J Skin Stem Cell. 2018 June; 5(1-2):e81732. doi: 10.5812/jssc.81732.

Published online 2018 August 15. **Review Article**

Inflamma-miRs, Mito-miRs, and SA-miRs: Are They at the Crossroads of Inflammaging?

Samila Farokhimanesh,[1,*] Ali Komeili,[2,**] Mohammad Ali Nilforoushzadeh,[3] and Mehrak Zare[3]

[1]Department of Biotechnology, Islamic Azad University, Tehran, Iran
[2]Applied Biophotonics Research Center, Science and Research Branch, Islamic Azad University, Tehran, Iran
[3]Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran

[*]*Corresponding author*: Department of Biotechnology, Science and Research Branch, Islamic Azad University, Tehran, Iran. Email: s.farokhimanesh@srbiau.ac.ir
[**]*Corresponding author*: Applied Biophotonics Research Center, Science and Research Branch, Islamic Azad University, Tehran, Iran. Email: ali_komeili43@yahoo.com

Received 2018 July 04; **Revised** 2018 July 24; **Accepted** 2018 July 29.

Abstract

Context: Inflammaging is the latest theory of aging, which is the chronic, low-grade, and systematic inflammation developing the major risk factors for age-related diseases. Inflammaging is characterized by increasing the circulating pro-inflammatory factors and decreasing the circulatory anti-inflammatory factors. Recent findings propose that several classes of microRNAs are differentially expressed during inflammaging.

Evidence Acquisition: Inflamma-miRs are a class of miRs capable of regulating the inflammatory status owing to their ability to modulate pro-inflammatory molecules. Since the role of miRNAs in aging is not restricted to inflammation, mito-miRs and SA-miRs are also involved in organismal aging. Considering the important role of mitochondria in aging, dysfunctional mitochondria in aged cells may induce an inflammatory response by producing ROS, as well as oxidized mtDNA and mito-miRNAs. Another important subset of miRNA that fuels inflammaging is senescence-associated miRNA (SA-miRs) that promotes senescence-associated secretory phenotype. Senescent cells have dysfunctional mitochondria, which can promote inflammaging through continuous immune system stimulation.

Results: The evaluation of three classes of miRNAs involved in inflammaging shows that there are some miRs at the intersection of inflamma-miRs, SA-miRs, and mito-miRs, called SA-inflamma-mitomiRs subset, which contains miR-19b, miR-20a, miR-146a, and miR-181a.

Conclusions: This overlap shows that this panel of miRNAs has mitochondrial targets whose modulation is implicated in senescence-associated secretory phenotype and the formation of SASP might be an important contributor to chronic inflammation.

Keywords: Inflammaging, Senescence, Inflamma-miR, Mito-miR, SA-miR

1. Context

Geriatric syndromes (including neurodegenerative diseases, cardiovascular diseases, type 2 diabetes mellitus, cancer, arthritis, frailty, sarcopenia, and so on) arising from the chronic, low-grade inflammation (inflammaging) are associated with aging (1).

Inflammaging is a dynamic and systematic process in which particular combinations of pro- and anti-inflammatory mediators are involved. If the balance between pro- and anti-inflammatory mediators is impaired, inflammaging may arise (2). This imbalance could be at different levels: Molecular (heat shock protein, DNA repair mechanism, chaperones, turn-over of proteins in organelles, detoxifying and anti-oxidant systems), cellular (cell senescence, apoptosis, autophagic cell death, etc.), and systematic (inflammatory, immune and stress response) (2, 3).

Findings indicate the implication of microRNAs as a post-transcriptional regulator in aging.

Since miRNAs are the micromanagers and master regulators of the most pathways that might be related to inflammation, they could exert their effects on inflammaging at all levels (molecular, cellular, and systematic) (1, 4).

At the molecular level, one of the most important sets of miRNAs that can affect inflammaging is mito-miRs (5). Accumulating evidence has suggested that mitochondrial dysfunction is associated with the aging process (6). Aging is accompanied by a decline in the mitochondrial function, during which dysfunctional mitochondria are not removed via autophagy. These dysfunctional mitochondria produce reactive oxygen species that can contribute to oxidative damages and eventually cause inflammaging (7, 8).

MitomiRs are miRNAs that can localize in mitochondria whether transcribed from the mitochondrial or nuclear genome. Some of them may play a role in controlling mitochondrial function and consequently their modulation could mediate the loss of mitochondrial integrity and function, inducing inflammaging (9).

