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Review

MicroRNAs linking inflamm-aging, cellular senescence and cancer

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ABSTRACT

Epidemiological and experimental data demonstrate a strong correlation between age-related chronic inflammation (inflamm-aging) and cancer development. However, a comprehensive approach is needed to clarify the underlying molecular mechanisms. Chronic inflammation has mainly been attributed to continuous immune cell activation, but the cellular senescence process, which may involve acquisition of a senescence-associated secretory phenotype (SASP), can be another important contributor, especially in the elderly. MicroRNAs (miRs), a class of molecules involved in gene expression regulation, are emerging as modulators of some pathways, including NF-κB, mTOR, sirtuins, TGF-β and Wnt, that may be related to inflammation, cellular senescence and age-related diseases, cancer included. Interestingly, cancer development is largely avoided or delayed in centenarians, where changes in some miRs are found in plasma and leukocytes. We identified miRs that can be considered as senescence-associated (*SA-miRs*), inflammation-associated (*inflamma-miRs*) and cancer-associated (*onco-miRs*). Here we review recent findings concerning three of them, miR-21, -126 and -146a, which target mRNAs belonging to the NF-κB pathway; we discuss their ability to link cellular senescence, inflamm-aging and cancer and their changes in centenarians, and provide an update on the possibility of using miRs to block accumulation of senescent cells to prevent formation of a microenvironment favoring cancer development and progression.

Contents

1. Inflamm-aging, cellular senescence and cancer

Human aging is attended by a low-grade systemic inflammation characterized by elevation of circulating acute-phase proteins and proinflammatory cytokines, a condition that we have designated inflamm-aging (Franceschi et al., 2000, 2007). Such inflammatory

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imbalance is associated with frailty and the development and progression of severe, age-related conditions that include cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and neurodegenerative diseases (Franceschi et al., 2007; Vasto et al., 2007; Cevenini et al., 2013). The chronic inflammation seems largely attributable to progressive activation of immune cells over time (Franceschi et al., 2007). However, recent studies show that the cellular senescence process could be an important additional contributor to the maintenance of low-grade chronic systemic inflammation (Campisi, 2011; Freund et al., 2010; Olivieri et al., 2012a,b). Besides limitations in cell replication properties, senescence may involve acquisition of the senescence-associated secretory phenotype (SASP), a distinctive phenotype characterized by enhanced secretion of the main proinflammatory mediators, *i.e.* proteases, cytokines, chemokines and growth factors (Campisi, 2011). Interestingly, the SASP has been documented not only in immune cells like macrophages (Sikora et al., 2011), but also in fibroblasts (Freund et al., 2010) and endothelial cells (Olivieri et al., 2012a,b; Donato et al., 2008). SASP acquisition helps explain some of the biological activities of senescent cells, notably their contribution to tissue repair; indeed increased production of cytokines and chemokines is capable of inducing recruitment of phagocytes, which can eliminate dysfunctional cells thus favoring the reparative capacity of tissues (Rodier and Campisi, 2011). Moreover cellular senescence, by limiting cell proliferation, can prevent the growth of cells with damaged DNA, which are at risk of neoplastic transformation (Rodier and Campisi, 2011). Although senescent cells contribute to repair processes and are protected from malignant transformation, their age-related accumulation can at the same time promote a systemic chronic proinflammatory status that favors the development of the major age-related diseases sharing an inflammatory background and creates a pro-tumorigenic environment, contributing to carcinogenesis and metastasis formation (Rodier and Campisi, 2011; Schetter et al., 2010; Bonafè et al., 2012). In fact the inflammatory cytokines, chemokines, growth factors and extracellular matrix-degrading proteases secreted by senescent cells are capable of enhancing proliferation, invasiveness and angiogenesis of nearby premalignant tumor cells (Rodier and Campisi, 2011). Specifically, the SASP turns senescent fibroblasts into proinflammatory cells with the ability to promote tumor progression, partly by inducing epithelial-mesenchymal transition (EMT) in nearby epithelial cells (Laberge et al., 2012). Further, senescent fibroblasts and mesothelial cells secrete vascular endothelial growth factors (VEGF) (Coppè et al., 2006; Li et al., 2012a,b) that stimulate endothelial cell migration and invasion, two critical steps in tumor-initiated angiogenesis (Coppè et al., 2010; Kapoor and Deshmukh, 2012). Senescent fibroblasts and keratinocytes also secrete matrix metalloproteinases, which facilitate tumor cell invasion. Moreover the SASP is not a mere consequence of the senescence status, since its maintenance requires sustained and continuous signaling (Angelini et al., 2013). Cellular senescence, which is a well-established anticancer mechanism in young and adult individuals, can thus paradoxically promote cancer at an advanced age through its secretory phenotype. Clearly cancer is primarily an age-related disease, and accumulation of senescent cells during aging has been reported in a variety of mitotically competent mammalian tissues prone to cancer development and progression (Erusalimsky and Kurz, 2005; Jeyapalan et al., 2007; Wang et al., 2009). Moreover, the observation that the SASP is a feature not only of replicative senescence but also of oncogene-induced senescence (OIS) reinforces the hypothesis linking senescence-associated inflammation to cancer development (Ren et al., 2009). In particular, up-regulation of several inflammatory modulators has been described in different cell types undergoing OIS (Kuilman et al., 2008). In addition, introduction of oncogenic *RAS* into arterial smooth muscle cells induced OIS and enhanced expression of proinflammatory cytokines and chemokines (Minamino et al., 2003). Taken together these findings demonstrate that both replicative senescence and OIS activate an inflammatory response in cells of different origins.

Interestingly, the genetic patterns of cellular senescence show a high degree of similarity to those of the major age-related diseases, including CVD, T2DM and cancer (Jeck et al., 2012; Tacutu et al., 2011). Global transcriptome analysis of senescent cells disclosed a unique gene expression pattern that differs from those seen in proliferating cells and in cells undergoing quiescence or growth arrest induced by contact inhibition. Besides cell cycle regulatory genes other genes, including inflammation and stress-associated genes, DNA damage checkpoint genes, genes encoding extracellular matrix-degrading enzymes, cytoskeletal genes, and metabolic genes usually exhibit an altered expression during replicative and premature senescence and during development of age-related diseases (Jeck et al., 2012; Hardy et al., 2005).

