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MicroRNAs and the Metabolic Hallmarks of Aging

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Abstract

Aging, the natural process of growing older, is characterized by a progressive deterioration of physiological homeostasis at the cellular, tissue, and organismal level. Metabolically, the aging process is characterized by extensive changes in body composition, multi-tissue/multi-organ insulin resistance, and physiological declines in multiple signaling pathways including growth hormone, insulin/insulin-like growth factor 1, and sex steroids regulation. With this review, we intend to consolidate published information about microRNAs that regulate critical metabolic processes relevant to aging. In certain occasions we uncover relationships likely relevant to aging, which has not been directly described before, such as the miR-451/AMPK axis. We have also included a provocative section highlighting the potential role in aging of a new designation of miRNAs, namely fecal miRNAs, recently discovered to regulate intestinal microbiota in mammals.

INTRODUCTION

Aging, the natural process of growing older, is characterized by a progressive deterioration of physiological homeostasis at the cellular, tissue, and organismal level. Both, stochastic and genetic factors contribute to the functional decline that takes place during aging (Herndon et al., 2002; Rozhok et al., 2014; Stroustrup et al., 2016). In a 2013 landmark paper, López-Otín and collaborators highlighted nine hallmarks of aging that included genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (López-Otín et al., 2013). This categorization defined key contributors to the aging process that are conserved in different organisms and act in interconnected ways that only recently have started to be elucidated.

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Metabolically, the aging process is characterized by extensive changes in body composition, multi-tissue/multi-organ insulin resistance, and physiological declines in multiple signaling pathways including growth hormone (GH), insulin/insulin-like growth factor 1 (IGF-1), and sex steroids regulation (Bartke et al., 2016; Barzilai et al., 2012; Griffin et al., 2016; Herndon et al., 2002; Kume et al., 2014; López-Otín et al., 2013; Rozhok et al., 2014; Solon-Biet et al., 2015; Stroustrup et al., 2016). Accordingly, the mammalian somatotrophic axis, involving GH and the insulin/IGF-1 signaling pathways, plays fundamental roles in modulating physiological and pathophysiological aging by altering nutrient sensing, insulin sensitivity, and mitochondrial function among others (Brown-Borg, 2015; López-Otín et al., 2013).

The discovery of microRNAs (miRNAs) and their mechanisms of action has dramatically widen and clarified our understanding of gene regulation (Ambros, 2001; Bartel and C.-Z. Chen, 2004; Filipowicz et al., 2008; Krol et al., 2010; Yates et al., 2013). These small non-coding RNAs generally act as post-transcriptional regulators of gene expression by binding to miRNA-recognition elements (MREs) in target transcripts. This sequence specific binding generally results in either suppression of translation or degradation of the targeted mRNA, or both (Breving and Esquela-Kerscher, 2010; Filipowicz et al., 2008). There is also some evidence, that under particular circumstances, miRNAs can enhance mRNA translation (Vasudevan et al., 2007; X. Zhang et al., 2014). It is well established now that miRNAs play crucial roles in a broad range of biological processes, controlling over 60% of all protein-coding genes in mammals (Friedman et al., 2009; Selbach et al., 2008) and covering almost every physiological function examined so far. From an evolutionary viewpoint, miRNAs are suggested to reduce genetic noise by decreasing variation in gene expression. By simultaneously regulating a variety of target genes, miRNAs allow fine-tuning of its target expression levels. Importantly, miRNAs confer robustness to cellular networks of molecular interactions and functions by permitting or preventing the expression/translation of target genes in a temporal and tissue-specific manner, or by buffering fluctuations in their expression levels (Hornstein and Shomron, 2006; Peterson et al., 2009). As the emergence of biological process regulation by miRNAs played/plays a central role in the evolution of complex life, the deregulation (caused either by environmental, genetic, or stochastic factors) of miRNA expression and/or function consequently represents a key driver of detrimental alterations of life.

In this review, we consider the hallmarks described by López-Otín and colleagues as a starting point, then focus on those more directly involved in metabolic processes affecting aging and that have been shown to be regulated, at least in part, by miRNAs (Table 1). Those “metabolic” hallmarks are: deregulated nutrient sensing, mitochondrial dysfunction, and metabolic inflammation (as a special case of altered intercellular communication). In addition, we include a provocative section (potentially novel landmark) on miRNAs that are regulated by or can regulate commensal microbiota and may impact aging. If we consider the commensal microbiota as part of another tissue/organ in the human body, as suggested by Baquero and Nombela (Baquero and Nombela, 2012), this landmark could be considered another special case of altered intercellular communication.

MICRORNAS AND METABOLIC MANIPULATIONS IN THE STUDY OF AGING

Metabolic manipulations caused either by natural or engineered mutations (e.g., in nutrient sensing pathways discussed below), drug treatments (e.g., metformin, RNAi to reduce activity of the mitochondrial electron transport chain), or dietary interventions (e.g., reduced food intake) have been found to alter the healthspan and lifespan from yeast to humans (Anisimov, 2015; Bartke, 2008; Dillin et al., 2002; Dubnikov and Cohen, 2015; Luigi Fontana et al., 2010; Masternak and Bartke, 2012; Suh et al., 2008). These metabolic manipulations are suggested to increase the organism's ability to resist environmental insults and consequently reduce the rate of damage accumulation by promoting the maintenance of proteostasis (Dubnikov and Cohen, 2015).

Moderate calorie restriction (CR), a metabolism-modifying dietary intervention, is one of the most powerful interventions that can extend mammalian longevity (Figure 1). Research shows that the metabolic restriction caused by CR causes extension of the lifespan by decreasing signaling through nutrient-sensing pathways [e.g., mammalian target of rapamycin (mTOR), insulin/insulin-like growth factor 1 (IGF-1)] as well as by increasing the expression of endothelial nitric oxide synthase [eNOS, involved in mitochondrial biogenesis and sirtuin 1 (SIRT1) expression] (Blagosklonny, 2010; Luigi Fontana, 2009; Nisoli et al., 2005).

Mounting evidence support that CR alters the expression pattern of genes and microRNAs (miRNAs) that are affected by aging in multiple species (Bates et al., 2010; Capel et al., 2009; Csiszar et al., 2014; Çiçek et al., 2016; Dhahbi, 2014; Dhahbi et al., 2013; Kulkarni et al., 2013; Masternak et al., 2004; 2005; Mercken et al., 2013; Mori et al., 2014; Sangiao-Alvarellos et al., 2014; Victoria et al., 2015). Vice versa, miRNA manipulations can also activate dietary restriction to extend healthspan and lifespan, as demonstrated by Vora and colleagues after deleting miR-80 in *C. elegans* (Vora et al., 2013). Our studies of gene and miRNA expression profiling in the Ames dwarf mouse, a valuable model of extended healthspan and longevity characterized by growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH) deficiency, have shed light on a variety of relevant physiological modifications that are shared by CR interventions and improved aging of the Ames dwarf mice, although the two processes are not identical (Bartke et al., 2016; Victoria et al., 2015; Wiesenborn et al., 2014). Interestingly, by implementing high throughput miRNA profiling, we and others have shown a general trend towards reduction of circulating levels of specific miRNAs (despite distinct subsets) during normal aging in disparate species such as mouse and nematode [i.e., 17 out of 21 differentially abundant miRNAs in Ames dwarf mouse including miR-34b/c, miR-127-5p, miR-136-5p, miR-154-5p, miR-195a-5p, miR-342-5p, miR-344d-3p/d-1-5p/d-2-5p/d-3-5p, miR-369-5p, miR-376c-5p, miR-381-5p, miR-410-5p, miR-411-5p, miR-449a-5p, miR-540-5p, and miR-5107-5p (Victoria et al., 2015); and 23 out of 34 differentially expressed miRNAs in the nematode *C. elegans* including let-7, miR-45, miR-37, miR-36, miR-85, miR-63, miR-41, miR-58, miR-74, miR-42, miR-64, miR-77, miR-70, miR-233, miR-273, miR-73, miR-39, miR-1, miR-229, miR-67, miR-59, miR-38, and miR-43 (Ibáñez-Ventoso et al., 2006)]. On the other hand, a general trend towards elevation (i.e., miR-34b/c, miR-344d-2-5p, and miR-592-5p) or maintenance (i.e., miR-127-5p, miR-136-5p, miR-146a-5p, miR-154-5p, miR-195a-5p,

miR-342-5p, miR-344d-3p/d-1-5p/d-3-5p, miR-369-5p, miR-376c-5p, miR-381-5p, miR-410-5p, miR-411-5p, miR-449a-5p, miR-540-5p, and miR-5107-5p) of specific miRNAs is characteristic of the long-lived Ames dwarf mouse mutant (Victoria et al., 2015), several of which are also maintained at stable levels in an CR mouse model [i.e., individual miRNAs: miR-146a-5p and miR-5107-5p; and members of miRNA families: miR-15, miR-154, miR-342, miR-368, and miR-592 (Dhahbi et al., 2013; Dluzen et al., 2016; Victoria et al., 2015)]. In addition, knockout of Dicer induces premature senescence in cultured mouse adipocytes, and a fat-specific Dicer knockout mouse shows hypersensitity to oxidative stress (Mori et al., 2012). Based on these observations, we speculate that miRNAs play an active role in the downregulation of transcripts that would otherwise wreak havoc cellular homeostasis as the organism age. This is consistent with observations of age-associated phenotypes in several miRNA mutants that suggest that specific miRNAs promote healthspan by contributing to systemic and cellular robustness (Ibáñez-Ventoso and Driscoll, 2009).