On the other hand, many miRNAs can act as inducers of senescence. These discrete sets of miRNAs are involved in the cellular senescence, which is the state of stable and irreversible cell cycle arrest in normal cells with active metabolism occurring after a finite number of divisions. As the senescent cells accumulate in tissues, they can affect bystander cells through the secretion of different biomolecules, called senescence-associated secretory phenotype. Cellular senescence plays its role in inflammaging at the cellular level (10-12).

Inflamma-miRs are the important set of miRNAs capable of modulating inflammatory status at the systemic level and their abnormal expression causes chronic inflammatory status (13).

Since the miRNAs in all three sets (mito-miRs, SA-miRs, and inflamma-miRs) indicate their concurrent role in these pathways, these miRNAs may have a role in the loss of mitochondrial integrity and function resulting in the formation of SASP, promoting inflammaging. In addition, they can correlate molecular, cellular, and systematic levels to each other. Here, we investigated the three sets including mito-miRs, SA-miRs, and inflamma-miRs and their interconnection and intersection with each other to gain a new insight into their mode of action (14).

2. Evidence Acquisition

2.1. MitomiRS

Mitochondria are organelles indisputably involved in the heart of the aging process (15). A large body of evidence indicates that dysfunctional organelles (mainly mitochondria) and their defective disposal can start inflammation inside the cells. The decreases of autophagic clearance have effects on mitochondrial dynamics (fusion and fission), eventually causing inflammation (6, 16, 17).

As mentioned before, mitomiRs, the mitochondrial-located miRNAs, are involved in crucial biological processes like proliferation, apoptosis, mitochondrial metabolism, mitochondrial dynamics (fusion, fission, and mitophagy), inflammation, and aging (9).

Interestingly, mitomiRs show organelle, cell, and tissue-specific functions depending on their cellular metabolic demand, origin, and microenvironment. These miRNA can be sensitive to the changing microenvironment and respond dynamically (18).

miRNAs that are implicated in apoptosis include miR-1, 7, 15b, 16, 125b, 143, 145, 214, 24, 181, 221/222, 326, 491, and 497. miRNAs that are associated with mitochondrial metabolism are miR-15b, 16, 195, 133a, b-1, 210, 378, 424, and so on. miRNAs 27, 30, 106-b, 532, 181c, 484, 499, and 761, among the other, are involved in mitochondrial dynamics (9, 19, 20).

Let-7b, miR-19b, miR-20a, miR-34a, miR-106a, miR-133b, miR-146a, miR-181a, and miR-221 have roles in altering the mitochondrial function, affecting inflammaging. MiR-19b and miR-20a are the most down-regulated miRs in different aging cells. Transcription of the CDK inhibitor p21 is correlated with down-regulation of miR-19b and miR-20a. MiR-20a also modulates the macrophage inflammatory response in leukocytes. MiR-146a is up-regulated in aging cells and controls the expression of IRAK-1 and TRAF-6, which are inflammation mediators. MiR-181a up-regulation is adequate for inducing the cell senescence. miR-34a suppresses SIRT1. SIRT1 has been reported to be involved in the regulation of diverse biological processes, including mitochondrial biogenesis, inflammation, and cell senescence and miR-133b targets glutathione-S-transferase p1. MiR-106a inhibits cell survival by down-regulating Mcl-1(which encodes an anti-apoptotic protein). MiR-221/222 regulates cell growth and cell cycle progression by targeting p27 and p57. In addition, mitomiRs like miR-328, 494, 513, and 638 have roles in mitochondrial hemostasis. Others like Let-7b, let-7g, miR-107, 221, and 320a are involved in different signaling pathways (5, 14, 21-23).

2.2. SA-miRs

The senescence, as previously mentioned, is a state in which normal cells divide for a finite number of times before they terminate propagation indefinitely although they are metabolically active (24).

There are two models of senescence: Replicative senescence in which cells proliferate until their telomeres become critically short and consequently they are terminally arrested, and premature senescence or stress-inducible senescence that are caused by exposing cells to stress like oxidants, toxins, radiation, and so on.

MiRNAs are involved in senescence through three pathways:

1. p53/p21 senescence pathway
2. p16/RB senescence pathway
3. Senescence-associated secretory phenotype (SASP)

A large number of miRs can control the expression levels of protein components in the three senescence pathways. They can influence senescence by modulating the abundance of key senescence regulatory proteins (12).