According to a recent unified model, altered autophagy ("self-eating") could interconnect aging, inflammation and cancer (Lisanti et al., 2011). Autophagy is involved in major cancer networks, including those driven by p53, mammalian target of rapamycin (mTOR) complex, RAS and glutamine pathways, and also protects organisms against the development of other diseases, including inflammatory and neurodegenerative conditions (Liu et al., 2012). The aging process is associated with a decline in autophagic capacity that can lead to aberrant protein aggregation and accumulation of dysfunctional mitochondria (He et al., 2013a,b). These phenomena induce production of reactive oxygen species (ROS), which in turn can trigger inflammation *via* activation of inflammasomes, facilitating the development and progression of a number of human diseases including cancer (Salminen et al., 2012). In hepatocellular carcinoma, the most common primary malignant liver tumor, loss of toll-like receptor 2 (TLR-2)-mediated immune activity and the senescence status impair the autophagic process, leading to increased ROS production and DNA damage (Lin et al., 2012a,b).

Thus, even though cellular senescence is emerging as an effective transcriptional program that can be adaptively activated to promote the regenerative ability of damaged or aged tissues, it can paradoxically promote the development of the major age-related diseases at the same time. SASP identification therefore seems to have clinical relevance. Several markers have been identified that can, at least partially, discriminate senescence from other forms of growth arrest such as quiescence: (i) increased expression of senescence-associated β-galactosidase (SA-β-gal), a pH-dependent lysosomal β-gal encoded by the GLB1 gene, which partly reflects the increased lysosomal mass found in senescent cells (Lee et al., 2006); (ii) increased expression of $p16^{INK4A}$ and $p15^{INK4B}$, two small proteins involved in cell cycle arrest as inhibitors of cyclin-dependent kinases (CDKs) (Ren et al., 2009); (iii) increased expression of distinct chromatin structures known as senescence-associated heterochromatic foci, which may be responsible for the selective gene expression silencing required for the stability of the senescence transcriptional program (Ren et al., 2009); and (iv) telomere attrition and reduced telomerase activity, which impair replicative ability.

Notably, although most of these markers have been identified in senescent cells *in vitro*, a relationship between senescence of cultured cells and the organismal life span has never been proved conclusively (Campisi, 2001; Zhao et al., 2009). A recent study using stationary cells as an *in vitro* model of aging found more intracellular changes similar to those of an aging organism in stationary cell cultures than in cells undergoing replicative senescence (Khokhlov, 2013).

Several reports have documented the accumulation of senescent cells *in vivo* and their effects on the micro- and macroenvironment (Campisi and Sedivy, 2009). Progressive age-related accumulation

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Table 1
Main pathways linking inflammation, cellular senescence and cancer.

Pathways	Physiological effects
NF-κB signaling	Stress response
mTOR complex	Optimization of energy harvesting, autophagy
Sirtuins	Optimization of energy harvesting
TGF-β	Stress response
Wnt	Cell proliferation

mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; TGF-β, transforming growth factor β; Wnt, glycoproteins acting as ligands to produce cell responses playing a variety of important roles.

of senescent mesenchymal stem cells (MSCs) was reported in bone marrow of rhesus monkeys (Yu et al., 2011). Intrinsic age-related changes were also observed in human MSCs, contributing to the process of skeletal aging (Zhou et al., 2008). Increased numbers of senescent cells were noted in human tissues not only during normal aging, but also in damaged or wounded tissue (Campisi, 2011; Collado et al., 2005; Michaloglou et al., 2005). Senescent cells were also demonstrated in pathological states, such as degenerative aging diseases (Burton, 2009). Senescent cell accumulation was reported in hyperplastic, preneoplastic, and early neoplastic lesions, suggesting that they could stimulate proliferation of premalignant and malignant cells, thus contributing to carcinogenesis (Burton, 2009).

However, the extension of these findings to clinical research is currently hampered by the lack of specific cell senescence markers and of non-invasive techniques capable of assessing cellular senescence *in vivo* (Erusalimsky and Kurz, 2005).

Identification and validation of new molecules involved in SASP modulation would enhance our understanding of the molecular mechanism involved in physiological and pathological aging and provide new diagnostic tools and treatment options for patients with the major age-related diseases, including cancer. In this context, miRs are highly promising biomarkers of inflamm-aging, cellular senescence and cancer. Their emerging role as regulators of inflamm-aging, cellular senescence and cancer pathways is discussed herein and the hypothesis that some miRs modulate the processes involved in longevity is advanced and examined in relation to evidence obtained in centenarians.

1.1. Main pathways linking aging, cellular senescence and cancer

Over the past few years, several lines of evidence have disclosed that a number of pathways may be molecular interfaces connecting aging, senescence and cancer (Table 1).

Nuclear factor (NF)-κB signaling is among the pathways most closely involved in stimulating SASP acquisition and cancer development, and may therefore have an important role in inflammation as well as tumorigenesis (Ben-Neriah and Karin, 2011; Li et al., 2011; Karin, 2006; Salminen et al., 2012a; Olivieri et al., 2011; Quinn and O'Neill, 2011; Gorospe and Abdelmohsen, 2011). NF-κB is a family of structurally related transcription factors, that in mammals include RelA (p65), RelB, c-Rel, p50/p105, and p52/p100, which bind to DNA and regulate target gene transcription as homo- and heterodimers.

Interestingly, non-NF-κB-mediated pathways may also link inflammation, senescence and cancer. mTOR is a highly conserved serine/threonine kinase that controls cell growth and metabolism in response to nutrients, growth factors, cell energy imbalance and stress (Blagosklonny, 2011). mTOR complex 1 and 2 (mTORC1 and 2) regulate other important kinases, such as S6 kinase (S6K) and AKT (Zoncu et al., 2011). Over-activation of such sensory signal transduction pathways can cause cellular senescence and age-related diseases, including cancer, and shorten life span (Hall, 2008; Berman et al., 2012).