By comparing results from high throughput miRNA profiling studies, we have identified several miRNA families (including miR-146, miR-34, and miR-449 among the most relevant) that are both responsive to CR and modulated in long living animals (Victoria et al., 2015). Differential expression in specific tissues as well as differential abundance in circulation have been reported for these miRNAs (Csiszar et al., 2014; Dhahbi et al., 2013; Kulkarni et al., 2013; Mercken et al., 2013; Victoria et al., 2015). Relevantly, miRNA species found in biological fluids have been suggested to act in cell-cell communication or as endocrine genetic signals during various physiological and pathophysiological processes (Lawson et al., 2016; Shan et al., 2015; Turchinovich et al., 2013). One would expect that elevated miRNAs in circulation originated from certain tissue(s) that overexpress and secrete the respective miRNAs. Vice versa, miRNAs with reduced levels in circulation could originate from tissues where the expression and secretion of the miRNA is downregulated.

The miR-146 family, for example, has been found at reduced levels in the circulation of old CR mice (Dhahbi et al., 2013) and old long lived Ames dwarf mice (Victoria et al., 2015) as compared to *ad libitum* and normal old controls, respectively. Consistent with a role for adipose tissue (AT) and liver cells in the secretion of this miRNA family, miR146a have been found downregulated in Ames dwarf epididymal AT (our unpublished results) and miR-146b downregulated in the livers of C57BL/6 and Keap1-KD mice after CR (Kulkarni et al., 2013).

On the other hand, miR-34b have been found at elevated levels in the circulation of old Ames dwarf mice (Victoria et al., 2015) and also elevated in the livers of C57BL/6 and Keap1-KD mice after CR (Kulkarni et al., 2013), which suggest that liver cells could also be one of the sources secreting this miRNA into the circulation. Puzzlingly, another member of this family, miR-34a has been found downregulated in the same livers of calorie restricted C57BL/6 and Keap1-KD mice (mentioned above) and in primary cultures of cerebromicrovascular endothelial cells (CMVECs) of CR rats (Csiszar et al., 2014), whereas upregulated in skeletal muscle tissue from aged rhesus monkeys (Mercken et al., 2013). Yet, this apparent heterogeneity in the levels of miR-34 family members in distinct tissues could be explained due to unique specialized functions for each member. Consequently,

upregulation of miR-34a has been associated with age-related neurodegenerative diseases (X. Li et al., 2011) and with induction of senescence in AT, liver, and kidney (Bai et al., 2011; H. Park et al., 2015; Xu et al., 2015), whereas downregulation of the miR-34b/c cluster has been suggest to cause mitochondrial dysfunction in human brains with Parkinson's Disease (N. Liu et al., 2012; Minones-Moyano et al., 2011). Surprisingly, in its association with brain disorders, miR-34b can play either a causative or protective role, depending on the species/disease being studied and the cellular/tissue context where the miRNA action takes place, among other reasons (Gaughwin et al., 2011; N. Liu et al., 2012; Minones-Moyano et al., 2011). We should also note that because the seed sequence of miR-34b slightly differ from that of miR-34a and miR-34c, miR-34b might target a slightly different subset of transcripts (Rokavec et al., 2014). This could account for some of the differences regarding their actions in aging. Notably, an interaction network of differentially abundant circulating miRNAs and miRNA-overtargeted mRNA interactions from our study of genotype-by-age interactions in the Ames dwarf mouse underscored a central role for miR-34b in the regulation of calcium-modulating Wnt receptor signaling, by targeting three distinct Wnt ligands, two of which (Wnt3 and Wnt5a) are not targeted by miR-34c (Victoria et al., 2015). Importantly, activation of the canonical Wnt signaling cascades are frequently associated with cancer and tightly regulated by miRNAs including the miR-34 family (N. H. Kim et al., 2011). Other biological functions highlighted by our network and functional enrichment analyses for miR-34b/c were the central roles in the regulation of cell projection morphogenesis, positive regulation of transcription, and the regulation of ankyrin repeats-containing proteins (Victoria et al., 2015). Supporting our findings, ankyrin G (Ank3), one of the genes overtargeted by miRNAs in the Ames mouse including miR-34b/c1, is overexpressed in Hutchinson-Gilford progeria syndrome (HGPS; MIM 176670), a rare disease characterized by accelerated aging (J. Wang et al., 2006).

Our miRNA/overtargeted mRNA networks also uncovered common roles for circulating miR-34b/c and miR-449 (Victoria et al., 2015), which is supported by the fact that the miR-449 family share many targets with the miR-34 family (Rokavec et al., 2014), and members of these families are suggested to function redundantly in the regulation of cellular processes such as male germ cell development in murine testes (S. Zhang et al., 2012). Similar to miR-34b/c, the abundance of miR-449a was elevated in the circulation of our aged Ames dwarf mice as compared to chronologically matched normal controls (Victoria et al., 2015). More recently, we have found that miR-449 is also significantly elevated in the liver and marginally elevated in the muscle tissue of Ames dwarf mice (unpublished data). These results are consistent with the downregulation of miR-449a found in the livers and kidneys from both progeroid Ercc1$^{-/\Delta}$ and old wild type mice (Nidadavolu et al., 2013). These observations are in line with the activation of senescent processes (in the aging animals) associated with downregulation of miR-449a and deregulation of miR-449a target Hnf4a, a transcription factor essential to liver development and maintenance (Ramamoorthy et al., 2012). However, studies of CR in mice and rats found miR-449a downregulated in calorie restricted rat CMVECs (Csiszar et al., 2014) and miR-449b downregulated in the livers of calorie restricted C57BL/6 and Keap1-KD mice (Kulkarni et al., 2013). These apparent contradictory findings might account, at least in part, for differences occurring between CR and Ames dwarf mutation-induced extension of lifespan (Ikeno et al., 2013).

MICRORNAS AND DEREGULATED NUTRIENT-SENSING DURING AGING

The relationship between nutrient-sensing and aging is well demonstrated by multiple studies and reviewed elsewhere (Bartke et al., 2016; Barzilai et al., 2012; Griffin et al., 2016; Kume et al., 2014; López-Otín et al., 2013; Solon-Biet et al., 2015). In this section, we will focus on the involvement of miRNAs in these pathways with special emphasis on those miRNAs that regulate four main nutrient-sensing pathways involved in the pathogenesis of age-related diseases, namely insulin/IGF-1 (glucose-sensing), mTOR (high aminoacid level sensor), and low-energy state sensors AMP-activated protein kinase (AMPK) and sirtuins pathways (Figure 1). These systems independently and coordinately regulate metabolism in multiple organs (Barzilai et al., 2012; Kume et al., 2014; López-Otín et al., 2013).

Glucose sensing and the Insulin/IGF-1 signaling

Alteration of the glucose sensing capability of cells and tissues, mediated by the insulin/IGF-1 pathway, is a major factor affecting healthspan and lifespan from yeast to humans (Bartke, 2008; Luigi Fontana et al., 2010). Enhanced insulin sensitivity has been associated with extremely long survival in centenarians, who show lower levels of insulin resistance and preserved pancreatic beta cell function (Paolisso et al., 2001). However, our understanding of the controversial roles of the pathway is far from being clear at present. On one hand, low IGF-1 signaling is associated with extended longevity, but is paradoxically linked with several age-related diseases and with normal aging in humans, which is supported by mutations in mice, rats, and other mammals (Barzilai et al., 2012; Ford et al., 2002; Schumacher et al., 2008a). A current attempt at explaining this apparent paradox considers the downregulation of the GH-insulin/IGF-1 signaling pathway (namely, the somatotrophic axis) as an adaptive response to reduce metabolism and cell growth and to increase tissue maintenance in the context of genomic instability and systemic damage (Garinis et al., 2008; López-Otín et al., 2013; Schumacher et al., 2008b). Several miRNA families including let-7, miR-1, miR-29, miR-143/145, miR-182, miR-206, miR-221/222, miR-223, miR-470, miR-669, and miR-681 have been implicated in the regulation of this pathway and will be the focus of this section.

The let-7 family, well know for its developmental and oncogenic roles in vertebrates, has been recently found to play a role in mammalian aging (Jun-Hao et al., 2016; Keane and de Magalhães, 2013) and in glucose metabolism by potently repressing multiple components of the insulin/IGF-1 signaling pathway, including the receptor of IGF-1 (IGF1R), the insulin receptor (INSR), and the insulin receptor substrate-2 (IRS-2) in skeletal muscle and liver tissues (Jun-Hao et al., 2016; Zhu et al., 2011). In addition, let-7 can suppress mTOR-induced anabolism and autophagic catabolism without turning off the insulin signaling pathway by targeting three members of the mTOR pathway, namely, Map4k3, RagC, and RagD (Dubinsky et al., 2014). This ability of the let-7 family to regulate the crosstalk between multiple nutrient-sensing pathways underscores the central function of this miRNA in regulating mammalian metabolism and aging. Notably, a SNP in the let-7 targeted region of LIN28 was reported to increase the risk for type 2 diabetes in a case-control study (J. Zhang et al., 2013). These associations further implicate the let-7 family in aging-induced insulin resistance.

