

## EFFECTS OF MICROVESICLES ON CARDIOVASCULAR AGING

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### Summary:

Cardiovascular aging is associated with a loss of homeostasis of cells systems and the incidence of cardiovascular diseases (CVDs). Dysfunction of the endothelium, by acting on NO, expression of enzymes, such as angiotensin and elevation of electrolytes such as  $Ca^{2+}$ , leads to spread of diseases such as diabetes, hypertension and atherosclerosis among others CVDs. Cells progressing to senescence acquire prominent phenotypes, and the levels of many proteins that govern with each of these phenotypes are influenced by miRNA. The release of the microparticles contributes to the progression of endothelial damage, promoting senescence and development of CVDs. The present exploratory study aims to determine the association of microvesicles activity in cardiovascular aging, *in vitro* and *in vivo*, as well as the action of microvesicles in CVDs. Senescence is associated with metabolic and gene factors. The miRNAs miR-217, miR-9a and miR-34a act in reducing the expression of SIRT1. The p53 and miR-22 lead pRb inducing senescence. Consequently, decreasing longevity. However, in conjunction with senescence, there is emergence of CVDs. The influence of microvesicles, is on the carrying of genes and proteins that stimulate the progression of diseases. It can therefore conclude that, the release microvesicles into the senescent cells, promotes aging, as well as the spread of cardiovascular diseases.

**Keywords:** Microvesicles, aging, cardiovascular.

### 1. INTRODUCTION

Cardiovascular aging is associated with a loss of homeostasis of physiological systems. The damage done to DNA predicts the decline in functionality. These reduce the cellular adaptation capacity to stress, triggering cellular senescence [1] and the incidence of cardiovascular diseases (CVDs) [2-3].

Any molecules of endocrine and inflammatory signaling, by their presence or absence, may contribute to a compromised tissue function [4]. Thus, the activity of secretion and formation of microvesicles in senescent cells is emphasized [5].

#### 1.1 Mechanisms of Action of the Microvesicles in the aging

Microvesicles (MV) are vesicles that issue from the of membrane contain.

Microvesicles can change according to their origin. Derivatives from receptors, enzyme, mRNAs, miRNAs and / or DNA. Distinguished by the size, shape, density, origin and composition of the mother cell protein membrane. The cellular communication mechanisms, can be independent of contact, captured by membrane endocytosis [6-7].

The microRNAs (miRNAs) present in the microvesicles have 21 nucleotides with post-transcription regulatory action, processed from primary transcripts (pri-miRNAs), which are transcribed by RNA polymerase II from independent genes [8]. Pri-miRNAs are originated in precursors (pre-miRNAs) by Drosha and Pasha RNA endonucleases, and are exported to the cytoplasm becoming mature miRNAs. With silencing action of mRNA, by complexing with RNA in the 2-8 region of their nucleotids (seed region of activated miRNA) [7-9]. The stability of the miRNA is influenced by the final sequence of bases which can lead to senescence [10].

Cells progressing to senescence acquire several prominent phenotypes, and the levels of many proteins that govern with each of these phenotypes are influenced by miRNA associated with senescence. Senescent cells have high levels of p53, which increases expression of miR-34, which in turn suppresses proliferative protein levels (E2F, c-Myc, cyclins and cdk) and anti-apoptotic proteins (Bcl-2, SIRT1) [11]. It also

