International Research Journal of Advanced Engineering and Science
ISSN (Online): 2455-9024

The Role of MicroRNA as Regulator of Aging Cell

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Abstract*—Cells are exposed to various stresses on lifespan. The cell reacts in two ways to long-term stress. One is cell senescence and the other is tumor cell. The gene expression pattern changes in both the process of normal cells leading to cell senescence or cancer cells. miRNAs play a leading role in changes in gene expression patterns. In near future, miRNA ATLAS will give us a great deal of hints for treating the disease. Recent miRNAs have emerged as a central theme in recent medical research*.

***Keywords*—** *Cell Senescence, Senescence-Associated Secretory Phenotype (SASP). Senescence-Associated Heterochromatic Foci (SAHF). Oncogene-Induced Senescence (OIS).*

I. INTRODUCTION

Aging is the progressive loss of tissue and organ function over time.[1.] A person getting older is cell senescence. The aging of a cell is the arrest of an irreversible cell cycle. The condition in which a cell no longer replicates is called cell senescence. Even if cells become senescent, cell metabolism continues and cell death does not occur. The arrest of the cell cycle is a loss of replicative ability. Cell senescence is different from the loss of permanent replicative ability. Studies show that cancer cells are produced in senescent cells. This is because cancer cells represent the operation of the cell cycle. Aging cells have a double destiny. One is choosing apoptosis to death and the other is rejecting apoptosis and surviving. aged cells that chronically accumulate damage ultimately reach a threshold of cellular stress that prompts their permanent withdrawal from the cell cycle. Cell senescence is another way of cell survival. However, cell senescence sometimes develops into cancer cells. The expression pattern of genes differs between aged cells in which the cell cycle is stopped and young cells in which the cell cycle returns. The number of replication has been determined from cell birth. Cells with high numbers of replication are slower in cell aging than those with few replicative times. For the scientific discovery for anti-aging, it necessary to know the mechanism of aging, ie, cellular senescence. Recent molecular biology has provided us with specific causes of cell senescence. For prolong life through antiaging, it is necessary to understand aging mechanism first. Recently, studies on antiaging by miRNA have been actively carried out. This study purposes to identify the mechanism of anti-aging by miRNA and to diagnose the future of biotechnology to antiaging.

Cellular Senescence

In 1961, and in contradiction to what was thought at the time, Leonard Hayflick and Paul Moorhead discovered that human cells derived from embryonic tissues could only divide a finite number of times in culture[1].

The seminal discovery of replicative senescence by Hayflick and Moorehead was the beginning of speculation that senescence and aging might be causally linked[2]. Barbara McClintock showed that the ends of chromosomes are capped by a structure called the telomere to prevent chromosome fusions[3]. The ends of linear chromosomes are capped by specialized nucleoprotein structures termed telomeres. Telomeres, noncoding hexanucleotide repeat sequences, protect against degradation, rearrangement, and chromosomal fusion events. A net loss of telomeric sequences occurs at each cell division. The cumulative telomeric erosion is a limiting factor in replicative capacity and elicits a signal for the onset of cellular senescence. Cellular senescence, a state of irreversible growth arrest, can be triggered by multiple mechanisms including telomere shortening, oncogene activation, irradiation, DNA damage and oxidative stress. It is characterized by enlarged flattened morphology, senescence-associated beta-galactosidase (SA-b-gal) activity, secretion of inflammatory cytokines, growth factors and matrix metalloproteinases, as part of the senescence-associated secretory phenotype (SASP). Cellular senescence is functionally associated with many biological processes including aging, tumor suppression, placental biology, embryonic development, and wound healing. The senescence growth arrest is essentially permanent and cannot be reversed by known physiological stimuli. However, some senescent cells can resume growth after genetic interventions, such as mutation of p53 tumor suppressor[4.] Cellular senescence is an important mechanism for preventing the proliferation of potential cancer cells. The limited growth of human cells in culture is due in part to telomere erosion, the gradual loss of DNA at the ends of chromosomes (telomeres)[4]. Senescent cells increase in size, sometimes enlarging more than twofold relative to the size of non-senescent counterparts[1]

Cellular senescence Stage 1, 2, 3

The mammalian cell cycle is divided into four phases that include mitosis (M), DNA synthesis (S), and the gap phases G1 and G2. Cell cycle entry and progression require that specific proteins are expressed at well-defined time points. Progression through the cell division cycle is driven by cyclin-dependent kinase (CDK), which are bound and activated by cyclins. p53 is a sequence-specific DNA-binding transcription factor that promotes senescence in part through its ability to induce the cyclin-dependent kinase (CDK) inhibitor p21 and the anti-proliferative microRNA miR-34[9]. In contrast, RB promotes senescence by stimulating a repressive chromatin environment that leads to the stable suppression of proliferative genes, perhaps through the production of senescence-associated heterochromatic foci (SAHF)[8] or by facilitating the accumulation of repressive histone marks on proliferation-responsive genes[9.] RB plays a nonredundant role in its ability to promote E2F target gene repression and cell

