DOWNLOAD PDF REGULATION OF METABOLISM, AGING AND LIFESPAN BY MICRORNAS JUNLONG ZHANG

Chapter 1 : Aging, Metabolism, and Cancer Development: from Petoâ€™s Paradox to the Warburg Effect

Zhang, Junlong () Regulation of metabolism, aging and lifespan by microRNAs. In: Lyland, Roger T. and Browning, Irving B., (eds.) RNA interference research progress.

Solexa sequencing technology was used for an initial miRNA screening of serum samples pooled from 21 healthy Chinese subjects with an average age of 22 years, 10 subjects with an average age of 40 years, 10 subjects with an average age of 59 years, and 9 subjects with an average age of 70 years. Other serum samples were obtained from normal people with approximately 31 samples in each age period. A stem-loop quantitative reverse transcriptionâ€”PCR assay was conducted to confirm the concentrations of the miRNAs altered in the aging process. Solexa sequencing demonstrated 10 markedly altered miRNAs in the aging process. Their target genes, related diseases, molecular and cellular functions, and participated pathways were further analyzed. The measurement of miRNAs in serum provides a novel, noninvasive approach for the identification of the aging process. Our bioinformatic analyses could form a useful knowledge base for the potential future development of novel therapeutic treatments. They are involved in a wide range of biological and pathological processes, including the cell cycle, differentiation, development, metabolism, patterning, aging, etc. In , Lee and coworkers had demonstrated for the first time that the lin-4 gene and its target lin regulate the lifespan of Caenorhabditis elegans 3. Several downregulated miRNAs have been found in aged mice brain and liver tissues 4 , 5 , whereas there are no obvious miRNA changes identified in lung tissues with age. Another group used liver from different time points to screen miRNA expression and revealed that some miRNAs are involved in liver function while others are associated with regeneration ability 6. Additionally, these aging-related miRNAs with altered expression during the aging process also showed tissue-specific characteristics 8. A group examined the differential expression of miRNAs in young and aged human skeletal muscle before and after anabolic stimulation 9. Furthermore, the comparative profiling of genes and miRNAs showed differences between newborn, young adult, and aged human epididymides, and few miRNAs showed an age-enriched expression pattern in the adult and aged epididymides Moreover, mononuclear cells from peripheral blood were used as a model to evaluate miRNA expression in samples from young and old individuals, and they identified nine miRNAs that were significantly lower in older individuals Here, we combined the high-throughput Solexa sequencing screening with a stem-loop quantitative reverse transcriptionâ€”PCR qRTâ€”PCR assay that uses a hydrolysis probe to systematically and comprehensively evaluate miRNA expression profiles in the sera of healthy individuals at different steps of the aging process. Finally, the targeted genes, related diseases, molecular functions, and related pathways of these miRNAs were further analyzed. Participants who showed no evidence of disease were selected. The cohort consists of Chineses residing in Jiangsu province, China. All participants gave written informed consent and the Research Ethics Committee of Jinling Hospital approved this investigation. A total of serum samples were collected and divided into four groups based on the average age difference; these groups are 22 years old, 40 years old, 59 years old, and 70 years old. For detailed methodology, see Supplementary Data. We obtained the protein class from the PATHER analysis results and then clustered the same functional class of protein with the top 10 classes. The web-based functional annotation tool Database for Annotation, Visualization and Integrated Discovery DAVID has key components for disease analysis, gene ontology analysis, and pathway analysis. For each miRNA, the top two items were listed out for each analysis. The multiple comparison p values were corrected by Bonferroni correction. A p value less than. The demographic features of all participants are listed Table 1. A miRNA was considered altered if Solexa sequencing detected copies in one of these groups and the miRNA showed at least twofold difference Figure 1. A total of 10 common miRNAs in both the female and male groups were found to be altered in the aging process, with 4 upregulated let-7b, miRa, miR, and miR and 6 downregulated miRNAs miRb, miRb, miRb, miRb, miRp, and miR during the aging process.

Chapter 2 : - NLM Catalog Result

Regulation of Metabolism, Aging and Lifespan by MicroRNAs pp. $ Authors: (Junlong Zhang, Clinical Sciences Research Institute, Walsgrave Hospital Campus, Coventry).