Muscle-specific miR-1 was reported to directly target IGF-1 and be upregulated in the liver, kidney, and muscle tissue from a progeria mouse model and in culture fibroblast from patients with Hutchinson-Gilford progeria syndrome (Mariño et al., 2010). These authors suggested that miR-1 up-regulation likely contributes to suppression of the somatotrophic axis by reducing IGF-1 synthesis, even in the presence of elevated circulating GH levels. Others also found miR-1 upregulated and repressing IGF-1 in rat model of myocardial infarction (Shan et al., 2009), which in humans is a condition more prevalent in the elderly (Mozaffarian et al., 2016). This miRNA also possitively crosstalks with the mitochondria, by efficiently entering the compartment and coordinately activating mitochondrial translation and ATP production, while simultaneously repressing translation in the cytoplasm (X. Zhang et al., 2014).

The miR-29 family is one of the most abundantly expressed in the pancreas and liver, and "dictates the balance between homeostatic and pathological glucose handling in diabetes and obesity" (Dooley et al., 2015). Dooley and collaborators demonstrated that, in the pancreas, miR-29a functions as a positive regulator of insulin secretion, whereas in the liver, both miR-29a and miR-29c are important negative regulators of insulin signaling via PI3K regulation. These authors demonstrated that deregulation of miR-29 expression induced a dose-dependent effect on premature death (Dooley et al., 2015). In addition, activation of the miR-29 family by Wnt-3a in aged mouse and rat muscles has been implicated as a mechanism for aging-induced sarcopenia through the suppression of p85α (the regulatory subunit of PI3K), IGF-1, and B-myb signaling (Z. Hu et al., 2014). These changes coordinately impair proliferation of muscle progenitor cells and promote muscle atrophy. IGF-1, in particular, plays a critical role in myogenesis by stimulating myoblast proliferation and differentiation that can restore the proliferation of satellite cells in skeletal muscles of old mice (Chakravarthy et al., 2000). Members of the miR-29 family were also found upregulated in the brain of aged mice and this increase correlated with the reduction of two important regulators of microglia, namely IGF-1 and CX3CL1. Consequently, in addition to limiting central glucose-sensing ability, these changes contribute to enhancing the inflammatory profile of microglia in the aged brain (Fenn et al., 2013).

Another miRNA with important functions in muscle regeneration is miR-143, which was identified as a regulator of the insulin growth factor-binding protein 5 (Igfbp5) in primary mouse myoblasts (Soriano-Arroquia et al., 2016). These authors reported that downregulation of miR-143 during aging may act as a compensatory mechanism to improve myogenesis efficiency. However, they also pointed out that concomitant upregulation of its target gene, Igfbp5, is associated with increased cell senescence, therefore negatively affecting myogenesis. The role for the bicistronic miR-143–145 cluster in the regulation of the IGF-1 signaling pathway is also supported by experimental validation of the direct interaction between miR-143/145 and the IGF1R transcript in colorectal cancer tissue (J. Su et al., 2014). Furthermore, overexpression of miR-143 in the liver of genetic and dietary mouse models of obesity has been shown to impair insulin-stimulated protein kinase B (AKT/PKB) activation and glucose homeostasis, whereas mice deficient for the cluster are protected from the development of obesity-associated insulin resistance, in the absence of altered adipogenesis (Jordan et al., 2011).

In an effort to detect estrogen-regulated miRNAs that would have an effect in muscle aging in women, Olivieri and colleagues studied monozygotic post-menopausal twin pairs discordant for estrogen-based hormone replacement therapy (HRT) and found that miR-182, miR-223, and miR-142-3p expression levels were significantly elevated in muscle samples from the HRT-nonusing co-twins (Olivieri et al., 2014). Two of these miRNAs (i.e., miR-182 and miR-223) were confirmed to directly target IGF-1R, FOXO1A, and FOXO3A transcripts, therefore reducing insulin/IGF-1 signaling. Estradiol treatment induced the downregulation of these miRNAs and subsequent activation of the insulin/IGF-1 pathway via phosphorylation of AKT and mTOR (Olivieri et al., 2014). Also relevant to bone aging, overexpression of miR-182 inhibited osteoblast differentiation in culture and impaired bone formation in zebrafish through repression of FoxO1 (K. M. Kim et al., 2012). Adding support for miR-223 role in aging, this miRNA was found upregulated in aged bone marrow derived dendritic cells under both normal and activated conditions (S. Park et al., 2013). Although upregulation of these miRNAs negatively affect the activity of the insulin/IGF-1 signaling pathway, an important role for miR-223 in maintenance of intestinal homeostasis by limiting pro-inflammatory responses in intestinal dendritic cells and macrophages, through targeting of CCAAT/enhancer-binding protein (C/EBP) has been reported (Zhou et al., 2015). From our viewpoint, these examples of “miRNA regulatory yin and yang” identify a recurrent theme in aging research underscoring the importance of maintaining physiologically balanced miRNA levels for biological systems to promote organismal homeostasis and longevity.

Amminoacid sensing and mTOR signaling

The serine/threonine kinase mTOR, a member of phosphatidylinositol-3-OH kinase (PI3K)-related family, is another central regulator of metabolism, cellular growth pathways, and age-related disorders in response to nutrient (i.e., aminoacids), growth factors, cellular energy imbalance, and stress (Blagosklonny, 2011; Johnson et al., 2013). Deregulation of this pathway has been associated with neurodegenerative diseases, cancer, obesity, and diabetes (Dann et al., 2007; Laplante and Sabatini, 2012). This pathway crosstalks with the insulin/IGF-1 pathway at multiple levels, including a negative feedback loop that comprises activation of the mTOR Complex 1 (mTORC1) by the insulin/IGF-1 pathway through AKT, and eventual inhibition of IRS-1 by mTORC1, through its substrate ribosomal protein S6 kinase (S6K) (Takano et al., 2001). MiRNAs appear to regulate this crosstalk, as it was recently reported that miR-182, miR-223, and miR-142-3p respond to hormonal changes in female skeletal muscle to mediate expression of IGF-1R and FOXO3A as well as activation of the insulin/IGF-1 pathway signaling via phosphorylation of AKT and mTOR (Olivieri et al., 2014).

Furthermore, Rubie and collaborators demonstrated that human miR-496 targets two binding sites within the 3’UTR region of the mTOR transcript. These authors also showed that the levels of miR-496 negatively correlated with mTOR protein levels in peripheral blood mononuclear cells, with old individuals harbouring high levels of this miRNA as compared to young people. (Rubie et al., 2016). Notably, miR-496 was found downregulated in human centenarians (ElSharawy et al., 2012). These results are consistent with a key role of miR-496 in promoting aging, possibly by interfering with mTOR signaling.

Other miRNAs regulate the AKT/mTOR signaling pathway via targeting of phosphatase and tensin homolog (PTEN). One of those is miR-19, a miRNA encoded in the miR-17~92 cluster, which was found downregulated in four different cell types undergoing replicative senescence and three different *ex vivo* tissue types representing organismal aging (Hackl et al., 2010; Olive et al., 2009). Other members of the miR-17~92 family including miR-17, miR-20a, and miR-106a also target PTEN and inhibit this pathway while crosstalking with the IGF-1 pathway (Patel et al., 2014). By targeting PTEN, miR-21 induces mTOR activation and tumor progression (Cingarlini et al., 2012). This miRNA crosstalks with inflammatory pathways (discussed later in the section covering age-related metabolic inflammation) by inducing the expression of adhesion molecules in vascular cells and inhibiting anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) (Merline et al., 2011). In addition, increased miR-21 levels are detected in other age-related diseases such as cardiovascular disease and diabetes and diabetes-related conditions, among others (Olivieri et al., 2013a; 2012; Sekar et al., 2016). Importantly, it was demonstrated that, by reducing PTEN expression and concomitantly increasing Akt phosphorylation and TOR Complex 1 (TORC1) activity, overexpression of miR-21 mimics the action of high glucose and mediate the pathological features of diabetic kidney diseases (Dey et al., 2011).

Low-energy state sensing through AMPK and sirtuins signaling

AMPK (an heterotrimeric Ser/Thr-kinase) senses low-energy states by detecting high levels of AMP within the cells, whereas sirtuins (a conserved family of NAD^+-dependent deacetylases), perform a similar function by detecting high levels of NAD+ (Houtkooper et al., 2010). Their activation, in turn, trigger adaptive responses aimed at inhibiting anabolic processes (e.g., those mediated by mTOR pathway) and at activating mitochondrial ATP production. By reciprocally enhancing each other's activity, AMPK and sirtuins crosstalk in the regulation of energy metabolism and inflammation (Cantó et al., 2009; Ruderman et al., 2010). They coordinately function to ensure appropriate cellular responses and adaptation to environmental fluctuations in response to stress and reduced nutrients. However, "while in skeletal muscle they seem to coherently regulate metabolic processes (fatty acid oxidation, mitochondrial biogenesis, glucose uptake), their roles diverge when considering hepatic glucose production in response to energy deprivation and in the insulin release from pancreatic β cells" (Fulco and Sartorelli, 2008).