Chae Rin Oh, "The Role of MicroRNA as Regulator of Aging Cell," *International Research Journal of Advanced Engineering and Science*, Volume 3, Issue 4, pp. 39-42, 2018.

cycle arrest during senescence, particularly on E2F-responsive genes required for DNA replication[9]. The senescence program is driven by a complex interplay of signaling pathways[6]. To promote and support cell cycle arrest, p16, accompanied by the p53 (TP53)[7], target p21, inhibits cyclin-dependent kinases (CDKs), thereby preventing phosphorylation of the retinoblastoma protein (pRb) and thus in turn suppressing the expression of proliferation-associated genes such as E2F[5]. Cellular senescence is associated with ageing and cancer *in vivo* and has a proven tumour-suppressive function. Common to both ageing and cancer is the generation of DNA damage and the engagement of the DNA-damage response pathways[10]. The DNA damage response (DDR) orchestrates DNA repair and halts cell cycle. If damage is not resolved, cells can enter into an irreversible state of proliferative arrest called cellular senescence.[11] Cellular senescence is a potent tumor-suppressive mechanism that arrests cell proliferation[13]. Because senescence plays the important role in both normal physiology and diverse pathologies it is important to well understand its molecular bases. Down-regulation of lamin B1 is a novel biomarker for senescence[14]. The inner surface of the nuclear envelope is lined by a lamina, which contributes to the size, shape, and stability of the nucleus[14]. The lamina is a dynamic structure because each time a cell enters mitosis, it is disassembled and then reassembled in the next cell cycle[14]. While loss of lamin B1 plays a key role in senescence-associated changes in chromatin organization[15.] Senescent cells adopt development of a senescence-associated β-galactosidase (SA-βgal) activity[13], which is often used to detect senescent cells in culture and in vivo[14] Senescent cells also show widespread changes in gene expression, leading in part to a senescence-associated secretory phenotype (SASP)—the robust secretion of numerous cytokines, growth factors, and proteases[13] . The loss of LB1 might be involved in the architectural changes to chromatin and formation of SAHF. The down-regulation of Lamin B1 in the beginning of senesce results in the detachment of centromeric heterochromatin containing the H3K9me3 modification from lamina, relocation to the nucleoplasm and distension showing that this down-regulation of Lamin B1 is necessary for the release of heterochromatin from binding to the lamina, to achieve changes in chromatin architecture and regulation of gene expression leading to stop of cell proliferation[16]. Oncogene-induced cellular senescence (OIS) is a complex program that is triggered in response to aberrant activation of oncogenic signaling.oncogene-induced senescence is caused by an accumulation of DNA damage[17]. The DNA damage response is triggered by excessive replication caused by a sustained oncogenic signal[16]. Oncogene-induced senescence is triggered by high level of RAS/RAF/MAPK signaling that can be caused, for example, by oncogenic mutations in RAS or RAF proteins, or by oncogenic mutations in growth factor receptors, such as EGFR, that act upstream of RAS/RAF/MAPK cascade[17]. Oncogene-induced senescence can also be triggered by high transcriptional activity of E2F1, E2F2 or E2F3 which can be caused, for example, by the loss-of-function of RB1 tumor suppressor[17]. Activation of oncogenic signaling paradoxically results in the permanent withdrawal from cell cycle and induction of senescence (oncogene-induced senescence (OIS)). OIS is a fail-safe mechanism used by the cells to prevent uncontrolled tumor growth, and, as such, it is considered as the first barrier against cancer. In order to progress, tumor cells thus need to first overcome the senescent phenotype[18]. Histone modifications have critical roles in regulating the expression of genes during in mammals[19]Histone H3 lysine 4 trimethylation (H3K4me3) and histone H3 lysine 27 trimethylation (H3K27me3) are associated with gene activation and repression[19]. This bivalent chromatin is characterized by being marked with opposing histone modifications that correlate with both "repressive" and "active" gene expression. It is important to note that while total histone H3 decreases significantly during senescence as measured by Western blot, the relative levels of H3K4me3 and H3K27me3 (normalized to histone H3) do not significantly change between proliferating and senescent cells[20]. Notably, H3K4me3 is surprisingly enriched across the genome in extremely large domains, often hundreds of kilobases in senescent cells[20].

Enhancers near key senescence genes are often contained within K27me3, where the H3K27me3 loss is also associated with up-regulated SASP(the senescence-associated secretory phenotype) gene expression[20]. The level of H3K27me3 significantly decreases in somatic cells during aging[21]. H3K27me3 loss at enhancer regions may play an important role in regulating transcriptional changes in senescence.[20] During replicative and oncogene-induced senescence, chromatin fragments are extruded from the nucleus, where they are targeted and processed by the autophagy/lysosomal pathway. This leads to the depletion of histone proteins and may contribute to the stability of senescence. The SASP in senescent cells alter tissue microenvironments, attract immune cells, and, ironically, induce malignant phenotypes in nearby cells[22]. Proteins that are associated with the SASP, such as TNF-α, IL-6, MMPs, monocyte chemoattractant protein-1 (MCP-1), and IGF binding proteins (IGFBPs), increase in multiple tissues with chronological aging[22], and occur in conjunction with sterile inflammation[21]. Furthermore, expression of the SASP components is much higher in $p16^{INK4a}$-positive senescent cells compared with non-senescent cells from the same tissue[22].