Sirtuins, a class of NAD(+)-dependent deacetylases, also play important roles in aging and common age-associated diseases (Morris, 2013). Whereas SIRT1 is well explored (Morris, 2013), a role is now emerging for other sirtuins as enhancers of fat metabolism and modulators of mitochondrial respiration to optimize energy production. Down-regulation of sirtuins can largely account for the patho-physiological changes taking place during aging, including cancer development. Indeed recent data indicate that down-regulation of SIRT genes may contribute to cancer development and trigger an increase in its malignancy (Lai et al., 2013).

The transforming growth factor (TGF)-β signaling pathway can interconnect inflammation, senescence and cancer. TGF-β has a dual role in tumor progression, initially as a suppressor and subsequently as a promoter. Autocrine TGF-β signaling is an integral part of the cellular anti-transformation network, inducing senescence in tumor cells and/or suppressing the expression of several genes, including p21-regulated genes, that mediate oncogene-induced transformation (Lin et al., 2012a,b; Wu et al., 2009; Senturk et al., 2010). However, even though TGF-β can hinder tumorigenesis by preventing cell proliferation or inducing apoptosis, during tumorigenesis cells can acquire invasive and metastatic phenotypes in response to it (Parvani et al., 2011). Recent findings indicate that the initiation of the oncogenic activity of TGF-β is dependent on imbalances between its canonical and non-canonical signaling systems (Parvani et al., 2011).

Canonical Wnt signaling, governed by its effector β-catenin, has long been known to play an important role in cell development, tissue homeostasis, and cancer (Kim et al., 2013). Wnt expression declines during aging, and activation of multiple pathways suppressing β-catenin-dependent signaling contributes to the initiation of senescence (Varecza et al., 2011). Moreover, it has recently been shown that expression of TRF2 protein, the DNA-binding protein essential for telomere protection and chromosome stability, is activated by the Wnt/β-catenin signaling pathway both in human cancer and normal cells (Diala et al., 2013). Overall, the Wnt/β-catenin pathway seems to play a critical role in aging (Zhang et al., 2011; Tsaousi et al., 2011). Interestingly, endothelial inflammation is regulated by β-catenin-independent Wnt signaling, suggesting an involvement of this pathway also in modulating inflammation (Kim et al., 2010). Recent studies describe deregulated Wnt signaling in degenerative and inflammatory CNS disorders, suggesting an involvement of Wnts in inflammation-driven brain damage and inflammation-directed brain repair (Marchetti and Pluchino, 2013).

1.2. MiRs targeting the NF-κB pathway: new potential biomarkers of inflamm-aging, cellular senescence and cancer

MiRs are a broad class of small, non-coding RNAs that have revolutionized our understanding of gene transcription and translation. More than 1000 human miRs have been identified, making them one of the most abundant classes of regulatory molecules (Park and Kim, 2013; Neilsen et al., 2012). MiRs were thought to act mainly as negative regulators of gene expression by binding to 3′-UTR regions of their target protein-coding mRNAs in a sequence-dependent manner (Nilsen, 2007; Baek et al., 2008). However, recent data show that miR regulation entails a far more complex post-transcriptional control, both repressing and activating gene expression, by interacting with complementary sequences in coding and non-coding regions of their mRNA targets (Breving and Esquela-Kerscher, 2010). Since the specificity of miR targeting is mediated only by 6–11 nucleotides, a single miR can target hundreds of mRNAs (Park and Kim, 2013). However, groups of miRs can induce regulation of specific biological processes by acting in a co-ordinated manner on pathways of functionally related genes (Cloonan et al., 2011). Thus, miRNAs have been proposed as the

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main players in the evolution of organismal complexity (Berezikov, 2011). Not surprisingly, miRs have recently been indicated also as regulators of organismal aging (Inukai and Slack, 2013).

MiRs have been reported to act through autocrine and/or paracrine mechanisms (Raitoharju et al., 2011; Kumarswamy et al., 2011). In addition, circulating miRs can act as hormones, eliciting a systemic response (Wahlgren et al., 2012). Recent studies show that transfer of nucleic acids, including miRs, can be an important means of intercellular communication. Transfer of information can occur by direct cell–cell contact, for instance *via* gap junctions, or by cell-contact-independent mechanisms, including release of microvesicles into surrounding tissue (Collino et al., 2010; Hosoda et al., 2011) or the blood stream; for example, plasma exosomes can deliver exogenous short interfering RNA to monocytes and lymphocytes (Wahlgren et al., 2012).

Discovery of the important role of miRs as gene expression regulators has shed light on a number of biological processes. Notably, several miRs contribute to the complex molecular mechanisms involved in cell growth, differentiation and survival, all processes related to cancer development and progression (Tacutu et al., 2011; Lovat et al., 2011; Keller et al., 2012). However they also play an important role in modulating inflammation and cellular senescence (Bhaumik et al., 2009; Tacutu et al., 2010), and miRs specifically involved in the inflammatory response have been shown to be modulated in both senescent and cancer cells (Paik et al., 2011; Schetter et al., 2010, 2009).

Most of the miRs targeting the NF-κB pathway and its modulators affect NF-κB signaling dynamics primarily through a negative feedback loop aimed at restraining the excessive proinflammatory response induced by signaling activation (Olivieri et al., 2012a,b; Zhao et al., 2011; Boldin and Baltimore, 2012; Vaz et al., 2011). An altered expression of the miRs targeting this pathway may thus contribute to the dysregulation of the inflammatory/anti-inflammatory balance, promoting carcinogenesis (Kundu and Surh, 2012). Moreover, it has recently been observed that miRs can act as agonists of single-stranded RNA-binding TLRs, inducing NF-κB signaling activation and interleukin secretion, thus triggering a proinflammatory response that can promote the creation of a microenvironment favorable to cancer development and growth (Fabbri et al., 2012, 2013). Therefore it is possible that senescent cells contribute to inflammation not only by producing proinflammatory and proangiogenic molecules typical of SASP, but also by transferring miRs into other proinflammatory cells, namely macrophages. This evidence raises a number of questions on the potential involvement of miRs in modulating two opposite phenomena, the irreversible growth arrest observed in replicative/OIS and carcinogenesis (Martinez et al., 2011a,b; Wang et al., 2012). It is therefore essential to identify the gene targets of these miRs and clarify how their products promote or inhibit senescence and/or cancer development.