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Chapter 3 : Regulation of metabolism, aging and lifespan by microRNAs - CORE

Regulation of metabolism, aging and lifespan by microRNAs. By Junlong Zhang. Abstract. RNA interference (RNAi) is a mechanism that inhibits gene expression by.

As IIS pathway governs growth and development, metabolism, reproduction, stress response, and longevity; temporal, spatial, and nutrient regulation of dilps encoding Drosophila insulin-like peptides DILPs provides potential mechanisms in modulating IIS. Identification of factors that influence dilp expression and DILP secretion has provided insight into the intricate regulatory mechanisms underlying transcriptional regulation of those genes and the activity of each peptide. Loss of dilp2 or adult fat body specific expression of dilp6 has been shown to extend lifespan, establishing their roles in longevity regulation. The exact role of DILP3 in aging awaits further clarification. This review highlights recent findings on the importance of conserved DILPs in metabolic homeostasis, DR, and aging, providing strong evidence for the use of DILPs in modeling metabolic disorders such as diabetes and hyperinsulinemia in the fly that could further our understanding of the underlying processes and identify therapeutic strategies to treat them. DILPs 1â€”8 have been identified mostly through their sequence homology to the mammalian insulin and the typical B-C-A domain structure as observed in mammalian insulin Gronke and Partridge, Functional conservation of DILP5 was recently revealed where DILP5 binds to and activates the human insulin receptor in lowering circulating glucose levels Sajid et al. Furthermore, altered expression of genes encoding DILP2, 3, 5, and 6 results in modulated IIS and profound metabolic and longevity consequences Broughton et al. In this review, we will discuss recent progress on our understanding of the diverse biological roles of DILPs in metabolic control, dietary restriction DR , and lifespan, with a focus on DILPs 2, 3, 5, and 6 given available emerging research findings. Consistent with the broad and diverse physiological consequences of IIS, specific temporal, and spatial expression patterns of individual dilps suggest potentially specialized interactions between each DILP and the DInR. Furthermore, we will discuss the regulation, functional diversity, and redundancy of the DILPs as circulating peptides and the physiology of the tissues producing them. Recent discoveries of the involvement of the nutrient sensing fat body in controlling DILP secretion from insulin-like peptide producing cells IPCs in the brain has provided a physiological link between those two major tissues governing nutrient sensing, metabolism, and aging Geminard et al. Finally, we will discuss how DILPs are modulated under DR and how such regulation affects the lifespan of the organism. Nutrient, Temporal, and Spatial Regulation of dilp Expression and DILP Secretion More than a decade ago, the search for the extracellular ligands for the DInR led to the identification of seven Drosophila insulin-like peptide genes dilp1â€”7 with diverse temporal and spatial specific expression patterns Brogiolo et al. The newest member dilp8, has recently been added to the family Colombani et al. During development, while dilp2, dilp4, and dilp7 transcripts are detected in midgut and mesoderm during late-stage embryogenesis, transcripts of dilp3, dilp5, or dilp6 are not detectable until larval stages Brogiolo et al. In larvae, low levels of dilp2 expression are detected in the imaginal discs whereas a high signal is measured in seven IPCs of each brain hemisphere and in salivary glands Brogiolo et al. Similarly, dilp5 transcripts, turned on in the second instar and dilp3 transcripts measured in the mid to late third instar are both detected in the brain IPCs Ikeya et al. Recent reports have revealed that dilp5 is a transcriptional target of a synergistic interaction between Eyeless and Dachshund Clements et al. Recent reports demonstrated dilp8 expression detected in larval imaginal discs Colombani et al. In the adult stage, expression of dilps2, 3, and 5 but not dilp1 is detected in IPCs Broughton et al. In addition to its expression in IPCs, dilp5 transcripts are also detected in follicle cells of stage 10 oocytes Ikeya et al. Adult expression of dilp4 is not known Gronke and Partridge, Transcripts of dilp6 are measured most abundantly in the adult fat body and at lower levels in head carcass and brain Bai et al. Finally, transcripts of dilp7 are detected in specific neurons of the ventral cord dMP2 and several neurons in the brain Miguel-Aliaga et al. The critical roles of DILPs in animal development and energy homeostasis are evidenced by the fact that their expression