The most important SA-miRs in the p53/p21 pathway that can regulate the expression of genes like MDM2,

p53, TERT, p21, MYC, MCD1, and SIRT1 will be focused. MDM2, which is a ubiquitin ligase suppressing p53, is post-transcriptionally controlled by miR-192, 194, 215, and 605. MiRNAs like 125b, 504, 25, and 30d suppress p53 protein levels. Telomerase reverse transcriptase expression, which is crucial for maintaining telomere length, is regulated by miR-195.

Several miRNAs can suppress the p21 expression and therefore can affect cell senescence including MiR-130b, miR-302 family (a, b, c, d), miR-106b, 19b, 20a, 208,519 family (a, b, c), and miR-29c-3p.

MYC is an oncoprotein that represses the p21 expression, thus modulating apoptotic response. Several miRNAs target the MYC expression like miR-34a, miR-429, miR-33b, miR-126, miR-136, miR-145, miR-449c, and let-7. The MCD1 (mediator of DNA damage checkpoint 1) controls the p53 expression. An increase in miR-22 could down-regulate MCD1 and bring about senescence. The SIRT1 (silent mating type information regulation 2 homologue 1) is a deacetylase that can modulate the metabolic activity in cellular stress. Deacetylation of p53 gene by SIRT1 represses the transcriptional induction of p21 expression. Up-regulation of miRNA 34a, 22, 138, 181a, and 217 reduces the SIRT1 expression.

The SA-miRNA is associated with p16/RB with some influences directly on the p16 expression like miR-24, 141, 300, 514 and 663 while other miRs in this group like 9, 26b, 29, 30, 141, 181, 210, 424, 138, 203, 205, 449a, etc. act upstream to modulate the p16 expression.

The SA-miRs in the SASP group include miRs that are involved in the secretion of growth factors, cytokines, and proteases. The most important members of this group are miR-146a and b (modulated IRAK1, TLR-8 expression), miR-9 (IL-6), miR-222 (MMP1), and miR-187 (TNF, IL6) (12, 24).

2.3. Inflamma-miRs

It has been widely shown that several miRNAs are implicated in inflammation. In normal condition, the transcription of inflamma-miRs is at the baseline level. However, the initiation of proinflammatory TLR signaling instantly gives rise to strong co-induction of their expression through a mechanism that is largely NF-κB-dependent. In fact, the consequent inflammaging results from the up-regulation of these miRs. Inflamma-miRs are categorized into two groups:

1. Cellular inflamma-miRs that modulate the proinflammatory response at the cell level like miR-9, 19b, 20a, 21, 29a, 125a, 125b, 126, 146a, 155, 195, 199a, 517a, 517c, and let-7. Most of the cellular inflamma-miRs are involved in TLR signaling as mentioned before and these miRs affect the responsiveness of inflammatory cells (monocytes, neutrophils, endothelial, macrophages, dendritic and immune cells, and fibroblasts) and the activation of pro-inflammatory pathways like NF-κB (by miR-9), TLR-4 (let-7), VCAM-1 (by miR-126), IRAK-1 (by miR-146a and miR-146b), IL-1α (miR-181a), and TNF-α (miR187).

2. The circulating inflamma-miRs that are cellular inflamma-miRs modulated in plasma/serum samples in different physiopathological conditions like miR-9, 21, 29a, 126, 146, and155, which are up-regulated in age-related diseases. A mounting body of evidence has documented that these miRs are found within exosomes, in which they are transported outside the cell where they can be taken up by neighboring cells. Therefore, they act in a paracrine manner or alternatively, they enter the blood circulation and act as hormones by provoking a systemic response (13, 25).

3. Results

Among the different factors influencing inflammaging, mitochondrial dysfunction is the most outstanding one. The maintenance of a sufficient number of functional mitochondria is essential for tissue hemostasis.

Recent studies show that there is an intersection between miRNAs involved in mitochondrial dysfunction, senescence, and inflammaging. When the turnover of mitochondria is disrupted, it contributes to the mitochondrial accumulation and senescence-associated mitochondrial dysfunction. Senescent cells undergo senescence-associated phenotype and secret pro-inflammatory molecules and matrix modifying peptides, which can cause inflammaging (26). Accordingly, there are overlaps between the three groups of miRS, pairwise or combined altogether.

MitomiR and SA-miRs share 9 miRs including let-7b, miR-19b, miR-20a, miR-34a, miR-106a, miR-133b, miR-146a, miR-181a, and miR-221, called SA-mitomiRs. MitomiRs and inflamma-miRs share 12 miRS including miR-9, 19b, 20a, 21, 29a, 125a, 125b, 126, 199, called inflamma-mitomiRs and three miR sets share four miRs containing miR-19b, 20a, 146a, 181a in common, called SA-inflamma-mitomiRs (14).