Several miRs exert pleiotropic effects in controlling a number of important biological functions *via* well-connected networks, thus modulating shared target pathways. It is conceivable that secretion of SASP-associated miRs could be a component of the SASP signature, and that these miRs are deregulated both in cancer and in damaged and aged tissues (Wang et al., 2011; Rodier and Campisi, 2011). Here we discuss some miRs exerting pleiotropic effects on pathways related to inflammation, senescence, and carcinogenesis. Quite a large number of miRs have been reported to play a role in modulating cellular senescence and inflammatory responses (*SA-miRs* and *inflamma-miRs*, respectively). The most extensively studied *SA-miRs* and *inflamma-miRs* are listed in Tables 2 and 3. Given the interest elicited by this new area of research, more and more miRs are expected to be identified in the near future; some of them are likely to be regulators of inflammation and senescence. We selected a subset of miRs belonging to *SA-miRs* and *inflamma-miRs* that includes miR-9, -19b, -20a, -21, -29, -126, -145a, -155, -181a and let-7 (in bold in Tables 2 and 3). Interestingly, all these miRs, which we have identified on the basis of our experimental work and of literature data as being both *SA-miRs* and *inflamma-miRs*, are modulated in human cancers (Table 4).

Here we review and discuss in detail the role of miR-21 and -146a on NF-κB pathway modulation in aging and age-related diseases, because there is considerable evidence that they act as *SA-miRs* and *inflamma-miRs* and play a role in modulating NF-κB signaling (Anad and Cheresh, 2011; Zhou et al., 2011; Kumarswamy et al., 2011; Olivieri et al., 2013). MiR-126 is also included because it is involved in vascular function and inflammation by targeting adhesion molecules and members of NF-κB signaling, two phenomena that are related to cancer development and progression (Tetè et al., 2012; Oglesby et al., 2012). The complex scenario of the pleiotropic and cross-linked functions of miR-21, -126 and -146a in relation to the main processes and diseases associated with inflammation and cancer is illustrated using Ingenuity Pathway Analysis (Fig. 1).

2. MiR-21

MiR-21 is a well-known cancer-associated miR *(onco-miR)* that is overexpressed in most human tumors; it promotes malignant growth and progression by acting on multiple targets (Kumarswamy et al., 2011). Global miR expression analysis has disclosed that it is overexpressed in highly aggressive tumors. MiR-21 targets phosphatase and tensin homolog PTEN, an upstream negative regulator of mTOR. By targeting PTEN miR-21 leads to mTOR activation and consequently to tumor progression (Cingarlini et al., 2012); it also induces tumor angiogenesis and through it activation of the AKT and ERK1/2 signaling pathways, thereby enhancing hypoxia-inducible factor 1, alpha subunit (HIF-1α) and VEGF expression (Liu et al., 2011). Interestingly, miR-21 overexpression and NF-κB activation have been described in cancer, even though further evidence is needed to dissect the role of miR-21 in NF-κB signaling and inflammation (Ma et al., 2011).

Recent data support a critical role for DNA damage-induced NF-κB activation in promoting metastasis in breast cancer following genotoxic treatment, and miR-21 seems to contribute to this induction (Niu et al., 2012). Cell-type specificity may cause differences of miR-21 expression in NF-κB activity: in epithelial cells, miR-21 acts to down-regulate PTEN, activate AKT, and increase NF-κB activation; in LPS-stimulated macrophages, miR-21 negatively regulates programmed cell death 4 (PDCD4), which activates NF-κB through a still unknown mechanism (Ma et al., 2011).

An additional pro-tumorigenic effect of miR-21 is the formation of ROS, which mediate tumorigenesis and modulate EMT and the presence of cancer stem cells in the tumor, factors that contribute to tumor invasion and metastasis formation (Han et al., 2012).

Intriguingly, MiR-21 is also involved in promoting inflammation. Its overexpression enhances the inflammatory response by augmenting the expression of adhesion molecules in vascular cells, hence monocyte adhesion. Furthermore miR-21 is able to reduce the expression of potent human anti-inflammatory molecules such as interleukin (IL)-10 and TGF-β (Merline et al., 2011). In line with these findings we have recently identified increased circulating levels of miR-21 as a biomarker of inflamm-aging (Olivieri et al., 2012a,b). MiR-21 constitutes a direct link between the tumor-associated-inflammatory status and cancer development/progression: on the one hand, increased miR-21 levels in cancer and other age-related diseases could impair the anti-inflammatory response by making the cytokine profile more proinflammatory, on the other miR-21 could promote endothelial activation, enhancing the proinflammatory response. These data

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Table 2
Main senescence-associated miRNAs (*SA-miRs*).