is not only regulated temporally and spatially during development but also by nutrient status. As DInR activity is reduced following starvation, it was posited that this could be due to lack of DILPs under low nutrient availability Britton et al. Indeed, upon starvation, expression levels of dilp3 and dilp5, but not dilp2 are reduced Ikeya et al. A recent study demonstrated a role of dSir2, the Drosophila homolog of mammalian histone deacetylase SIRT1 in regulating the expression of dilp2 and dilp5 where systemic knockdown of dSir2 up-regulates those two dilps Banerjee et al. In addition, fat body-specific knockdown of dSir2 is sufficient to up-regulate dilp2 and dilp5 expression with changes in dilp3 transcript levels in those flies not reported Banerjee et al. Finally, dSir2-mediated regulation of these two dilps is shown to act independently of dFOXO, a forkhead box-O transcription factor. As mammalian NPY positively regulates food intake, those results provide additional evidence linking nutrient status and dilp levels. A recent study by Yu et al. Neuronal and IPC-specific knockdown of dcbl results in up-regulation of dilps 2, 3, 5 whereas the Epidermal growth factor receptor EGFR signaling pathway mediates this regulatory effect of dCbl only on dilps 2 and 3. Thus, a likelihood of other mediators for dilp5 is speculated Yu et al. Interestingly, unlike dilp3 and dilp5 whose expression levels are suppressed upon starvation, dilp6 transcript levels are induced under nutrient deprivation and dFOXO is shown to modulate this response in larvae Slaidina et al. During late larval and pupal stages when animals cease to feed, dilp6 expression is strongly induced Okamoto et al. As this high level of dilp6 expression during the larval-pupal transition coincides with a surge of the hormone ecdysone, Slaidina et al. Although basal levels of ecdysone regulates growth through dFOXO during larval development Colombani et al. In addition, dilp6 also regulates the expression of dilp5, when over-expressed in the adult fat body Bai et al. Using a reverse genetic approach, Varghese et al. Interestingly, the hyperlipidemic defect seen in miR mutants was rescued by overexpressing dilp3 implying that miR regulates lipid metabolism through modulation of dilp3 and also outlines a role for dilp3 in this regard Varghese et al. Another miRNA found in the fat body, miR acts to improve insulin sensitivity. The involvement of miRNAs in regulating insulin response in the fat body as well as dilp expression in IPCs provide exciting evidence for the complexity of selective dilp regulation that warrants further investigation. There is a marked distinction between regulation of dilp expression and DILP secretion, as regulatory mechanisms exist in controlling the release of the DILPs. For example, while initial characterization of dilp expression pattern affected by diet conditions showed down regulation of dilp3 and dilp5 expression but not dilp2 under starvation Ikeya et al. Soon after this report, Geminard et al. In this study, it was elegantly demonstrated through ex vivo tissue co-culture experiments that the abdominal fat body, functionally homologous to mammalian liver and white adipose tissue and acting as a nutrient sensor, relays this information to brain IPCs by a hormonal signal that involves target of rapamycin TOR signaling Geminard et al. Consistent with the notion that fat body relays this secretory signal to the IPCs through a hormone it releases, Unpaired 2 Upd2 , a cytokine produced by the fat body was recently shown to fulfill this role Rajan and Perrimon, As expected, flies with upd2 knockdown exhibited increased DILP accumulation under a fed state, illustrating an inability of IPCs to respond to insulin demands Rajan and Perrimon, A recent study by Bai et al. Therefore, DILP6 cell non-autonomously decreases IIS by presumably serving as an adipokine or potentially regulating a downstream adipokine that represses dilp2 expression in the brain IPCs and its secretion Bai et al. Additional influences of nutrient status are likely to further contribute to differential regulation of dilp2, 3, 5, and 6, which predicts diverse functionality of each DILP in mediating IIS under diverse physiological environments. Regulation of dilp expression and circulating DILP levels in response to nutrient status, transcriptional factors, hormone, and a neuropeptide during larval development. Ecdysone regulates dilp6 during larval-pupal transition through unknown effectors. Transcriptional factors Dachshund Dac and Eyeless Ey synergistically promote the expression of dilp5. Arrows indicate positive regulation whereas blunt-ended lines indicate negative regulation. The first set of compelling evidence demonstrating the functional extent of DILPs in controlling growth, development, and glucose homeostasis was generated by the destruction of IPCs. Ablation of IPCs during the early larval stage results in severe developmental delay with a reduction of both cell numbers and body size accompanied by an increased level