4. Conclusions

Emerging data have shown that mitochondria dysfunction is necessary for the development of senescence and SASP resulting in inflammaging. In fact, mitochondrial turnover is a driving factor of inflammaging that might be the central regulator of cell senescence.

MiRNAs are master regulators of most cellular pathways involved in inflammation, especially the four miRNAs that are common between mitochondria, senescence,

and inflammation. Targeting these molecules could be a promising strategy for controlling inflammaging and eliminating senescent cells causing inflammaging. Thereby, this field deserves further investigation (27-29).

References

1. Franceschi C, Garagnani P, Vitale G, Capri M, Salvioli S. Inflammaging and 'Garb-aging'. *Trends Endocrinol Metab*. 2017;**28**(3):199–212. doi: 10.1016/j.tem.2016.09.005. [PubMed: 27789101].
2. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev*. 2007;**128**(1):92–105. doi: 10.1016/j.mad.2006.11.016. [PubMed: 17116321].
3. Flynn MG, Markofski MM, Carrillo AE. Elevated inflammatory status and increased risk of chronic disease in chronological aging: Inflamm-aging or inflamm-inactivity? *Aging Dis*. 2018. doi: 10.14336/ad.2018.0326.
4. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;**69 Suppl 1**:S4–9. doi: 10.1093/gerona/glu057. [PubMed: 24833586].
5. Bandiera S, Mategot R, Girard M, Demongeot J, Henrion-Caude A. MitomiRs delineating the intracellular localization of microRNAs at mitochondria. *Free Radic Biol Med*. 2013;**64**:12–9. doi: 10.1016/j.freeradbiomed.2013.06.013. [PubMed: 23792138].
6. Picca A, Lezza AMS, Leeuwenburgh C, Pesce V, Calvani R, Landi F, et al. Fueling inflamm-aging through mitochondrial dysfunction: Mechanisms and molecular targets. *Int J Mol Sci*. 2017;**18**(5). doi: 10.3390/ijms18050933. [PubMed: 28452964]. [PubMed Central: PMC5454846].
7. Lemasters JJ. Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging. *Rejuvenation Res*. 2005;**8**(1):3–5. doi: 10.1089/rej.2005.8.3. [PubMed: 15798367].
8. Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. *Cell*. 2011;**146**(5):682–95. doi: 10.1016/j.cell.2011.07.030. [PubMed: 21884931].
9. Duarte FV, Palmeira CM, Rolo AP. The role of microRNAs in mitochondria: Small players acting wide. *Genes (Basel)*. 2014;**5**(4):865–86. doi: 10.3390/genes5040865. [PubMed: 25264560]. [PubMed Central: PMC4276918].
10. Lafferty-Whyte K, Cairney CJ, Jamieson NB, Oien KA, Keith WN. Pathway analysis of senescence-associated miRNA targets reveals common processes to different senescence induction mechanisms. *Biochim Biophys Acta*. 2009;**1792**(4):341–52. doi: 10.1016/j.bbadis.2009.02.003. [PubMed: 19419692].
11. Markopoulos GS, Roupakia E, Tokamani M, Vartholomatos G, Tzavaras T, Hatziapostolou M, et al. Senescence-associated microRNAs target cell cycle regulatory genes in normal human lung fibroblasts. *Exp Gerontol*. 2017;**96**:110–22. doi: 10.1016/j.exger.2017.06.017. [PubMed: 28658612].
12. Munk R, Panda AC, Grammatikakis I, Gorospe M, Abdelmohsen K. Senescence-associated microRNAs. *Int Rev Cell Mol Biol*. 2017;**334**:177–205. doi: 10.1016/bs.ircmb.2017.03.008. [PubMed: 28838538].
13. Olivieri F, Rippo MR, Procopio AD, Fazioli F. Circulating inflammamiRs in aging and age-related diseases. *Front Genet*. 2013;**4**:121. doi: 10.3389/fgene.2013.00121. [PubMed: 23805154]. [PubMed Central: PMC3693036].
14. Rippo MR, Olivieri F, Monsurro V, Prattichizzo F, Albertini MC, Procopio AD. MitomiRs in human inflamm-aging: a hypothesis involving miR-181a, miR-34a and miR-146a. *Exp Gerontol*. 2014;**56**:154–63. doi: 10.1016/j.exger.2014.03.002. [PubMed: 24607549].
