9 , However, the effects of aging on skeletal muscle protein degradation appear to be more complex and are at present difficult to quantify. Therefore, the inability to respond to anabolic stimuli i. Several proanabolic inducers [e. In older humans, intake of essential amino acids EAAs induces a reduced increase in skeletal MPS compared with that in younger humans, and this difference was directly related to postprandial differences in the increase in circulating and intramuscular EAAs Both hyperinsulinemia and intravenous EAA infusion also induced less robust increases in protein synthesis in older humans and rodents 39 , After muscle contraction or physical activity, there is a robust increase in skeletal MPS, even in the fasted state. Similar to EAA and insulin treatment, there is a blunted protein synthetic response to contraction and exercise in older animals and humans Phosphorylation of specific anabolic signaling pathways was increased in skeletal muscle after a single bout of maximal contractions induced by high-frequency electrical stimulation in adult animals, but these responses were blunted in older animals Despite evidence of anabolic resistance in response to EAAs, contraction, and insulin, several studies have noted that anabolic resistance in older healthy individuals can be fully overcome with higher intakes of dietary protein, particularly when consumed in conjunction with carbohydrate 45 â€” Current data on the effects of protein supplementation with resistance training RT on body composition, muscle hypertrophy, strength, and physical function from protocols ranging in duration from 10 wk to 18 mo

have yielded mixed results 49 â€”

Chapter 5 : MedILS > Research > Groups > Macromolecular homeostasis in aging

This book examines the role of protein metabolism and homeostasis in aging. It offers an overview of the current knowledge in the area, including protein synthesis, accuracy and repair, post-translational modifications, and degradation and turnover.

Mechanisms of proteostasis[edit] The roles of the ribosome In proteostasis[edit] One of the first points of regulation for proteostasis is during translation. This is accomplished via the structure of the ribosome , a complex central to translation. These two characteristics shape the way the protein folds and influences the proteins future interactions. The synthesis of a new peptide chain using the ribosome is very slow and the ribosome can even be stalled when it encounters a rare codon , a codon found at low concentrations in the cell. This facilitates the correct folding of multi-domain proteins. For example, an alpha helix is one such structural property that is commonly induced in this exit channel. Molecular chaperones and post-translational maintenance in proteostasis[edit] In order to maintain protein homeostasis post-translationally, the cell makes use of molecular chaperones sometimes including chaperonins , which aid in the assembly or disassembly of proteins. Trigger factor works to stabilize the peptide, promotes its folding, prevents aggregation, and promotes refolding of denatured model substrates. Hsp70 surrounds an unfolded peptide chain, thereby preventing aggregation and promoting folding. Group 1 chaperonins are commonly found in bacteria, chloroplasts, and mitochondria. Group 2 chaperonins are found in both the cytosol of eukaryotic cells as well as in archaea. All chaperonins exhibit two states open and closed , between which they can cycle. This cycling process is important during the folding of an individual polypeptide chain as it helps to avoid undesired interactions as well as to prevent the peptide from entering into kinetically trapped states. Protein degradation occurs in proteostasis when the cellular signals indicate the need to decrease overall cellular protein levels. These degradable substrates include nonfunctional protein fragments produced from ribosomal stalling during translation, misfolded or unfolded proteins, aggregated proteins, and proteins that are no longer needed to carry out cellular function. Several different pathways exist for carrying out these degradation processes. When proteins are determined to be unfolded or misfolded, they are typically degraded via the unfolded protein response UPR or endoplasmic-reticulum-associated protein degradation ERAD. Substrates that are unfolded, misfolded, or no longer required for cellular function can also be ubiquitin tagged for degradation by ATP dependent proteases, such as the proteasome in eukaryotes or ClpXP in prokaryotes. Autophagy , or self engulfment, lysosomal targeting, and phagocytosis engulfment of waste products by other cells can also be used as proteostatic degradation mechanisms. Distinct surveillance mechanisms that respond unfolded protein have been characterized in the cytoplasm, ER and mitochondria. This response acts locally in a cell autonomous fashion but can also extend to intercellular signaling to protect the organism from anticipated proteotoxic stress. Cell-autonomous stress responses[edit] Cellular stress response pathways detect and alleviate proteotoxic stress which is triggered by imbalances in proteostasis. The cell-autonomous regulation occurs through direct detection of misfolded proteins or inhibition of pathway activation by sequestering activating components in response to heat shock. Cellular responses to this stress signaling include transcriptional activation of chaperone expression, increased efficiency in protein trafficking and protein degradation and translational reduction. Proteostasis stress signaling response Cytosolic heat shock response[edit] The cytosolic HSR is mainly mediated by the transcription factor family HSF heat shock family. HSF is constitutively bound by Hsp Upon a proteotoxic stimulus Hsp90 is recruited away from HSF which can then bind to heat response elements in the DNA and upregulate gene expression of proteins involved in the maintenance of proteostasis. ER unfolded protein response[edit] The unfolded protein response in the endoplasmatic reticulum ER is activated by imbalances of unfolded proteins inside the ER and the proteins mediating protein homeostasis. Mitochondrial unfolded protein response[edit] The mitochondrial unfolded protein response detects imbalances in protein stoichiometry of mitochondrial proteins and misfolded proteins. Systemic stress signaling[edit] Stress responses can also be triggered in a non-cell autonomous fashion by intercellular communication. The stress that is sensed in one tissue could thereby be communicated to other