Recently, miR-451 was found to be a potent inhibitor of the AMPK signaling pathway by directly targeting calcium-binding protein 39 (CAB39, also known as MO25). CAB39 is a necessary co-activator of the serine/threonine kinase 11 (STK11, also known as liver kinase B1 or LKB1), which subsequently phosphorylate AMP-bound AMPK (Godlewski et al., 2010). The capacity to transcriptionally regulate the CAB39/STK11/AMPK axis makes miR-451 a major effector of glucose-regulated AMPK signaling (Ansari et al., 2015). Interestingly, this miRNA was found at reduced levels in skeletal muscle of human subjects that were high responders to resistance exercise training (Davidsen et al., 2011). In addition, key research in aging primates demonstrated strong upregulation of miR-451 in skeletal muscle from old rhesus monkeys, which was halted by CR (Mercken et al., 2013). Furthermore, early elevation of miR-451 and miR-195 levels was detected in the hearts of

hypertrophic cardiomyopathy mice (H. Chen et al., 2012). Based on these observations, we reason that the miR-451/CAB39/STK11/AMPK (abbreviated herein as miR-451/AMPK) axis could be critical for physiological homeostasis in high-energy-demanding tissues, such as myocardial and skeletal muscles. Therefore, manipulation of this axis could represent an important therapeutic intervention to improve mammalian healthspan.

Mammalian sirtuins, which represent a conserved family of NAD^+-dependent deacetylases, have been implicated in the control of metabolism and lifespan. In particular, SIRT1 is a key regulator of cellular metabolism shown to mediate the beneficial metabolic effects of CR (Lee and Kemper, 2010). As expected, several miRNAs have been reported to target SIRT1, including miR-34a, which was identified as a highly elevated posttranscriptional regulator of SIRT1 during the regulation of cell death and metabolism (Lee et al., 2010; Yamakuchi et al., 2008). In addition, upregulation of miR-34a together with miR-93 in aging rat liver was reported to be responsible for the reduced levels of Sirt1 and Mgst (microsomal glutathione transferase), as well as two of their transcription factors Sp1 and Nrf2 (N. Li et al., 2011). These genes play an important role in eliciting a stress response to counteract the damaging effect of ROS, by intertwining signaling involving deacetylation and detoxification processes (Ribas et al., 2014). Interestingly, miR-34a was also reported to mediate an antagonistic crosstalk between nuclear factor-κB (NFκB) and SIRT1. As SIRT1 is a potent inhibitor of NF-κB signaling, downregulation of SIRT1 by NFκB-induced miR-34a closes a negative feedback loop that is critical for the co-regulation of inflammation and metabolic functions (Kauppinen et al., 2013).

Upregulation of miR-217 in human endothelial cells during aging similarly reduces SIRT1 activity and promotes senescence (Menghini et al., 2009). Also inducing senescence, miR-519 indirectly reduces the protein levels of SIRT1 through targeting of the RNA binding protein HuR in human diploid fibroblasts and human cervical carcinoma HeLa cells (Marasa et al., 2010). Furthermore, Kondo and colleagues reported that miR-195 targets SIRT1 to induce cellular senescence in aged skeletal muscle cells (Kondo et al., 2016). Remarkably, these authors demonstrated that inhibition of this miRNA increases the reprograming efficiency of old skeletal muscle cells during the generation of induced pluripotent stem cells (iPSCs) from aging donor subjects.

In the brain, SIRT1 was shown to normally function to limit expression of miR-134 via a repressor complex containing the transcription factor Yin Yang 1 (YY1) (Gao et al., 2010). Consequently, expression of miR-134 due to deficiency in SIRT1 results in downregulation of CREB and brain-derived neurotrophic factor (BDNF), which impairs synaptic plasticity. Other authors has reported that brain-specific miR-134 causes neuronal death after ischemia/reperfusion, also through targeting of the CREB/BDNF pathway (Huang et al., 2015). Notably, research on the *in vivo* effects of resveratrol on the decline of brain function during aging suggested that the underlying mechanism likely involves the downregulation of miR-134 and miR-124, presumably through upregulation of CREB expression and BDNF synthesis (Zhao et al., 2013).

Mitochondrial SIRT4 is another sirtuin implicated in aging and regulated by miRNAs such as miR-15b. This miRNA has been reported to be up to four-fold downregulated in various

models of organismal aging (Faraonio et al., 2012; Holly et al., 2015; Marasa et al., 2009) and its reduction associated with upregulation of SIRT4 expression in models of cellular senescence and in photoaged skin (Lang et al., 2016). Mechanistically, inhibition of miR-15b induced the generation of mitochondrial reactive oxygen species (ROS), reduction of mitochondrial membrane potential, and deregulation of transcripts of nucleus-encoded mitochondrial genes and components of the senescence-associated secretory phenotype (SASP) in a SIRT4-dependent manner (Lang et al., 2016).

SIRT6 was recently identified as a critical factor in the regulation of transcription, genome stability, telomere integrity, DNA repair, and metabolic homeostasis, causing accelerated aging when knocked out in mice (Mostoslavsky et al., 2006). The expression of this sirtuin appears regulated through a feedback loop with miR-766, which was found upregulated in human dermal fibroblast from old adults (Sharma et al., 2013) and in mesenchymal stem cells from old rhesus macaque bone marrow (Yu et al., 2011).

Surprisingly, mammalian sirtuins appear to play both protective and pro-aging roles depending on the tissue involved (Fulco and Sartorelli, 2008). Research from the Longo group and others suggested that SIRT1, in addition to play roles important for normal growth and lifespan, can contribute to oxidative damage in mammals by activating IRS-2/Ras/ERK signaling downstream of insulin/IGF-I receptors (Y. Li et al., 2008). Further studies are needed to better understand the pro-aging effects of chronic SIRT1 activation and how protective or pro-aging actions are elicited under specific cellular contexts.

DEREGULATION OF MITOMIRS INDUCE MITOCHONDRIAL DYSFUNCTION DURING AGING

Studies have shown that increased mitochondrial function (e.g., by inhibition of mTOR signaling or by dietary restriction) contributes to lifespan extension in model organisms (Bonawitz et al., 2007; Zid et al., 2009). This is consistent with a conserved program that can extend the lifespan by compensating for the reduction of ATP synthesis (characterized by the repression of genes involved in mitochondrial oxidative respiration) and the decline in physiological activity observed in multiple tissues (brain, muscle, and excretory system) during aging (Finley and Haigis, 2009; McCarroll et al., 2004). The key roles that mitochondria play in cellular energy metabolism and overall cell viability are well known, and are especially important for tissues with high energetic demands such as skeletal muscle, heart, kidney, and the central nervous system (Szeto and Birk, 2014). In addition, mitochondria are crucial for the coordination and integration of the crosstalk between insulin/IGF-1 signaling and the mTOR pathway via ROS signaling (Narasimhan et al., 2009), as well as regulating apoptosis and autophagy (Palikaras and Tavernarakis, 2012), which are deregulated in multiple age-related diseases.

MitomiRs are miRNAs that dynamically sense and respond to changes in the mitochondrial microenvironment (Figure 1) (Bandiera et al., 2013). Generaly, mitomiRs are described in two main “flavors” depending on how they exert their functions: 1) as nucleus-encoded miRNAs that function in the cell nucleus or the cytosol regulating genes encoding mitochondrial proteins [e.g., Figure 1: miR-15b –| SIRT4; miR-34b/c –| DJ-1 (Minones-

Moyano et al., 2011); miR-335 –| SOD2/TXMD2 (Bai et al., 2011); miR-378 –| CRAT (Carrer et al., 2012)] and 2) as nucleus-encoded miRNAs that act at the mitochondria [e.g., Figure 1: miR-181 –| mt-Cox1 (Das et al., 2012); miR-1 → mt-ND1/mt-COX1 (X. Zhang et al., 2014)]. However, recent findings pointing towards the existence of mitochondria-encoded miRNAs (Bandiera et al., 2013; 2011; Barrey et al., 2011; Bianchessi et al., 2015; Borralho et al., 2014; Mercer et al., 2011) sugest that mitomiRs could perform additional roles such as: 3) mitochondria-encoded miRNAs that act at the mitochondria itself [e.g., putative mitochondria-encoded miR-1974, miR-1977, and miR-1978 (Bandiera et al., 2013; 2011)], and 4) as mitochondria-encoded miRNAs that act at the cell nucleus or cytoplasm, therefore displaying mitochondrial retrograde signaling [e.g., Figure 1: miR-4495 and miR-1973 (Bianchessi et al., 2015)].

Rippo and colleagues recently reported that some mitomiRs, namely let-7b, mir-146a, miR-133b, miR-106a, miR-19b, miR-20a, miR-34a, miR-181a and miR-221, are also among those miRNAs primarily involved in aging (Rippo et al., 2014). By conducting pathway enrichment analysis on the gene targets of this mitomiR subset, these authors showed that members of the Bcl-2 family (critical for maintenance of mitochondrial integrity and cell survival) are among the main mitomiR targets that may play a role in controlling mitochondrial function and dysfunction during cellular aging. Miñones-Moyano and collaborators reported that two other members of the miR-34 family (i.e., miR-34b/c) were downregulated in damaged brain areas of Parkinson Disease (PD) brains since early during disease development and were responsible for the mitochondrial dysfunction and oxidative stress characteristic of this age-related neurodegenerative disease (Minones-Moyano et al., 2011). These authors found that downregulation of miR-34b/c correlated with downregulation of DJ-1 and Parkin, and suggested that these two genes associated with recessive forms of familial PD are indirect targets of miR-34b/c. Because deficiency in DJ-1 or Parkin have been shown to induce mitochondrial dysfunction and oxidative damage (Irrcher et al., 2010; Palacino et al., 2004), this group suggested that miR-34b/c deficiency may cause mitochondrial dysfunction, at least in part, through a mechanism involving Parkin and DJ1 downregulation (Minones-Moyano et al., 2011). In the kidneys, the influence of miR-34a and miR-335 upregulation was found to contribute to renal aging by inhibiting mitochondrial anti-oxidative enzymes superoxide dismutase 2 (SOD2) and thioredoxin reductase 2 (TXNRD2) (Bai et al., 2011).