MicroRNAs	Cell types	mRNA Targets	References
MiR-9	Mouse embryonic fibroblasts	SIRT1	Saunders et al. (2010)
MiR-10A*	Bone marrow-derived EPCs from mouse	Hmga2	Zhu et al. (2013)
MiR-17	Replicative cell aging models		Hackl et al. (2010)
MiR-19b	Replicative cell aging models		Hackl et al. (2010)
MiR-20◦	Replicative cell aging models		Hackl et al. (2010)
MiR-21	Human endothelial cells, bone marrow-derived EPCs from mouse	NFIB, CDC25A, Hmga2	Dellago et al. (2013), Zhu et al. (2013)
MiR-22	Human fibroblasts	CDK6, SIRT1, Sp1	Xu et al. (2011)
MiR-29◦	HeLa cell lines	B-Myb	Martinez et al. (2011a,b)
MiR-30	HeLa cell lines	B-Myb	Martinez et al. (2011a,b)
MiR-34◦	Rat bone marrow-derived EPCs, HUVECs, Primary human TIG3 fibroblasts, Mesangial cells	SIRT1, MYC, Txnrd2	Zhao et al. (2010), Ito et al. (2010), Christoffersen et al. (2010), Bai et al. (2011)
MiR-101	Human diploid fibroblasts	Ezh2	Greussing et al. (2013)
MiR-106	Human mammary epithelial cells, Replicative cell aging models	p21	Borgdorff et al. (2010), Hackl et al. (2010)
MiR-126	HAECs	VCAM-1	Rippe et al. (2012)
MiR-138	ATC	hTERT	Mitomo et al. (2008)
MiR-146a, miR-146b	Bone marrow derived DCs, Dermal fibroblasts, HUVECs, Trabecular meshwork cells, Fibroblasts, Primary human TIG3 fibroblasts	IRAK-1, TRAF-6	Park et al. (2012), Olivieri et al. (2011), Li et al. (2010a,b), Bhaumik et al. (2009), Christoffersen et al. (2010)
MiR-152	Dermal fibroblasts	integrin α5, collagen XVI	Mancini et al. (2012)
MiR-155	Bone marrow-derived DCs, HDFs	DC-SIGN c-Jun	Park et al. (2012), Song et al. (2012)
MiR-181◦	Dermal fibroblasts, CD4(+) T cells	integrin α5, collagen XVI	Mancini et al. (2012), Li et al. (2012a,b)
MiR-191	Keratinocytes	SATB1, CDK6	Lena et al. (2012)
MiR-217	HUVECs, HAECs, HCAECs	SIRT1	Menghini et al. (2009)
MiR-221	HAECs	eNOS	Rippe et al. (2012)
MiR-222	HAECs	eNOS	Rippe et al. (2012)
MiR-299-3p	Endothelial cells	IGF1	Jong et al. (2013)
MiR-335	Mesangial cells	SOD2	Bai et al. (2011)
MiR-519	WI-38 human diploid fibroblasts	HuR	Marasa et al. (2010)
Let-7	MEFs Premalignant cancer cells	EZH2 RB1/E2F	Toledano (2012), Tzatsos et al. (2011), Benhamed et al. (2012)

ATC, anaplastic thyroid carcinoma; B-Myb, transcription factor involved in cell cycle progression; CDC25A, cell division cycle 25 homolog A; DCs, dendritic cells; HUVECs, human umbilical cord vein endothelial cells; HAECs, human aortic endothelial cells; HeLa, cervical carcinoma cells; Hmga2, high-mobility group AT-hook 2; HCAECs, human coronary aortic endothelial cells; HDFs, human dermal fibroblasts; hTERT, human telomerase reverse transcriptase; HuR, an RNA-binding protein that regulates mRNA turnover and/or translation; EPCs, endothelial progenitor cells; MEFs, primary mouse embryonic fibroblasts; SIRT1, silent information regulator 1; Txnrd2, thioredoxin reductase 2; SOD2, superoxide dismutase 2; SIRT1, silent information regulator 1; RB1/E2F, retinoblastoma (RB1)/E2F repressor complex; EZH2, Histone-lysine N-methyltransferase; NFIB, nuclear factor I/B; In bold miR common to *SA-miRs* and *inflamma-miRs*.

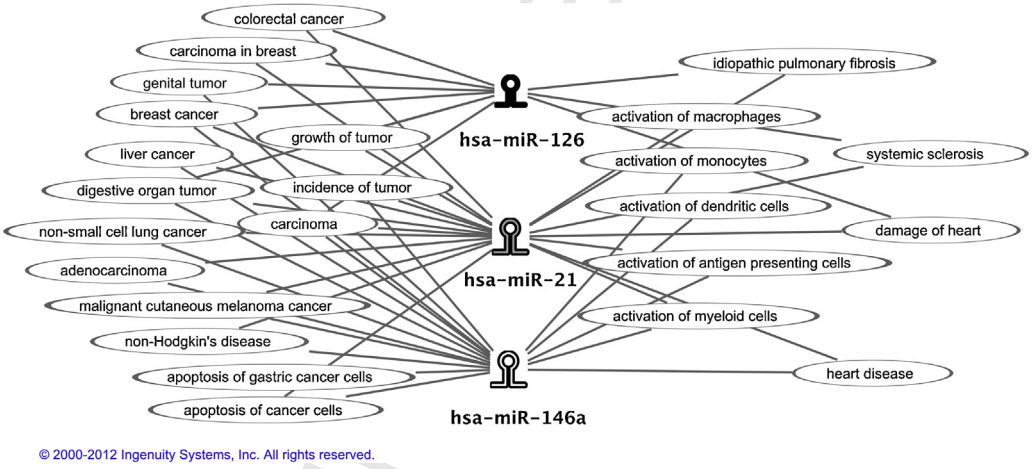

Fig. 1. Involvement of miR-21, miR-126 and miR-146a in carcinogenesis and the proinflammatory response. Diagram generated by Ingenuity Pathway Analysis summarizing the diseases related to cancer and inflammation where miR-21, -126 and -146a were reported to be involved. Has: human.

suggest that accumulation of dysfunctional circulating endothelial progenitor cells during aging may contribute to miR-21 release into the blood stream. As mentioned above, it has recently been reported that cancer cell-secreted miRs can be internalized *via* endocytosis by macrophages close to the tumor interface and interact with TLRs (Fabbri et al., 2012). In particular, miR-21 binds to TLR-8, and induces secretion of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-6.

A clinical model where inflammation and cancer are closely linked is inflammatory bowel disease (IBD), which includes

Table 3
Main inflammation-associated miRNAs (*inflamma-miRs*).