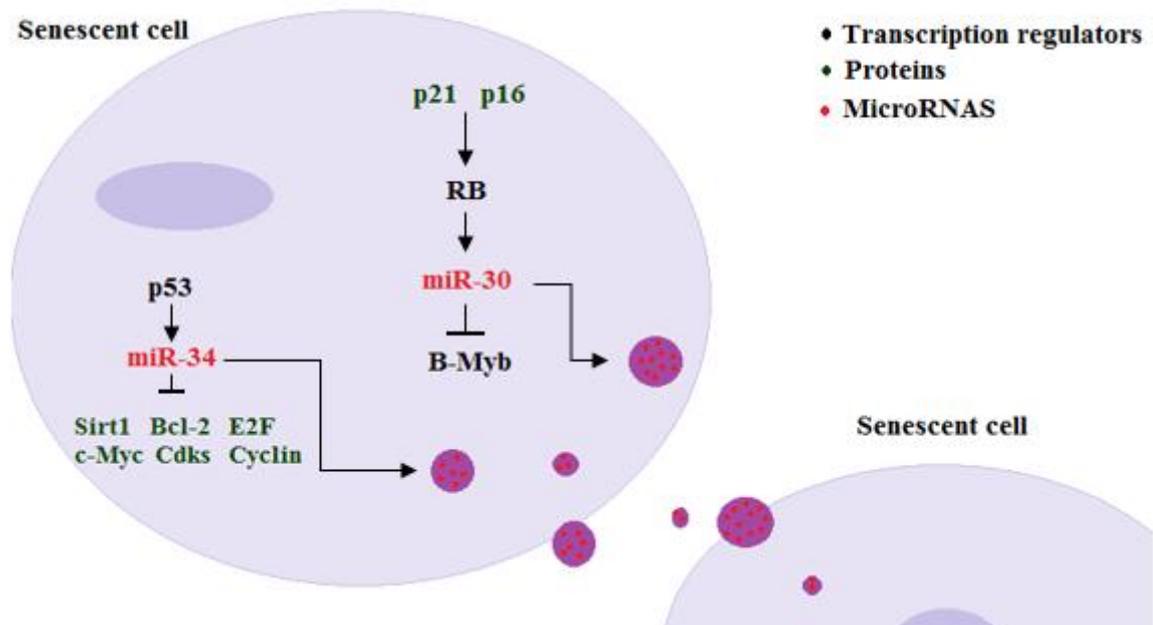
high levels of p21 and p16 retinoblastoma (RB) activator that stimulates B-Myb-blocking miRNA-30, as well as factors, secretory phenotype associated with, senescence (SASP) cells inflammation. These pathways inhibit the machinery of cell division and the implementation of gene expression patterns associated with senescence, provoking cellular responses to cellular damage by genotoxins and oxidants. SASP leads to secretion of factors that cause inflammation and compromise the integrity of the extracellular matrix (Figure 1) [5].

The release of the microparticles contributes to the progression of endothelial damage, promoting senescence and development of CVDs [12-7]. The present study aims to determine the association of microvesicles activity in cardiovascular aging, *in vitro* and *in vivo*, as well as the action of microvesicles in CVDs.

## 2. METHODS

The work to be developed will follow the precepts of the exploratory study, from scientific articles, which will be accessed in the database Scielo, PUBMED, Google Scholar, with the following descriptors: microvesicles in cardiovascular aging, microvesicles and cell senescence, microvesicles and cardiovascular diseases. For the construction of this review study, articles were counted 24 between the years 2005 and 2017.

Figure 1: Production and release of microvesicles



### 3. RESULTS AND DISCUSSIONS

#### 3.1 Activity of microvesicles in aging

Senescence is associated with metabolic and genetic factors, such as microvesicles. These have, in their interior, uncoded miRNAs, which in turn control the expression of genes from the signaling pathways (Table 1).

The miRNAs have action in the sirtuins (SIRT1-SIRT7), which are NAD<sup>+</sup> dependent deacetylases that control a large amount of processes involved in the regulation of homeostasis [17] promoting the reduction of the aging process. MiR-217, miR-9a, miR-34a, miRNAs act to reduce the expression of SIRT1, regulating it by, decreasing longevity.