On the other hand, in response to hypoxia, miR-210 expression is stimulated by hypoxia-induced factor 1α (HIF-1α) and downregulates the expression of iron-sulfur cluster assembly proteins (ISCU1/2) and other subunits of the electron transport chain complexes I and II, therefore directly controlling mitochondrial metabolism and respiration (Chan et al., 2009; Kulshreshtha et al., 2007). By disrupting the balance in the electron transport chain and the tricarboxylic acid (TCA) cycle relative to the intracellular levels of oxygen, miR-210 can affect apoptosis, ROS production, and cellular senescence (Faraonio et al., 2012; Puisségur et al., 2010; Semenza, 2007; Taddei et al., 2014), as well as the regulation of the animal lifespan and aging (Ham and Raju, 2016; Mishur et al., 2016). Another important mitochondrial enzyme, which activity is negatively impacted by aging and is associated with fatty acid metabolism, is carnitine O-acetyltransferase (CRAT) (Noland et al., 2009). This enzyme was recently reported to be regulated by miR-378 (Carrer et al., 2012). Both,

miR-378 as well as its associated antisense form miR-378* (which targets MED13, one of the components of the Mediator complex that controls nuclear hormone receptor activity) were identified as integral regulators of systemic energy homeostasis and the overall oxidative capacity of metabolically active tissues, specifically during periods of dietary stress conditions characteristic of the metabolic syndrome (Carrer et al., 2012).

Interestingly, mitochondria-encoded miRNAs that appear to function in mitochondrial retrograde signaling, have been recently suggested to play a role in aging (Bianchessi et al., 2015). These authors reported that a mitochondrial long non-coding RNA (lncRNA), denominated ASncmtRNA-2, may serve as a non-canonical precursor of two miRNAs (i.e., miR-4495 and miR-1973) that are induced by aging in mice and by replicative senescence in human endothelial cells. Overexpression of the two lncRNA-encoded miRNAs induced a similar phenotype to that of the parental ASncmtRNA-2, with cell cycle delay in the G1 and G2/M phases (Bianchessi et al., 2015). Although the evidence suggesting the non-canonical mitochondrial contribution of miR-4495 and miR-1973 to the cytosolic mature miRNA pool and the processing of additional mitochondria-encoded miRNAs is not definitive, further effort to validate the concept of mitochondrial retrograde signaling mediated by non-coding RNAs with an impact in aging is warranted.

AGE-RELATED METABOLIC INFLAMMATION IS REGULATED BY MIRNAS

During the last few decades, the chronic metabolic dysfunction in tissues such as the white AT has been realized as a major landmark of physiological and accelerated aging (Pérez et al., 2016). Metabolic inflammation, “metainflammation”, and more recently “metaflammation” are terms coined to refer to the chronic low-grade systemic inflammation that is central to obesity and metabolic syndrome (Egger and Dixon, 2009; Hotamisligil, 2006; Hotamisligil et al., 1993; Lumeng and Saltiel, 2011). This inflammatory process is distinct from the classical inflammatory paradigms (e.g., infection, autoimmune disease) as it appears to respond to intrinsic signals (nutrient-induced inflammatory response initiated by metabolic cells), appears to remain unresolved, and involves a variety of immune and metabolic cells. Metaflammation is also characterized by the infiltration of innate immune cells into metabolically involved tissues and by local and systemic release of pro-inflammatory cytokines that lead to a chronic subclinical inflammatory state in affected tissues and organs (Connaughton et al., 2016). Consequently, the steady-state of metabolic homeostasis is detrimentally affected overtime (Lumeng and Saltiel, 2011). Importantly, metaflammation does not promote energy expenditure and is associated with a reduced metabolic rate (Gregor and Hotamisligil, 2011). One key regulator of the inflammatory response in general is the Toll-like receptor (TLR) family. This family is better known for its innate immune functions sensing infection by bacteria and viruses among others; however, accumulating evidence implicate TLRs in the recognition of endogenous ligands (Gill et al., 2010; Olivieri et al., 2013a). To our surprise, miRNAs can even act as ligands for TLRs, as let-7 was demonstrated to signal by interacting with TLR-7 (likely binding via additional unidentified proteins) in the CNS and cause neurodegeneration (Lehmann et al., 2012). Importantly, the hepatocyte TLR-4 has been implicated in the regulation of chronic low-grade inflammation and insulin resistance induced by obesity (L. Jia et al., 2014). In addition, human aging has been recently associated with metabolic endotoxemia, which is a

condition characterized by increased plasma levels of endotoxin in metabolic disease (Boutagy et al., 2016; Cani et al., 2007). This phenomenon appear mediated by elevated TLR-4 signaling through the TLR4-NFκB-MAPK pathway in muscle and may play a role in insulin resistance and sarcopenia in human aging (Ghosh et al., 2015).

Emerging evidence has shown that inflammatory responses are regulated by miRNAs such as miR-15a, miR-16, miR-21, miR-146a, miR-155, miR-223, among others (Aalaei-andabili and Rezaei, 2013; Christian and Q. Su, 2014; Johnnidis et al., 2008; Olivieri et al., 2013a; 2012; 2013b). Evidence shows, for example, that TLR signaling can modulate miRNA expression and that this generally depends on NFκB, exclusively inducing upregulation of miRNAs (Nunez et al., 2013; O'Neill et al., 2011). The trio miR-21, miR-146, and miR-155, with crucial functions in many immune and inflammatory processes is also critical in the regulation of TLR signaling and consequently implicated in animal and human aging (Frasca et al., 2015; Noren Hooten et al., 2010; Olivieri et al., 2012; 2015; Quinn and O'Neill, 2011; Victoria et al., 2015). Olivieri and colleagues found miR-21, for example, elevated in the circulation of patients with cardiovascular disease and reduced in healthy centenarian offspring, as compared to age-matched controls, and levels of this miRNA significantly correlated with inflammatory markers such as C-reactive protein and fibrinogen levels in a validation cohort (Olivieri et al., 2012). Importantly, this trio and others "inflammaging" miRNAs including miR-17~92, miR-126, and miR-223 have been found enriched in inflammatory microvesicles and associated with metabolic and cardiovascular diseases, therefore dubbed "cardiometabolic miRNAs" (reviewed in (Hulsmans and Holvoet, 2013)). Karkeni and collaborators (Karkeni et al., 2016), studying the effect of gain and loss of function of miR-155 in mice showed its effect on adipocyte function. These authors also showed that miR-155 overexpression in 3T3-L1 adipocytes induced inflammatory response, chemokine expression, and macrophage migration. On the other hand, Zhuang and colleagues (Zhuang et al., 2012) demonstrated that miR-223 (through inhibition of Pknox1) is a key regulator of macrophage polarization and protects against diet-induced AT inflammatory response and systemic insulin resistance.

Metaflammation also induces changes in the expression of specific miRNAs that can affect tissues and organs. This is the case for the metaflammation-induced alteration of the miRNA-connexin/Rho kinase regulatory pathway triggered by the selective downregulation of miR-10a, miR-139b, miR-206, and miR-222, which was reported the main mechanism for vascular hyperreactivity and organ damage (i.e., kidney and renal artery) in diabetic and hyperlipidemic rats (T. Li et al., 2015). In addition, obesity-related inflammation was found to increase the production of miRNAs and alter their expression pattern in both cells and culture supernatants (Ortega et al., 2015). Notably, these authors demonstrated that inflamed adipocytes and M1 macrophages share a large number of upregulated miRNAs that are only expressed in one or the other cell type under basal conditions (effect that was more noticeable when studying miRNAs secreted into the supernatants). An example of that was miR-146a and miR-146b, which were detected in adipocytes upon inflammation but not under basal conditions. Based on those results, Ortega and collaborators suggested that the expression and release of "miRNokines" such us miR-146b, miR-376c, miR-411, and miR-19a by inflamed adipocytes and AT from obese people may be evidence of adipocytes'

functional activities beyond adiposity [e.g., recruitment of immune cells (Meijer et al., 2011) and/or modulation of insulin-secreting cells (Nesca et al., 2013)].

Our study of genotype by age interaction in Ames dwarf mice (Victoria et al., 2015) revealed that circulating levels of several of these metaflammation-relevant miRNAs (i.e., miR-146a, miR-376c, miR-411) are altered in the longed-lived mice as compared to normal control mice. Specifically, levels of plasma miR-146a increases as control normal mice age, but remains unchanged in the long-lived dwarf mice. This is consistent with the reduced metaflammation demonstrated in the Ames dwarf mice (Hill et al., 2016; Masternak and Bartke, 2012). On the other hand, both miR-376c and miR-411 have (counter-intuitively) reduced abundance in the circulation of old normal mice, while their levels remain constant in the Ames dwarf mice (Victoria et al., 2015). Perhaps, miR-376c and miR-411 reduction in old normal mice represent an adaptive response aimed at limiting the ongoing metaflammation induced by miR-146a, among other factors. Apparently, the long-lived mouse is able to properly maintain youthful levels of relevant metaflammation miRNAs, consequently maintaining a beneficial local and systemic immune response. This suggests that for an organism to maintain physiological homeostasis capable of extending its lifespan, there must exist a fine balance among metaflammation miRNAs.

