Ageing Research Reviews xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

MicroRNAs linking inflamm-aging, cellular senescence and cancer

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ARTICLE INFO

Article history:
Received 31 January 2013
Received in revised form 30 April 2013
Accepted 8 May 2013
Available online xxx

Keywords:
MicroRNA
Cancer
Inflamm-aging
Centenarians
Cellular senescence
NF-κB

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.

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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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1568-1637/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.arr.2013.05.001

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

Please cite this article in press as: Olivieri, F., et al., MicroRNAs linking inflamm-aging, cellular senescence and cancer. Ageing Res. Rev. (2013), http://dx.doi.org/10.1016/j.arr.2013.05.001