of circulating sugars suggesting a diabetic-related phenotype Rulifson et al. Importantly, a partial rescue of growth and circulating sugar phenotypes with dilp2 overexpression strongly supported the notion that loss of DILP2 was responsible for the phenotypes Rulifson et al. Ablation of IPCs in late larval stages results in a minor developmental delay and slightly decreased body size Ikeya et al. It was later demonstrated by Buch et al. Similar to the larval effects on glucose homeostasis, adult-specific partial ablation of IPCs renders flies hyperglycemic and glucose intolerant but insulin sensitive as measured by peripheral glucose disposal upon insulin injection and serine phosphorylation of a key insulin-signaling molecule, Akt Haselton et al. In addition, a significant increase in stored glycogen and triglyceride levels as well as an elevated level of circulating lipids was measured in adult IPC knockdown flies with an extended lifespan thus demonstrating that it is possible to modulate DILP action in adult flies to achieve lifespan extension without insulin resistance. With the development of an oral glucose tolerance test in the adult fly, this report documented that adult IPCs indeed are responsible for executing an acute glucose clearance response Haselton et al. While this study clearly demonstrates profound metabolic and longevity phenotypes as the result of impaired DILP-producing IPCs in an adult-specific manner, it remains to be determined the specific involvement in metabolism and aging of each DILP produced in IPCs. However, the role of individual DILPs in controlling the aging process has proven difficult to ascertain due to functional redundancy and compensation among DILPs. Down-regulation of dilp2 is associated with lifespan extension under several conditions. First, activation of dFOXO in the pericerebral fat body extends lifespan with an accompanied reduction in dilp2, but not in dilp3 or dilp5 mRNA levels Hwangbo et al. Third, expression of a dominant negative form of p53 in adult neurons extended lifespan and reduced dilp2 transcript levels, again indicating that the reduction of dilp2 expression was closely associated with extended longevity under those genetic conditions Bauer et al. Although those results indicate a close association between decreased dilp2 expression and increased lifespan, direct modulation of dilp2 levels was needed to assess the causal relationship between dilp2 expression and lifespan control. To this end, surprisingly, while causing a severe reduction of dilp2 transcripts, targeted knockdown of dilp2 in IPCs did not result in any lifespan extension Broughton et al. But interestingly, an increase in dilp3 and dilp5 expression was observed in those flies raising the possibility that a compensatory mechanism exists to modulate overall dilp expression in the IPCs. However, this compensatory increase in dilp3 and dilp5 expression could not completely account for the lack of lifespan extension in dilp2 knockdown flies as a similar increase of dilp3 and dilp5 transcripts was observed in long-lived dilp2 null mutant flies and increased dilp5 expression levels in long-lived dilp2â€”3 mutants Gronke et al. Thus, it remains possible that dilp2 knockdown elicits additional genetic alterations neutralizing the effect on lifespan associated with reduced dilp2 transcripts. The extended lifespan measured in dilp2 null mutants, however, confirms a major role of DILP2 in longevity control. The absence of any change in lifespan in flies with a dilp3 deletion is intriguing as both dilp2 and dilp5 transcript levels are lowered in those flies Gronke et al. A lack of consistent correlation between dilp transcript levels and lifespan effects in dilp2, dilp2â€”3, and dilp3 null mutants requires further clarification with measurements of DILP peptide levels as possible compensatory mechanisms to modulate IIS and lifespan regulation. An involvement of DILP3 in longevity control is worth further investigation, however as dilp3 transcript levels appeared to be specifically reduced in long-lived flies with increased mitochondrial uncoupling in adult IPCs Fridell et al. While a dilp5 null mutant appeared to have no effect on lifespan under standard diet Gronke et al. A dilp6 loss-of-function mutation neither had any effect on adult Drosophila survival nor on any compensatory increase in the expression of other dilps Gronke et al. On the other hand, Bai et al. This study also shed light on the fact that the longevity effect of dFOXO when overexpressed in the pericerebral fat body requires dilp6 Bai et al. Taken together, creation of individual or combinatorial dilp mutants has confirmed lifespan extension as the result of dilp2 deficiency suggesting a major role of DILP2 in modulating IIS. On the other hand, targeted expression of dilp6 in the adult fat body results in profound longevity and metabolic consequences that underlies its role in lifespan regulation. To aid a better understanding of the significance of DILP2 and DILP6, physiological alterations that accompanied