miRNA & Cellular Senescence

MicroRNAs are small (~22 nt), noncoding, regulatory RNAs that control gene expression post-transcriptionally by binding to the 3 UTR of mRNA and promote mRNA degradation or inhibit protein translation[23]. The most studies about miRNAs are well explored for their roles in various physiological and pathological conditions. The biogenesis of miRNA begins in the nucleus where miRNA genes are transcribed by RNA polymerase II or III into long primary transcripts (pri-miRNAs) that are polyadenylated at the 3 end and capped at the 5 end[23]. miRNAs, these short non-coding molecules ranging in size from 19 to 22 nucleotides are highly conserved and regulate protein expression through interactions

with the 3′ untranslated region (UTR) of mRNA[23,24]. The binding of a miRNA to the 3′UTR causes inhibition of translation through steric hindrance or degradation of the mRNA, depending on the degree of complementarity between the two sequences[24].The evidence for a regulatory role of the miR-34 family of miRNAs in senescence is growing and has stemmed from the investigation of p53 and its role in senescence[24]. Recent research has found that up-regulation of miR-34a in various cancer cell lines leads to cell cycle arrest, increased expression of β-galactosidase and down-regulation of E2F family target genes[24]. miRNAs are not only important modulators of E2F mRNA translation[25]. On the other hand, there are miRNAs to promote cell senescence. miRNAs target E2F, CDK4, c-myc, and SIRT1 lead to cell senescence. In particular, miRNA-22 induces cellular senescence by stimulating target factors. Senescence-associated microRNAs (SA-miRNAs) control cell transition, mainly through the G_1/S checkpoint during cell cycle progression by targeting the components of cell cycle including cyclin-dependent kinases (CDKs)[26]. Exosomes, membrane-bound vesicles of 40–100 nm in diameter, are present in almost all biological fluids[27,28]. They are released from most cell types into the extracellular space after fusion with the plasma membrane[27,28]. Lipids and proteins are the main components of exosome membranes, which are enriched with lipid rafts[27,28]. In addition to the proteins, various nucleic acids have recently been identified in the exosomal lumen, including mRNAs, microRNAs (miRNAs), and other non-coding RNAs (ncRNAs)[29]. These exosomal RNAs can be taken up by neighboring cells or distant cells when exosomes circulate, and they subsequently modulate recipient cells[30]. The discovery of their function in genetic exchange between cells has brought increasing attention to exosomes. Exosomes can be released from many cell types, such as blood cells, endothelial cells, immunocytes, platelets, and smooth muscle cells[31]. miRNAs are transferred between cells via exosomes[32]. Variable miRNAs carried by exosomes may regulate many different signaling pathways, and will generate integral effects on recipient cells. Level of exosomal miRNAs differ between patients with disease and healthy individuals. Thus, exosomal miRNAs show potential for use as noninvasive biomarkers to indicate disease states[33]. In bone marrow stromal cells (BMSCs) exosomes derived from donors of different ages, exosomes from young BMSCs significantly inhibited multiple myeloma (MM) induced angiogenesis in Matrigel plugs[33]. Expression of the exosomal microRNA (miRNA) was different between young and older BMSCs. The antiangiogenic effect of older BMSCs was enhanced by direct transfection of miR-340 expressed in exosomes derived from young BMSCs[33].

II. Conclusion

Cells that have been exposed to oxidative stress for a long time lead to deformation of the chromosome structure. The physical modification of the chromosomal structure induces changes in gene expression patterns. This also changes miRNA expression patterns that interfere with gene expression. We do not know all miRNAs yet. It is necessary to identify and classify miRNAs of young cells, miRNAs of senescent cells, and miRNAs of cancer cells using Big Data algorithm. When this process is completed, miRNAs that prevent cell senescence, miRNAs that induce cancer cells, and miRNAs that cancer cells transcript are known. Based on this, it is possible to develop new medicines with anti-aging effect or to prevent cancer.

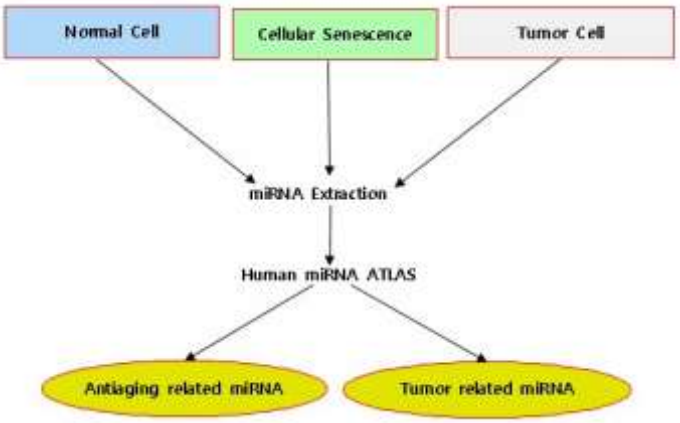

Fig. 1. The Potential of microRNAs (miRNAs).

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