Aging of cardiac cells is associated

with regulation by microRNAs that are involved in the remodeling of the extracellular matrix (ECM) of the heart. Proteins of the proteoglycan family that are rich in leucine, such as mimecan / osteoglycine (OGN), are emerging as regulatory proteins within the extracellular matrix [18], as well as thrombospondin-1 (TSP-1) and connective tissue growth factor, regulators of the remodeling of ECM. The miR-22 induced the depletion of OGN and miR17-19 regulator of the expression of CTGF and TSP-1, contributed to cardiac aging and consequently to diseases associated with the cardiovascular system.

#### 3.2 Microvesicle develops CVDs

The microvesicles, induced by apoptosis [23], attribute of the senescent cell,

can trigger cardiovascular diseases (Table 2), as these affect relevant factors in the quality of life, such as intracellular calcium levels

(Ca<sup>2+</sup>) which are fundamental for muscle contraction and communication between cells.

TABLE 1: Microvesicles that cause senescence

References	MicroRNA	Cell	Effect
[13]	miR-217	Endothelial	<i>In vitro</i> and <i>in vivo</i> studies have shown that there is regulation in SIRT1-eNOS expression and indirectly in FoxO1.
[14]	miR-9a and miR-34a	Peripheral blood mononuclear cells	Decrease SIRT1 expression.
[15]	miR-22	Cardiac fibroblasts	It induced cell senescence in the mouse heart mediated by the osteoglycin (OGN) pathway.
[16]	miR17-19	Cardiomyocytes	Regulates the expression of CTGF and TSP-1, extracellular matrix (ECM) regulators, influencing in human cardiac aging.

*Subtitle:* SIRT1: Sirtuin 1; eNOS: Endothelial nitric oxide synthase; FoxO1: Forkhead box O1; CTGF: Connective tissue growth factor; TSP-1: Thrombospondin-1.

TABLE 2: Development of CVDs by Microvesicles

References	Pathology	Effect
[19]	Atherosclerosis	Microvesicles derived from senescent endothelial cells, carry high amounts of pro-calcification proteins such as A6 and A2, by endocytosis enter by aortic smooth muscle cells, producing vascular calcification, apoptotic signals, thus marking atherosclerosis development.
[20]	Diabetes	Microvesicles derived from cells in apoptosis (senescent cell characteristics) T lymphocytes, impair the shear stress-induced dilatation of the mesenteric arteries, affecting the production of NO and prostacyclin's.
[21]	Hypertension	The released microvesicles inhibit the production of nitric oxide by cultured endothelial cells. Thus inducing endothelial dysfunction and affecting vascular homeostasis.
[22]	Coronary arterial disease	Microvesicles derived from cells in apoptosis and endothelial, transfer miR-10a to mRNA by increasing NF-kB activation components, as well as depressing NO production.

*Subtitle:* A2 and A6: Annexin; NO: Nitric oxide; NF-kB: Nuclear factor kappa B.

Ca<sup>2+</sup> exacerbation causes the senescent cell to produce procalcificant microvesicles A6 and A2 in order to maintain electrolyte balance. However, the released proteins such as interact with members of the

actin cytoskeleton and multiple signaling proteins [24] negatively affecting the dilatation of the mesenteric arteries. The microvesicles indirectly act on the production

of nitric oxide (NO) and prostacyclins, which are relaxing factors derived from endothelium, decreasing them, besides increasing the activating components of NF- $\kappa$ B by incorporating miR-10a (RNA gene) into mRNA.

Nitric oxide, essential for vasodilation, when inhibited, entails functional lack of control of this process. Some microvesicles act to inhibit NO production and reduce vase relaxation, resulting in hardening and in CVDs, such as hypertension.

#### 4. CONCLUSION

The release of microvesicles in senescent cells, can produces development the spread of cardiovascular diseases inducing and proliferating cellular aging. The main pathways of this cellular event are characterized by elevated expression of miRNAs, such as miR-34, miR-217, miR-9a, miR-10a, miR-22 and miR17-19, thus suppressing proliferative protein levels p53 and anti-apoptotic, reducing gene expression and cell divisions associated with senility. Configuring the release of microvesicles by the senescent cells, harmful to the quality of life.

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