lifespan extension in respective dilp mutants have paved the way. IPC ablated flies exhibit high levels of trehalose, lipid and glycogen stores, accompanied by increased stress resistance Broughton et al. With respect to DILP2, the phenotypic changes as a result of its down-regulation were associated with higher trehalose storage levels and slight resistance to starvation Broughton et al. Increased trehalose levels were also seen in a dilp2 loss-of-function mutant with no change in lipid or glycogen levels Gronke et al. Nevertheless, those findings imply a role for DILP2 in trehalose metabolism, which may explain a moderate starvation resistance in those flies. Surprisingly, neither dilp2 null mutants nor dilp 2â€”3, 5 deletion mutants, created by homologous recombination, were resistant to starvation Gronke et al. The evidence that IPCs, independent of insulin signaling, mediate response to starvation Mattaliano et al. However, neither the dilp2 RNAi hypomorphs Broughton et al. These studies thus, point to a role for DILP2 in trehalose metabolism, which could contribute to lifespan extension as the result of increased energy storage. While adult flies harboring dilp6 over expression in the abdominal fat body exhibit metabolic phenotypes reminiscent of those seen as a consequence of reduced IIS Bai et al. This is substantiated by the fact that DILP6 plays an important role in reallocating energy stores during the non-feeding pupal stage in preparation for metamorphosis Slaidina et al. While the exact molecular mechanisms behind DR-mediated lifespan extension are yet to be completely elucidated, several molecular pathways have emerged as important players involved in DR responses Narasimhan et al. While Clancy et al. A potential explanation for this discrepancy may be the different DR regimens used in those studies.

Chapter 4 : Table of contents for Library of Congress control number

Download Citation on ResearchGate | Regulation of metabolism, aging and lifespan by microRNAs | MicroRNAs (miRNAs) are small RNA molecules (~22 nucleotides) that regulate gene functions either via.

Chapter 5 : Regulation of SIRT1 by MicroRNAs - Europe PMC Article - Europe PMC

Recent studies have shown that metabolism plays an important role in regulating epigenetic modifications and that this regulation dramatically affects the aging process. This review focuses on current knowledge regarding the mechanisms of stem cell aging, and the links between cellular metabolism and epigenetic regulation.

Chapter 6 : Microbiology and molecular bio..ï¼•[]

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Chapter 7 : Regulation of metabolism, aging and lifespan by microRNAs - WRAP: Warwick Research Arch

Genetic pathways in aging and lin The genes and pathways that are involved in aging rate and lifespan determination have been studied extensively.

Chapter 8 : Frontiers | MicroRNA Regulation of SIRT1 | Physiology

[et al.] -- Biological functions of microRNAs in animals / Marie-HÃ©lÃ¨ne Renalier, Samantha Tirmarche, HervÃ© Seitz -- Regulation of metabolism, aging, and lifespan by microRNAs / Junlong Zhang -- Herpesvirus microRNAs in infection and cancer / Andrea J. O'Hara, Dirk P. Dittmer.

Chapter 9 : Dianzheng Zhang, PhD | PCOM Faculty

MicroRNAs (miRNAs) are a class of short non-coding RNAs that bind mRNAs through partial base-pair complementarity with their target genes, resulting in post-transcriptional repression of gene expression. The role of miRNAs in controlling aging processes has been uncovered recently with the discovery.