The miR-17~92 family, consisting of 15 mature miRNA species including miR-17, miR-18a/b, miR-20a/b, miR-93, and miR-106a/b, is reported downregulated in omental AT of people with diabetes and is negatively correlated with visceral fat area (Klöting et al., 2009). Importantly, members of this family are strongly induced upon T cell activation (Kuchen et al., 2010) and can potentiate T helper cell proliferation in a DGCR8-deficient background (Steiner et al., 2011). In addition, enhanced levels of family members miR-17-5p, miR-20a, and miR-106a strongly promotes blast-cell proliferation and inhibit monocytic differentiation and maturation, whereas their knockdown induce the opposite effects (Laura Fontana et al., 2007). These effects were found to be dependent on the direct regulation of and negative-feedback loop with transcription factor acute myeloid leukemia-1 (AML-1) and transactivation of the M-CSF receptor (M-CSFR).

MICRORNAS ARE POTENTIALLY INVOLVED IN AGE-RELATED MICRO-BIOME CHANGES

Trillions of commensal microbes from 100–200 different bacterial species reside in the human gastrointestinal (GI) track. This large microbial community accounts for a metagenome encoding 2–4 million genes, which represent about 150-fold more unique genes than the human genome (Faith et al., 2013; Qin et al., 2010). Gut microbiota feeds on dietary fiber and produces short-chain fatty acids (SCFAs, mainly acetate, butyrate, and propionate) and other metabolites that can bind to metabolite-sensing receptors expressed in human cells (e.g., G protein-coupled receptors such as GPR43 and GPR109A) and activate the inflammasome to promote gut epithelia integrity and other health benefits (Macia et al., 2015; Maslowski et al., 2009). SCFAs can also modulate cell functions by inhibiting histone deacetylase activity, therefore affecting host gene transcription (Furusawa et al., 2013).

Growing evidence support the existence of a gut microbial–mammalian metabolic axis (Figure 2) and indicate that commensal microbes extend their effects on their host beyond disease to also affect the organismal rate of aging itself (Heintz and Mair, 2014; H. Li and W. Jia, 2013). Signaling triggered by secreted microbial metabolites such as nitric oxide (NO) has been shown to promote longevity in *C. elegans*, which lacks its own NO synthase (Gusarov et al., 2013). In addition, diet-induced imbalances in gut microbial populations (dysbiosis) have been reported to associate with increased risk of developing cardiovascular disease, metabolic disorders, cancer, and allergic disease (Clemente et al., 2012; Luigi Fontana and Partridge, 2015; Tang et al., 2013). Recent studies in humans with type 2 diabetes have suggested that both the therapeutic and adverse effects of metformin are mediated, at least in part, by interaction with the gut microbiota (Forslund et al., 2015). Importantly, using a gut-restricted form of metformin in human clinical trials, Buse and colleagues demonstrated that currently prescribed doses of metformin work predominantly through gut-based mechanisms to achieve its glucose lowering effects and that the contribution of systemic metformin is small (Buse et al., 2016). Furthermore, there is significant inter-individual variation in microbiota composition from adulthood to old age (O'Toole, 2012) that affects a variety of human pathologies including metabolic syndrome, cardiovascular disease, and cancer among others (Cho and Blaser, 2012; Rubinstein et al., 2013; Z. Wang et al., 2011).

Although the study of how genes in the mammalian metagenome interact with the host physiology to influence host longevity is at its very beginnings, its importance is being realized. In a leading opinion minireview, Heintz and Mair recently highlighted the "need to consider the holobiome when thinking about the impact of single gene manipulations on longevity" (Heintz and Mair, 2014). These authors underscored the role of the microbiome and the environmental context in mammalian longevity, for which anecdotal evidence they suggest may already exist in the long-lived Snell dwarf mice. About 40–50 years ago, this hypopituitary mouse was considered, instead, a model of accelerated aging (FABRIS et al., 1972). It was not until 2002 that it was discovered that the short lifespan was not an intrinsic effect of the $Pit1^{wd}$ mutation (which affect the GH, thyroid-stimulating hormone, and prolactin signaling pathways) but a consequence of detrimental husbandry conditions (Flurkey et al., 2002). Although husbandry factors other than microbes may be responsible for the reduced lifespan of the dwarf Snell mice under specific environmental conditions, Heintz and Mair use this example as an "striking reminder of how environmental context can drastically alter the effect of a single mutation on aging".

It is important to note that the human intestinal microbiota is relatively stable over time within an individual and that broad trends exist within a given species (Faith et al., 2013; Kostic et al., 2013; Schloissnig et al., 2013). Schloissnig and colleagues reported that the human metagenome exhibits individuality and temporal stability of SNP variation patterns despite considerable composition changes of their gut microbiota (Schloissnig et al., 2012). Therefore, these authors suggested that an individual might have a unique metagenomic genotype that may be exploitable for personalized diet or drug intake.

Relevant to our focus in this review, recent research has found that specific host-microbiota interactions are mediated by the action of miRNAs. In the following paragraphs, we portrait

these holobiome interactions as a two-way boulevard (Figure 2): on one direction, microbiota may influence host gene expression through the regulation of host miRNAs (Archambaud et al., 2013; Dalmasso et al., 2011; S. Hu et al., 2011; Vikram et al., 2016; D. Wang et al., 2012; Xue et al., 2011); on the other direction, host miRNAs released into the intestinal lumen can control the gut microbiota by regulating bacterial functions such as growth(S. Liu et al., 2016).

Regarding the microbiota → host direction, Wang and collaborators demonstrated that mouse intestinal microflora metabolize dietary flavonoids [i.e., anthocyanin cyanidin-3-*O*-B-glucoside (Cy-3-G)] to produce a circulating metabolite [i.e., protocatechuic acid (PCA)] that regulates cellular cholesterol metabolism and reverse cholesterol transport, through an miR-10b-mediated mechanism that promotes increased ATP-binding cassette A1 (ABCA1) and ATP-binding cassette G1 (ABCG1) expression levels in macrophages (D. Wang et al., 2012). As Hazen and Smith stated on accompanying editorial, “this finding suggests that increased macrophage efflux can actually reverse atherosclerosis in the face of continued hyperlipidemia” (Hazen and Smith, 2012). More recently, Vikram and colleagues demonstrated that gut microbiota may also (and oppositely) regulate second messengers (yet to be identified and distinct from SCFAs) in the systemic circulation to induce vascular miR-204 expression that, in turn, promotes endothelial dysfunction in the vessel walls by targeting Sirt1. The authors also demonstrated that “nutritional stress in the form of a western diet negatively impacts the endothelium via this same gut-vascular axis” (Vikram et al., 2016). As endothelial dysfunction is a precursor and strong predictor of atherosclerosis (Davignon and Ganz, 2004), the impact of these microbiota-regulated miRNAs on health and lifespan can be realized.

In addition, Hu and collaborators suggested that microbiota-derived SCFAs (i.e., butyrate) regulate host gene expression involved in intestinal homeostasis and carcinogenesis through downregulation of colonic epithelial miR-106b (S. Hu et al., 2011). Similarly, Xue and colleagues demonstrated that gut microbiota negatively regulates host miR-10a expression and contribute to the maintenance of intestinal homeostasis/inflammation by targeting IL-12/IL-23p40 expression in dendritic cells (Xue et al., 2011). We reason that, by modulating physiological (e.g., intestinal homeostasis) and pathophysiological (e.g., carcinogenesis) host functions, microbiota-regulated host miRNAs may dramatically impact host aging and lifespan. Furthermore, by colonizing germ-free mice with the microbiota from pathogen-free mice and conducting integrative miRNA-mRNA profiling, Dalmasso and colleagues identified an inverse correlation between downregulated miR-665 and its upregulated predicted target ATP binding cassette subfamily C member 3 (Abcc3) in the mouse colon. The authors validated the direct interaction between miR-665 and the Abcc3 gene in tissue culture (Dalmasso et al., 2011). Abcc3 (also known as Mrp3 for multidrug resistance protein 3) has been found predominantly expressed in the mouse colon and in the colon and ileum of the rat, and suggested to play a role in the ATP-dependent transport of lipophilic anions such as bile acids (BAs) and glucuronides, from the enterocyte to the blood in all higher mammals (Belinsky, 2005; Mutch et al., 2004). Interestingly, previous studies have demonstrated that short-term CR increases serum BAs (within non-cytotoxic levels) in mice, and that BA composition (e.g., increased ratio of 12α- *vs.* non-12α-OH BAs) correlates with improved glucose and lipid homeostasis (Fu and Klaassen, 2013). These findings underscore

a potential connection between microbiota-downregulated miR-665, upregulated Abcc3, increased BA transport (a CR-like effect), and improved glucose and lipid homeostasis. Consequently, the potential connection with aging could also be appreciated, as deregulated glucose and lipid homeostasis is key in the development of age-related diseases such as diabetes and cardiovascular disease (Paneni et al., 2013).