MiRs	Cell types	mRNA targets	Signaling	References
MiR-9	Polymorphonuclear neutrophils and monocytes	NFK-B1	TLRs	Bazzoni et al. (2009)
MiR-10a	HAECs	HOXA1	TLRs	Fang et al. (2010)
MiR-19a	FLCs	ASK	TLRs	Philippe et al. (2012)
MiR-19b				
MiR-20◦	FLCs	ASK	TLRs	Philippe et al. (2012)
MiR-21	Monocytes	TLR-8	TLRs	Fabbri et al. (2012), Yao et al.
	Myofibroblasts,	PDCD4	TLRs	(2011), Zhou et al. (2011)
	HUVECs	PPARα		
MiR-29a	Immune cells	TLR-8	TLRs	Fabbri et al. (2012)
MiR-125a	Diffuse large B-cell lymphoma	TNFAIP3	TLRs	Kim et al. (2012)
MiR-125b				
MiR-126	ECs, ECs, Human colon-derived	VCAM-1	Vascular inflammation	Harris et al. (2008), Oglesby et al.
	myofibroblasts, Renal	TOM1	TLRs	(2012), Angel-Morales et al. (2012),
	microvascular ECs	VCAM-1	vascular inflammation	Asgeirsdóttir et al. (2012)
		VCAM-1	"..."	
MiR-146a	Intestinal epithelial cells,	IRAK-1	TLRs	Chassin et al. (2012), Iyer et al.
	Astrocytes, HUVECs, HUVECs,	IRAK-1	TLRs	(2012), Olivieri et al. (2012a,b), Liu
	Myofibroblasts	IRAK-1	TLRs	et al. (2012)
		SMAD4	TGF-β	
MiR-155	MSCs	TAB2	iNOS	Xu et al. (2013), Nazari-Jahantigh
	Macrophages	BCL6	TLRs	et al. (2012), Sun et al. (2012a)
	Macrophages	SOCS1	TLRs	
MiR-181a	Monocytes and macrophages,	IL-1◦	ox-LDL-inflammation	Xie et al. (2013), Wu et al. (2012)
	Cultured bone marrow-derived	c-Fos	responses	
	DCs			
MiR-181b	Ecs	Importin-α3	NF-κB	Sun et al. (2012b)
MiR-187	Primary human monocytes	TNF-α	TLRs	Rossato et al. (2012)
		IκBζ		
MiR-195	Hepatocellular carcinoma Cultured	IKKα, TAB3	TLRs	Ding et al. (2013), Shi et al. (2013)
	microglia	ATG14	LPS-induction of inflammatory	
			cytokines	
MiR-199◦	Endometrial stromal cells	IKKβ	TLRs	Dai et al. (2012)
MiR-223	Macrophages	NLRP3	Inflammasome	Ismail et al. (2013), Haneklaus et al.
				(2012)
MiR-517a/c	Cell lines	TNIP1	TLRs	Olarerin-George et al. (2013)
Let-7	Primary cultured T cells,	TLR-4	IL-13	Kumar et al. (2011), Chen et al.
Let-7i	Biliary epithelial cells		TLRs	(2007)

ASK, apoptosis signal-regulating kinase 1; DCs, dendritic cells; ECs, endothelial cells; FLSs, fibroblast-like synoviocytes; HAECs, human aortic endothelial cells; HOXA1, Homeobox A1; HUVECs, human umbilical vein endothelial cells; IRAK-1, interleukin-1 receptor-associated kinase 1; IKK, IκB kinase; iNOS, inducible NO synthase; MSCs, mesenchymal stem cells; PDCD4, programmed cell death 4; PPARα, peroxisome proliferator-activated receptor-α; TNIP1, TNFAIP3-interacting protein 1; SOCS, suppressor of cytokine signaling; SMAD4, SMAD family member 4; TAB2, TAK1-binding protein 2; TNIP1, TNFAIP3 interacting protein1; TOM1, target of Myb1; VCAM-1, vascular cell adhesion molecule 1. In bold miR common to *SA-miRs* and *inflamma-miRs*.

Table 4
Q6 Common *SA-miRs* and *inflamma-miRs* involved in human malignancies.

MiRs	Cancers	References
MiR-9	NPC	Gao et al. (2013)
MiR-19b	DLBCL	Fassina et al. (2012)
MiR-20a	DLBCL	Fassina et al. (2012)
MiR-21	Virtually all human cancers	Ma et al. (2013)
MiR-29a	Breast cancer	Wang et al. (2013)
MiR-126	NSCLC OSCC	Yang et al. (2012), Jusufović et al. (2012), Sasahira et al. (2012)
MiR-146a	NSCLC Gastric cancer	Chen et al. (2013), Yao et al. (2013)
MiR-155	Various carcinomas	He et al. (2013a,b), Yang et al. (2013)
MiR-181a	Hematological malignancies	Lin et al. (2013)
Let-7	Various carcinomas	Wang et al. (2012)

NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; NPC, nasopharyngeal carcinoma; DLBCL, diffuse large B-cell lymphoma.

conditions such as ulcerative colitis and Crohn's colitis. IBD creates the pathological conditions for colorectal cancer (CRC) development (Ludwig et al., 2012); the PDCD4 tumor suppressor gene is involved in colon carcinogenesis and its down-regulation is significantly associated with miR-21 up-regulation. These data document a direct link among miRs, inflammation and CRC development (Okayama et al., 2012).

A recent paper has documented that miR-21 links senescence/replicative life span and angiogenesis in normal human endothelial cells (Dellago et al., 2013). Transfection of early passage endothelial cells with miR-21 resulted in reduced angiogenesis and cell proliferation rates, while its overexpression reduces the replicative life span while stable knockdown extends the replicative life span (Dellago et al., 2013).

3. MiR-126

Functional *in vitro* studies have shown that some miRs are critical for gene expression and endothelial cell function. Mir-126,

a human miR whose expression has been found to be typical of endothelial cells of capillaries and larger blood vessels, is considered as a master regulator of physiological angiogenesis. It acts on various transcripts by modulating vessel stabilization and maturation (Wang et al., 2008; Sessa et al., 2012). Among its main protein targets, the epidermal growth factor-like domain 7 (EGFL7) gene is involved in cell migration and blood vessel formation (Sun et al., 2010a). MiR-126 has recently been reported to be expressed in hematopoietic stem cells (HSCs) and to play a pivotal role in restraining HSC cell-cycle progression by targeting multiple genes belonging to the phosphatidylinositol 3-kinase (PI3K)/serine/threonine protein kinase AKT/glycogen synthase kinase 3 (PI3K/AKT/GSK3) pathway (Lechman et al., 2012). These data indicate that miR-126 sets a threshold for HSC activation, controlling their pool size. MiR-126 has also been assigned major developmental roles in the heart through activation of survival kinases ERK1/2 and AKT and enhancement of proangiogenic signaling (Shi et al., 2012).