tissues to protect the proteome of the organism or to regulate proteostasis systemically. Cell non-autonomous activation can occur for all three stress responses. Work on the model organism C. Stress induced in the neurons of the worm can in the long run protect other tissues such as muscle and intestinal cells from chronic proteotoxicity. These systemic responses have been implicated in mediating not only systemic proteostasis but also influence organismal aging. The classic examples are missense mutations and deletions that change the thermodynamic and kinetic parameters for the protein folding process. Disease develops when these mutations render a protein significantly more susceptible to misfolding, aggregation, and degradation. If these effects only alter the mutated protein, the negative consequences will only be local loss of function. However, if these mutations occur in a chaperone or a protein that interacts with many other proteins, dramatic global alterations in the proteostasis boundary will occur. Model systems of diverse misfolding-prone disease proteins have so far revealed numerous chaperone and co-chaperone modifiers of proteotoxicity. This increased protein synthesis is typically seen in proteins that modulate cell metabolism and growth processes. Cancer cells are sometimes susceptible to drugs that inhibit chaperones and disrupt proteostasis, such as Hsp90 inhibitors or proteasome inhibitors. Metabolic disease, such as that associated with obesity, alters the ability of cellular proteostasis networks adapt to stress, often with detrimental health effects. This disruption leads to the disease symptoms exhibited in individuals with diabetes. This risk is particularly high for intrinsically disordered proteins. Functional assays in C. The principle behind designing pharmacologic chaperones for intervention in diseases of proteostasis is to design small molecules that stabilize proteins exhibiting borderline stability. Previously, this approach has been used to target and stabilize G-protein coupled receptors, neurotransmitter receptors, glycosidases, lysosomal storage proteins, and the mutant CFTR protein that causes cystic fibrosis and transthyretin, which can misfiled and aggregate leading to amyloidoses. For example, some proteostasis regulators initiate stress responsive signaling, such as the unfolded protein response, which transcriptionally reprograms the endoplasmic reticulum proteostasis network. One theoretical mechanism for this approach includes upregulating the heat shock response response to rescue proteins from degradation during cellular stress.

Chapter 6 : Protein Metabolism And Homeostasis In Aging | Download eBook PDF/EPUB

[et al.] -- Protein synthesis and the antagonistic pleiotropy hypothesis of aging / Pankaj Kapahi -- Proteasome function determines cellular homeostasis and the rate of aging / Niki Chondrogianni and Efstathios S. Gonos -- Autophagy and longevity: lessons from C. elegans / Kailiang Jia and Beth Levine -- Autophagy and aging: lessons from.

Chapter 7 : Protein metabolism and homeostasis in aging - ECU Libraries Catalog

Protein Homeostasis and Aging: the importance of exquisite quality control Hiroshi Koga, Susmita Kaushik, and Ana Maria Cuervo Department of Developmental and Molecular Biology, Marion Bessin Liver Research Center, Institute for Aging Research, Albert Einstein College of Medicine, Bronx, NY, USA,

Chapter 8 : Protein Metabolism and Homeostasis in Aging : Nektarios Tavernarakis :

Protein Metabolism and Homeostasis in Aging Loss o f protein function due to oxidative modi fication can be due either to direct inhi bition of activity of a protein (for example, covalent modification of a side chain in proximity of an.

Chapter 9 : What Is Protein Homeostasis? (with pictures)

Protein Metabolism and Homeostasis in Aging by Nektarios Tavernarakis, , available at Book Depository with free delivery worldwide.