Regarding the host → microbiota direction, in seminal landmark work by the Weiner group, Liu and colleagues thoroughly demonstrated that the host controls the gut microbiota through inter-species gene regulation mediated by fecal miRNAs (S. Liu et al., 2016). These authors demonstrated that miRNAs produced by intestinal epithelial cells (IEC) and Hopx (HOP homeobox)-positives cells can enter bacteria in the gut such as *Fusobacterium nucleatum* (*F. nucleatum*) and *Escherichia coli* (*E. coli*) [species that has been reported to promote colorectal cancer (Rubinstein et al., 2013)], and specifically regulate bacterial transcripts that affect bacterial growth. Notably, by transplanting wild type fecal miRNAs into conditional Dicer-deficient ($Dicer1^{\Delta IEC}$) mice, Liu and colleagues restored the mutant mouse fecal microbiome and ameliorated the colitis characteristic of this IEC-miRNA-deficient strain (S. Liu et al., 2016). Based on sequence similarity, this group identified nucleic acid sequences from three bacterial species important for gut immune development that are predicted to be targeted by many miRNAs from mouse and humans (also from lower species such as worms and flies). Among relevant human miRNAs that can potentially target *F. nucleatum* nucleic acid sequences were miR-101, miR-515-5p, miR-876-5p, miR-325, and miR-1253; whereas miR-4747-3p, miR-1224-5p, miR-1226-5p, and miR-623 could potentially target *E. coli* nucleic acid sequences. In addition, by conducting validation experiment in culture, the authors demonstrated that human miRNAs can enter bacteria, colocalize with bacterial nucleic acids, alter the expression levels of bacterial transcripts, and directly affected bacterial growth (S. Liu et al., 2016). In particular, hsa-miR-515-5p promoted *F. nucleatum* growth, whereas hsa-miR-1226-5p promoted the growth of *E. coli*. Interestingly, some miRNAs induced the upregulation of respective bacterial gene targets (e.i., human miR-515-5p increased the ratio of *F. nucleatum* 16S rRNA/23S rRNA transcripts, whereas *E. coli* yegH mRNA was increased by miR-1226-5p and RNaseP was increased by miR-4747-3p), while others such as miR-1224-5p and miR-663 reduced the expression levels of *E. coli* rutA and fucO mRNAs, respectively (S. Liu et al., 2016).

Based on these reports, we hypothesize that specific host miRNAs acting on and being modulated by comensal microbiota play an important role in regulating holobiome interactions in the context of and with relevance to organismal aging. Further research to validate this hypothesis and discover novel modulators of the human-microbiota relationship with an impact on human aging is warranted..

CONCLUSIONS

The discovery of miRNAs involved in multiple metabolic alterations that occur during physiological and pathophysiological aging has witnessed major advances in the last decade. These small non-coding RNAs has proven critical for the maintenance of cellular homeostasis and the regulation of almost every metabolic process relevant to aging. Our understanding of the involvement of miRNAs in the deregulation of nutrient sensing,

mitochondrial dysfunction, and metabolic inflammation (metaflammation) in the context of aging has consequently revolutionized. However, further research is required to dissect the precise molecular mechanisms underlying the fine-tuned regulation of these protective or pro-aging miRNAs. For example, it would be important to identify transcription factors that regulate the expression of these miRNAs in a tissue-specific context. Also important will be the identification and validation of novel miRNA targets that could vary depending on the specific micro/macro-environmental context. Importantly, we should not loose perspective of translating these molecular and mechanistic findings into bedside clinical applications that could improve human and animal health.

With this review, we identify a recurrent theme in aging research underscoring the importance of maintaining physiologically balanced miRNA levels for biological systems to promote organismal homeostasis and longevity. We also think it is important to highlight the connection between the miR-451/AMPK axis and aging as an important finding of this review. Based on the evidence discussed here, we reason that this axis could be critical for maintenance of physiological homeostasis in high-energy-demanding tissues including myocardial and skeletal muscles. Manipulation of this axis could represent an important therapeutic intervention to improve mammalian healthspan.

Although great progress has been achieved in the study of host-microbiome interspecies communication mediated by host miRNAs, important knowledge gaps remain to be addressed including the elucidation of the mechanisms controlling the entry of miRNAs into bacteria and their processing once inside the bacteria. It will also be important to elucidate how miRNA regulation occurs in commensal bacteria, which appear different from the traditional post-transcriptional repression in eukaryotic cells. Given that fecal miRNA transplantation can help restoring the normal gut microflora and ameliorate pathological conditions in animal models, this strategy may prove clinically relevant for the development of therapeutic applications in humans, where fecal microbiota transplantation has already proven efficacious and safe, for example for the treatment of recurrent *Clostridium difficile* infections (Cammarota et al., 2014).

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HIGHLIGHTS

- MicroRNAs are involved in deregulated nutrient sensing during aging.
- Deregulation of mitomiRs induces mitochondrial dysfunction during aging.
- Age-related metabolic inflammation is regulated by miRNAs.
- MicroRNAs are potentially involved in age-related microbiome changes.

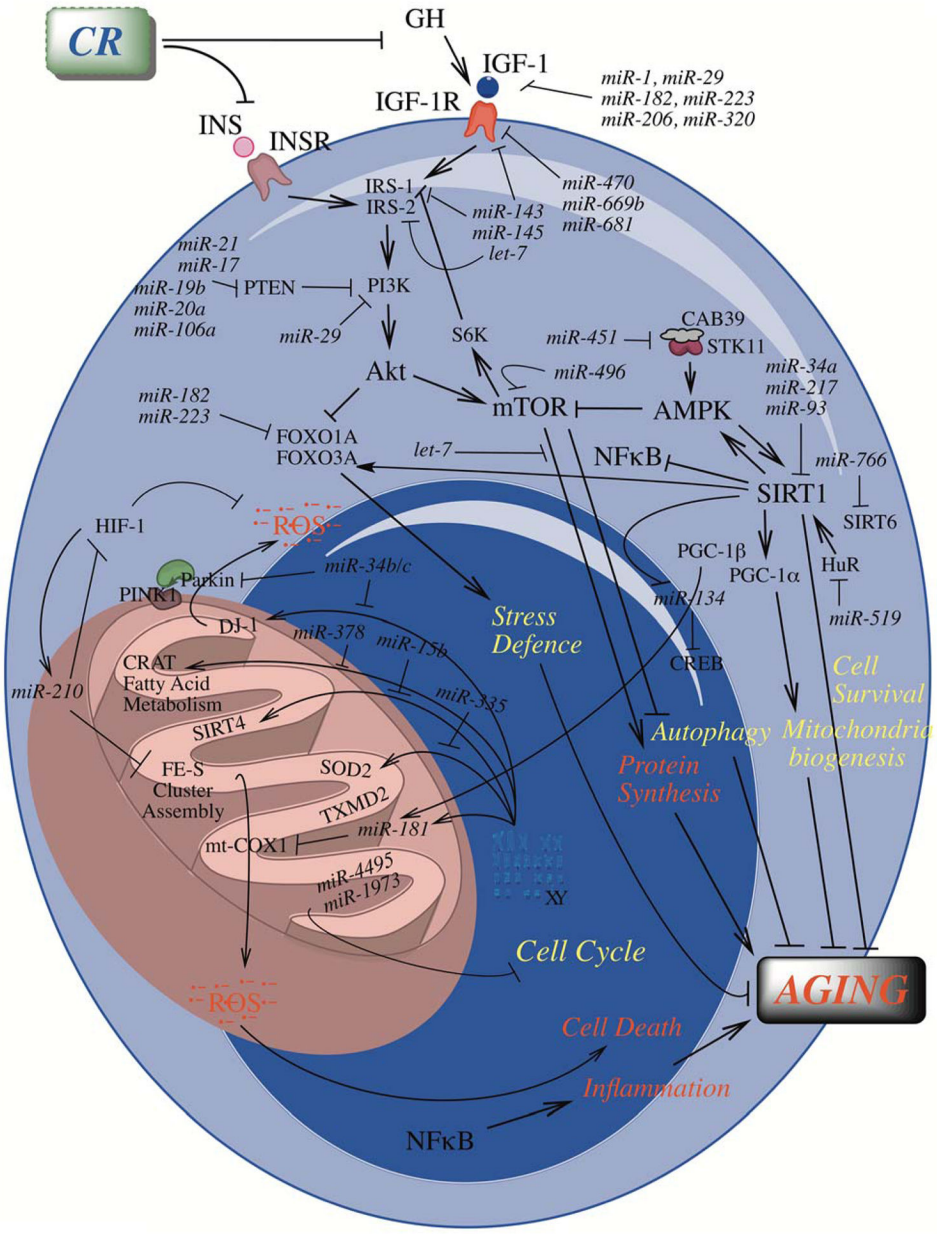

Figure 1. A maximalist view of microRNAs (miRNAs) in nutrient sensing, mitochondrial metabolism, and aging