Interestingly, tissue inflammation is critically regulated by miR-126 both *in vitro* and *in vivo, via* modulation of the expression of cell adhesion proteins such as VCAM-1 (Harris et al., 2008; Asgeirsdóttir et al., 2012; Qin et al., 2011). In a renal inflammation model, the inflammatory challenge unleashed VCAM-1 protein expression in the glomeruli of mice with knockdown of miR-126 function, suggesting that it has a major role in the response of renal microvascular endothelial cells to systemic inflammatory stimuli (Asgeirsdóttir et al., 2012). Accordingly, miR-126 is also deregulated in several disorders characterized by endothelial cell activation in response to systemic inflammatory stimuli, including CVD, diabetes mellitus and inflammatory diseases (Mocharla et al., 2013; Feng et al., 2012; Zampetaki et al., 2012). Interestingly, miR-126 can play an important role in the modulation of inflammatory activity by down-regulating the expression of IKBA, an important inhibitor of the NF-κB signaling pathway (Feng et al., 2012). MiR-126 was also reported to target TOM1 (target of Myb1), which has been shown to interact with toll-interacting proteins in TLR-2/-4 signaling pathways, forming a complex to regulate endosomal trafficking of ubiquitinated proteins (Oglesby et al., 2012).

Altered miR-126 expression has been documented in various cancers, acting as a tumor suppressor or as an oncogene depending on cancer type (Yang et al., 2012; Otsubo et al., 2011).

It is a tumor-suppressor gene in non-small cell lung cancer (NSCLC), repressing the activity of the PI3K-AKT pathway by targeting binding sites in the 3′-UTR region of PI3KR2 mRNA (Yang et al., 2012). Accordingly, NSCLC patients with low miR-126 expression had significantly shorter survival time than those with high miR-126 expression (Yang et al., 2012; Jusufović et al., 2012). EGFL7, which is involved in cell responses such as cell migration and blood vessel formation, was identified as miR-126 target in NSCLC cells (Sun et al., 2010b).

In gastric cancer, aberrant over-expression of miR-126 and down-regulation of its target SRY (sex-determining region Y)-box 2 (SOX2) contributes to carcinogenesis (Otsubo et al., 2011). SOX2 is a crucial transcription factor with important roles in growth inhibition through cell cycle arrest and apoptosis. Over-expression of miR-126 was also induced in oral squamous cell carcinoma (OSCC) cells, showing an association with tumor progression, nodal metastasis and vessel density (Sasahira et al., 2012). Interestingly, decreased miR-126 expression strongly correlated with disease-free survival in OSCC patients (Sasahira et al., 2012).

MiR-126 therefore has a dual role: as an oncosuppressor it inhibits cell proliferation, migration, invasion and survival; as an oncogene it supports cancer progression by promoting blood vessel formation and inflammation at the site of endothelial cell activation (Meister and Schmidt, 2010).

4. MiR-146a

It has recently been documented that miR-146a plays a key role as a modulator of the innate immune response (Labbaye and Testa, 2012). Such response is induced through TLRs, and two key adapter molecules in the TLR/NF-κB pathway, TRAF6 and IRAK1, have been identified as miR-146a direct targets (Hou et al., 2009). This suggests a negative regulatory loop where NF-κB activation up-regulates the miR-146 gene, which upon processing down-regulates IRAK1 and TRAF6 to reduce NF-κB activity. Macrophages are the main cell type involved in inflammatory response modulation, mainly through TLR pathway activation. However, our group has recently described increased *in vitro* expression of miR-146a in human umbilical vein cells (HUVECs) and in aortic and coronary endothelial cells (respectively HAECs and HCAECs) during replicative senescence, thus demonstrating that endothelial cells may play an important role in this process (Olivieri et al., 2012a,b). Similar to macrophages and fibroblasts all three cell types acquired the SASP during replicative senescence despite the fact that miR-146a overexpression should physiologically prevent its acquisition by promoting an anti-inflammatory response. Surprisingly, several studies have shown the pathological relevance of NF-κB/miR-146a dysregulation in human cancers, including breast and pancreatic cancer, anaplastic thyroid carcinoma, and brain tumors (Bhaumik et al., 2008; Lukiw et al., 2008; Hurst et al., 2009; Li et al., 2010a,b; Pacifico et al., 2010). A contribution of miR-146a deregulation to the development and maintenance of neoplastic processes has been documented by several researchers (Labbaye et al., 2012; Hurst et al., 2009; Li et al., 2010a,b). However, its mechanism of action remains unclear, since both increased and decreased levels have been described in different type of cancers: up-regulation in papillary thyroid carcinoma and cervical, breast, and pancreatic cancer, and down-regulation in prostate cancer (Williams et al., 2008). Since miR-146a participates in a negative feedback loop modulating inflammation, dynamic changes in its expression can be expected in tissues exhibiting different degrees of inflammation.

Interestingly, mice with miR-146a deletion spontaneously developed subcutaneous flank tumors (Zhao et al., 2011). Moreover miR-146a has been reported to suppress metastatic activity (Hwang et al., 2012; Hou et al., 2012). In particular, its up-regulation inhibits cancer cell invasion and metastasis *in vitro* and *in vivo* (Hou et al., 2012).

Low miR-146a expression in NSCLC correlated with advanced clinical TNM stages and distant metastasis, whereas high miR-146a levels in the tumor was associated with longer progression-free survival (Chen et al., 2013).

Altogether these findings show that by counteracting the proinflammatory status associated with cellular senescence, miR-146a can exert anti-inflammatory effects and a general tumor suppressor action by inhibiting tumor development and cancer cell invasion and metastasis.

4.1. SA-miRs and inflamma-miRs modulation in centenarians

Cancer incidence and mortality increase exponentially with age, peaking at 80–85 years (Fulop et al., 2010). Quite surprisingly they then decline; accordingly, cancer is relatively uncommon as a disease and as a cause of death among the very old (Pavlidis et al., 2012; Salvioli et al., 2009).