15. Kauppila TES, Kauppila JHK, Larsson NG. Mammalian mitochondria and aging: An update. *Cell Metab*. 2017;**25**(1):57–71. doi: 10.1016/j.cmet.2016.09.017. [PubMed: 28094012].
16. Chistiakov DA, Sobenin IA, Revin VV, Orekhov AN, Bobryshev YV. Mitochondrial aging and age-related dysfunction of mitochondria. *Biomed Res Int*. 2014;**2014**:238463. doi: 10.1155/2014/238463. [PubMed: 24818134]. [PubMed Central: PMC4003832].
17. Vilchez D, Saez I, Dillin A. The role of protein clearance mechanisms in organismal ageing and age-related diseases. *Nat Commun*. 2014;**5**:5659. doi: 10.1038/ncomms6659. [PubMed: 25482515].
18. Duarte FV, Palmeira CM, Rolo AP. The emerging role of mitomiRs in the pathophysiology of human disease. *Adv Exp Med Biol*. 2015;**888**:123–54. doi: 10.1007/978-3-319-22671-2_8. [PubMed: 26663182].
19. Srinivasan H, Das S. Mitochondrial miRNA (MitomiR): a new player in cardiovascular health. *Can J Physiol Pharmacol*. 2015;**93**(10):855–61. doi: 10.1139/cjpp-2014-0500. [PubMed: 26030833].
20. Li P, Jiao J, Gao G, Prabhakar BS. Control of mitochondrial activity by miRNAs. *J Cell Biochem*. 2012;**113**(4):1104–10. doi: 10.1002/jcb.24004. [PubMed: 22135235]. [PubMed Central: PMC3325319].
21. Barrey E, Saint-Auret G, Bonnamy B, Damas D, Boyer O, Gidrol X. Pre-microRNA and mature microRNA in human mitochondria. *PLoS One*. 2011;**6**(5). e20220. doi: 10.1371/journal.pone.0020220. [PubMed: 21637849]. [PubMed Central: PMC3102686].
22. Sripada L, Tomar D, Prajapati P, Singh R, Singh AK, Singh R. Systematic analysis of small RNAs associated with human mitochondria by deep sequencing: detailed analysis of mitochondrial associated miRNA. *PLoS One*. 2012;**7**(9). e44873. doi: 10.1371/journal.pone.0044873. [PubMed: 22984580]. [PubMed Central: PMC3439422].
23. Mercer TR, Neph S, Dinger ME, Crawford J, Smith MA, Shearwood AM, et al. The human mitochondrial transcriptome. *Cell*. 2011;**146**(4):645–58. doi: 10.1016/j.cell.2011.06.051. [PubMed: 21854988]. [PubMed Central: PMC3160626].
24. Bhaumik D, Scott GK, Schokrpur S, Patil CK, Orjalo AV, Rodier F, et al. MicroRNAs miR-146a/b negatively modulate the senescence-associated inflammatory mediators IL-6 and IL-8. *Aging (Albany NY)*. 2009;**1**(4):402–11. doi: 10.18632/aging.100042. [PubMed: 20148189]. [PubMed Central: PMC2818025].
25. Catana CS, Calin GA, Berindan-Neagoe I. Inflamma-miRs in aging and breast cancer: Are they reliable players? *Front Med (Lausanne)*. 2015;**2**:85. doi: 10.3389/fmed.2015.00085. [PubMed: 26697428]. [PubMed Central: PMC4678211].
26. Korolchuk VI, Miwa S, Carroll B, von Zglinicki T. Mitochondria in cell senescence: Is mitophagy the weakest link? *EBioMedicine*. 2017;**21**:7–13. doi: 10.1016/j.ebiom.2017.03.020. [PubMed: 28330601]. [PubMed Central: PMC5514379].
27. Wiley CD, Velarde MC, Lecot P, Liu S, Sarnoski EA, Freund A, et al. Mitochondrial dysfunction induces senescence with a distinct secretory phenotype. *Cell Metab*. 2016;**23**(2):303–14. doi: 10.1016/j.cmet.2015.11.011. [PubMed: 26686024]. [PubMed Central: PMC4749409].
28. Correia-Melo C, Marques FD, Anderson R, Hewitt G, Hewitt R, Cole J, et al. Mitochondria are required for pro-ageing features of the senescent phenotype. *EMBO J*. 2016;**35**(7):724–42. doi: 10.15252/embj.201592862. [PubMed: 26848154]. [PubMed Central: PMC4818766].
29. Correia-Melo C, Passos JF. Mitochondria: Are they causal players in cellular senescence? *Biochim Biophys Acta*. 2015;**1847**(11):1373–9. doi: 10.1016/j.bbabio.2015.05.017. [PubMed: 26028303].