This figure highlights the broad and generalized involvement of miRNAs in the regulation of multiple important signaling events related to nutrient sensing and mitochondrial metabolism relevant to mammalian aging (for additional details, references, abbreviation meaning, please refer to the main text). A theme “observable” in the milieu of cellular signaling and regulatory relationships presented on this cartoon is the apparently redundant “modus-operandi” of miRNAs while controlling homeostasis-promoting biological processes that would wreck havoc cellular and organismal life if left adrift. These processes ensure healthy living when harmonically coupled. Deviances from a “regulatory equilibrium” would induce the system to readjust (thanks, at least in part, to the above

mentioned redundancy) and efficiently recover back to the original steady state or related new state of “benign” equilibrium. These balancing acts of regulation would perform adequately until enough uncompensated regulatory damage accumulates and turns the system unstable, triggering a self-destructive chain of events. We think this is an expression of the robustness that characterizes miRNA regulation in metazoans. We reason that by better understanding these regulatory mechanisms, we will eventually be capable of automatically manipulating damaged regulatory events to exogenously contribute to cellular and organismal homeostasis, therefore improving animal and human healthspan. Drawings were done using BioDraw Ultra version 12.0.3.1216 (CambridgeSoft, Waltham, MA)

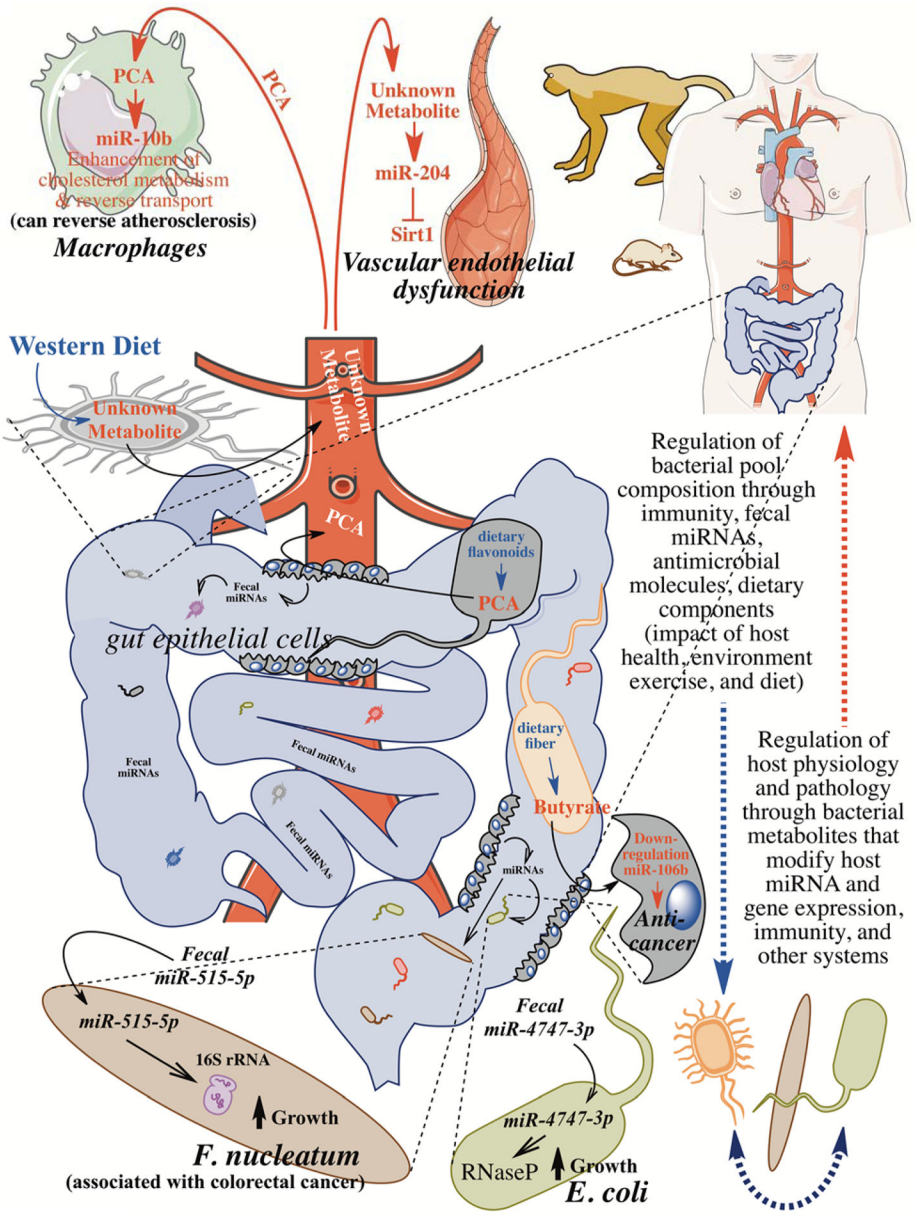

Figure 2. Fecal microRNAs as mediators of symbiotic relationships among microbiota and animal host: Potential impact in aging

This cartoon summarizes recent advances in the study of the mammalian microbiota in the context of symbiotically interacting with its animal host. The relationship host-microbiota has been shown critical for healthy living and also proven causative of pathological conditions when unbalanced or affected by dysbiosis. Specific host-microbiota interactions are mediated by the action of miRNAs. On one direction, microbiota may influence host gene expression through the regulation of host miRNAs. On the other, host microRNAs (fecal miRNAs secreted by intestinal epithelial cells) can control the gut microbiota through inter-species gene regulation (S. Liu et al., 2016). These host miRNAs can enter bacteria and specifically regulate bacterial transcripts that affect bacterial growth, therefore changing both the relative proportions and the absolutes amounts of microbes in the gut. Commensal

microbiota has been shown to impact host aging; therefore, we reason that fecal miRNA regulation of intestinal flora could be relevant to aging. Intriguingly, the regulation mediated by fecal miRNAs acting on gut microflora to activate expression of bacterial genes appear different from the traditional post-transcriptional repression in eukaryotic cells. Drawings were done using BioDraw Ultra version 12.0.3.1216 (CambridgeSoft, Waltham, MA). Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (http://www.servier.com/Powerpoint-image-bank).

Table 1

MicroRNAs described in this review in the context of metabolism and aging.

		Nutrient Sensing					
miRNA	**Genomic Cluster**	**GH/Ins/IGF-1**	**mTOR**	**AMPK/Sirtuins**	**Mitochondrial Disfuntion**	**Metabolic Inflamation**	**Microbiome**
miR-376c	*14q32.31*					✓	
miR-10a	*Hox clusters*					✓	✓
miR-10b	*Hox clusters*						✓
let-7	*let-7 clusters*	✓			✓		
miR-1	*mir-1/133a*	✓			✓		
miR-106a	*mir-106a~363*	✓	✓		✓	✓	
miR-20b	*mir-106a~363*					✓	
miR-134	*mir-134/487b/655*			✓			
miR-143/145	*mir-143/145*	✓					
miR-451	*mir-144/451*			✓			
miR-146a	*miR-146a/183*				✓	✓	
miR-15b	*mir-15b/16-2*			✓	✓		
miR-15a	*mir-16-1/15a*					✓	
miR-16	*mir-16-1/15a*					✓	
miR-17	*mir-17~92*	✓	✓			✓	
miR-18a	*mir-17~92*					✓	
miR-19a	*mir-17~92*	✓	✓			✓	
miR-20a	*mir-17~92*	✓	✓		✓	✓	

		Nutrient Sensing					
miRNA	**Genomic Cluster**	**GH/Ins/IGF-1**	**mTOR**	**AMPK/Sirtuins**	**Mitochondrial Disfuntion**	**Metabolic Inflamation**	**Microbiome**
miR-181a	*mir-181a/181b*				✓		
miR-182	*mir-183/96/182*	✓	✓				
miR-195	*mir-195/497*			✓			
miR-204	*mir-204/211*						✓
miR-133b	*mir-206/133b*				✓		
miR-206	*mir-206/133b*	✓				✓	
miR-217	*mir-217/216a*			✓			
miR-221	*mir-221/222*	✓			✓		
miR-222	*mir-221/222*	✓				✓	
miR-106b	*mir-25/93/106b*					✓	✓
miR-18b	*mir-25/93/106b*					✓	
miR-19b	*mir-25/93/106b*				✓		
miR-93	*mir-25/93/106b*			✓		✓	
miR-669	*mir-297/669*	✓					
miR-29	*mir-29a/b1*	✓					
miR-665	*mir-337/665*						✓
miR-34b/c	*mir-34b/c*				✓		
miR-411	*mir-379/411*					✓	
miR-496	*mir-379~410*		✓				
miR-1224-5p	-						✓

miRNA	Genomic Cluster	Nutrient Sensing			Mitochondrial Disfuntion	Metabolic Inflamation	Microbiome
		GH/Ins/IGF-1	mTOR	AMPK/Sirtuins			
miR-1226-5p	-						✓
miR-126	-					✓	
miR-139b	-					✓	
miR-142-3p	-	✓	✓				
miR-146b	-					✓	
miR-155	-					✓	
miR-1973	-				✓		
miR-21	-		✓			✓	
miR-210	-				✓		
miR-223	-	✓	✓			✓	
miR-335	-				✓		
miR-34a	-			✓	✓		
*miR-378/378**	-				✓		
miR-4495	-				✓		
miR-470	-	✓					
miR-515-5p	-						✓
miR-519	-			✓			
miR-663	-						✓
miR-681	-	✓					

miRNA	Genomic Cluster	Nutrient Sensing			Mitochondrial Disfuntion	Metabolic Inflamation	Microbiome
		GH/Ins/IGF-1	mTOR	AMPK/Sirtuins			
miR-766	-			✓			