A number of genetic variants predisposing to cancer have been described in healthy centenarians, who also displayed high levels of proinflammatory molecules (Bonafè et al., 1999). These findings seem to contradict the data regarding the interconnection of cancer and inflammation discussed above. To reconcile these conflicting notions it has been proposed that the large amounts of

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proinflammatory modulators found in centenarians are offset by high levels of anti-inflammatory molecules such as IL-10 and TGF-β (Vasto et al., 2007; Franceschi et al., 2007). According to another hypothesis the levels of proinflammatory molecules are not critical in themselves, but are more or less dangerous depending on the tissue where they are produced (muscle, adipose tissue, epithelia, *etc.*) (Salvioli et al., 2012). The latter concept has not yet been tested, since the capacity of different tissues and cells to produce proinflammatory molecules has not been compared in centenarians and young or younger (70–80 year olds) individuals. Similarly, no data are available on the body composition (total amount of fat mass, lean and fat mass ratio, *etc.*) of centenarians. Nonetheless these individuals seem to be endowed with a resistance to cancer whose underlying mechanisms are still unclear (Bonafè et al., 2011). Given the involvement of miRs in gene expression regulation, a peculiar modulation of their expression might contribute to efficient homeostasis in centenarians. To date only four studies have compared the miR expression profile of centenarians and younger subjects. Although they examined different samples from widely different individuals, *i.e.* peripheral blood mononuclear cells (PBMCs) from Spanish donors (Serna et al., 2012); B lymphocytes from Ashkenazi Jews (Gombar et al., 2012); plasma from Italian subjects (Olivieri et al., 2012a,b), and whole blood from German individuals (ElSharawy et al., 2012), all four studies found a significant overlap between the miR profiles of centenarians and of young individuals, and a different profile in octogenarians. These findings lend support to the hypothesis that achievement of extreme longevity probably requires a special gene expression regulation (Serna et al., 2012; Olivieri et al., 2012a,b).

Notably, age-related changes have been demonstrated in circulating miR-19b, miR-21, miR-126 and miR-146a, which are among the more common *SA-miRs*, *inflamma-miRs* and *onco-miRs* (Olivieri et al., 2012a,b; *our unpublished data)*. Different miR-19b levels were also reported in PBMCs from octogenarians compared with centenarians and young individuals (Serna et al., 2012).

Significant modulation of miR-20a, -106a, -126 and -155, but not of miR-19b, was reported in whole blood of old subjects (ElSharawy et al., 2012). Interestingly, miR-21 was deregulated in all studies comparing the miR expression profile of centenarians and younger subjects. Significant modulation of miR-21 expression in circulating cells and plasma of centenarians is not surprising to those who advocate that miR-21 lies at the intersection of senescence, inflammation and age-related diseases. However, its expression was significantly higher in PBMCs (Serna et al., 2012) and B lymphocytes (Gombar et al., 2012) *from* centenarians compared to 20-year olds and octogenarians, whereas its levels in plasma (Olivieri et al., 2012a,b) *and whole blood* (ElSharawy et al., 2012) were higher in old individuals than in 20-year olds, and higher in octogenarians than in centenarians. Only whole blood showed miR-21 down-regulation in centenarians compared to younger subjects (ElSharawy et al., 2012). Since whole blood is a combination of plasma and PBMCs, such discrepancies could be related to different age-related expression profiles in different biological samples. A direct comparison of the miRNome of whole blood and of serum and hematopoietic subpopulations (*e.g.* lymphocytes, monocytes and circulating progenitor cells) from subjects with different malignant and non-malignant diseases is clearly warranted.

5. Conclusions

MiRs are indisputably opening a new era in the fields of systemic and tissue-specific biomarkers, intercellular and perhaps inter-organ communication mechanisms, and therapeutic strategies. Recent evidence suggests that a number of miRs, including miR-21, -146a and -126, modulate some pathways (*e.g.* NF-κB) related to cellular senescence, inflammation, angiogenesis, physiological aging and development of age-related diseases, including cancer.

Cancer development is largely avoided or delayed in centenarians, subjects who have reached the extreme boundaries of the human life span. In these individuals changes in some miRs involved in cancer, like miR-21, are found both in plasma and leukocytes, further suggesting that a peculiar modulation of this family of small regulators may have a role in preventing development of aggressive cancer disease. It is therefore conceivable that strategies aimed to regulate their expression could help treat a number of age-related conditions (Nana-Sinkam and Croce, 2013; Zhong et al., 2013; Bao et al., 2012; Zhu et al., 2012; Bader, 2012). Given the complexity of *in vivo* miRNA targeting, including toxicity and target specificity issues, few studies using this approach have reached the clinical trial stage; the most advanced among them currently involves miR-122 targeting in hepatitis C (Machlin et al., 2012).

Modulation of miR-21, -126 and 146a to inhibit cancer cell growth and enhance the cytotoxicity of antitumor agents is being investigated. Some of the miR-21 protein targets modulate TNF-related apoptosis-inducing ligand (TRAIL) resistance both in human glioblastoma primary cells and in lung cancer cells (Quintavalle et al., 2012). High miR-21 expression levels are needed to maintain the TRAIL-resistant phenotype, making this miR a promising therapeutic target. *T*he combination of miR-21 knockdown with neural precursor cells that secrete a recombinant TRAIL (TNF ligand superfamily, member 10) protein sensitizes gliomas to cytotoxic therapy *in vitro* and *in vivo* (Corsten et al., 2007; Leal et al., 2013).

A greater understanding of miR sources and regulation, identification and validation of their target genes and target tissue specificity, and development of safe and effective delivery strategies would considerably enhance their therapeutic potential. Coupling engineered exosomes to nanotechnology would promote the development of immunotherapy approaches and cancer vaccines; eventually, the insertion of specific miRs (or antagomiR) directed against specific cells or tissues could be decisive to achieving therapeutic advances (Tan et al., 2010; Ohno et al., 2013).

Lowering the threshold of cellular senescence through inhibition of CDK regulators has recently been suggested as a new potential approach to cancer treatment (Ling et al., 2012) as has the use of strategies aimed at controlling NF-κB-related inflammation during normal and pathological aging (Osorio et al., 2012). However, modulation of cellular senescence and age-associated inflammation to destroy cancer cells requires further investigation. To do this, *in vivo* strategies to eliminate senescent cells or the effects of SASP acquisition from cancer-prone tissues need to be developed. MiR-21, miR-146a and miR-126 emerge as promising candidates for the development of new direct and indirect therapeutic strategies against several cancers and other age-related diseases.

Uncited references

Q4

Dommisch et al. (2011), Liu and Ryan (2012), and Yang and Ming (2012).

Conflicts of interest

The authors have no conflicts of interest.

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