World Journal of Hematology

Online Submissions: http://www.wjgnet.com/esps/
wjhematol@wjgnet.com
doi:10.5315/wjh.v2.i2.16

World J Hematol 2013 May 6; 2(2): 16-19
ISSN 2218-6204 (online)

EDITORIAL

Circulating microparticles and microRNAs as players in atherosclerosis

Nicoleta Alexandru, Adriana Georgescu

Nicoleta Alexandru, Adriana Georgescu, Petru Poni Institute of Macromolecular Chemistry, R-6600 Iasi, Romania
Nicoleta Alexandru, Adriana Georgescu, Department of Pathophysiology and Pharmacology, Institute of Cellular Biology and Pathology Nicolae Simionescu of Romanian Academy, 050568 Bucharest, Romania
Author contributions: Alexandru N and Georgescu A contributed equally to this paper.
Supported by Grants of the Romanian National Authority for Scientific Research, CNCS-UEFISCDI, Project ID PNII-CT-ERC-2012-1 (6ERC-like/July 18, 2012), Project ID PN-II-ID-PCE-2012-4-0124; by European Social Fund - "Cristofor I. Simionescu" Postdoctoral Fellowship Programme (ID POSDRU/89/1.5/S/55216), Sectoral Operational Programme Human Resources Development 2007-2013; and by Romanian Academy
Correspondence to: Adriana Georgescu, PhD, Department of Pathophysiology and Pharmacology, Institute of Cellular Biology and Pathology Nicolae Simionescu of Romanian Academy, 8, BP Hasdeu Street, PO Box 35-14, 050568 Bucharest, Romania. adriana.georgescu@icbp.ro
Telephone: +40-21-3194518 Fax: +40-21-3194519
Received: January 21, 2013 Revised: March 21, 2013
Accepted: April 27, 2013
Published online: May 6, 2013

Abstract

Microparticles (MPs) are extracellular membrane vesicles released from normal, apoptotic and pathological cells following a process of detachment from cells of origin. MPs are typically defined by their size, exposure of phosphatidylserine, the expression of surface antigens, proteins and genetic material, originating from their donor cells, and as important vehicles of intercellular communication across numerous biological processes. MPs contain the major source of systemic RNA including microRNA (miRNA) of which aberrant expression appears to be associated with stage and progression of atherosclerosis. The involvement and influence of miRNA during the onset and progression of atherosclerotic disease have generated a lot of interest in assessing the feasibility of therapeutic regulation of miRNAs to manipulate them with a special focus on cardiovascular disease. We speculate on the future developments of MPs which contain miRNA as new therapeutic targets for proliferative vascular diseases such as atherosclerosis.

Key words: Microparticles; MicroRNA; Atherosclerosis

Core tip: Circulating microparticles (MPs) and microRNAs (miRNA) play an important role in atherosclerotic disease. MPs contain the major source of systemic RNA including microRNA of which aberrant expression appears to be associated with stage and progression of atherosclerosis. We speculate on the future developments of MPs which contain miRNA as new therapeutic targets for proliferative vascular diseases such as atherosclerosis.

Alexandru N, Georgescu A. Circulating microparticles and microRNAs as players in atherosclerosis. *World J Hematol* 2013; 2(2): 16-19 Available from: URL: http://www.wjgnet.com/2218-6204/full/v2/i2/16.htm DOI: http://dx.doi.org/10.5315/wjh.v2.i2.16

ATHEROSCLEROSIS

Atherosclerosis is one of the most important and common cause of death and disability in the world and remains an occult but important precursor of significant cardiovascular events. Yet atherosclerosis is a systemic disease with important consequences in many other regional circulations, including those supplying the brain, kidneys, mesentery, and limbs. Atherosclerosis as a chronic inflammatory disease of the arterial wall is closely related to subendothelial lipoprotein retention, endothelial activation and migration of the immune cells to the inflamed intima

which result in formation of fatty streaks and subsequent atheromas[1,2]. Monocytes are prominently involved in initiation, progression and complication of the atherosclerotic lesions. They enter atherosclerotic plaque and transform to macrophage-like, lipid-loaded foam cells[3]. Also, it is now increasingly admitted that cell-derived microparticles (MPs) may contribute to the initiation, progression and clinical complications of cardiovascular diseases and they appear interesting biomarkers to predict this pathology[4]. In addition, the ratio of circulating MPs to endothelial progenitor cells may be a new and valuable cellular marker of vascular dysfunction in atherosclerosis[5].

MP

MPs were described as small (0.1-1 μm), pro-inflammatory vesicles released by various cell types (*e.g.*, leucocytes, endothelial cells, platelets, monocytes) in a tightly regulated process. MP vesiculation occurs as a cellular response to various physiological conditions including: apoptosis, senescence, cellular activation, shearing stress and biochemical triggers (such as cytokines and chemotherapeutics)[6]. They contain cytoplasm and surface markers of their cells of origin[7,8]. Once released into the circulation, MPs bind and fuse with their target cells through receptor-ligand interactions, thereby acting as biological vectors mediating vascular inflammation and coagulation[9]. Therefore, MPs have been shown to play a fundamental role in several cardiovascular diseases[10,11]. Increasing evidence indicates that inflammatory and pro-coagulatory effects of MPs on their target cells are caused by a specific lipid composition (*e.g.*, byphosphatidylserine) as well as by the transfer of inflammatory cell components from their cells of origin[7]. However, it was also shown that MPs transport messenger RNAs (mRNAs) thereby affecting protein expression of their target cells[12]. Recent progress in the understanding of microRNA (miRNAs) has prompted the questions of whether MPs also affect their target cells *via* transferring endogenous miRNAs and whether these MPs have different miRNA patterns than their maternal cells.

miRNA

miRNAs are a class of small (about 22 nucleotides long), non-coding RNA that bind to mRNAs thereby acting as endogenous post-translational gene regulators[13]. Since more then 1000 different human miRNAs have already been discovered, the interaction between miRNAs and mRNAs is highly complex and currently not completely understood. miRNAs are potent and crucial regulators of important cellular processes such as differentiation, growth, and survival. miRNAs regulate gene expression through binding to 3' UTRs of target mRNAs whereby inducing either messenger RNA degradation or inhibition of protein translation. However, approximately one-third of human protein-encoding genes are miRNAs regulated, underlining the extraordinary impact of miRNAs on protein expression[14,15].

Recent data indicate that miRNAs play a vital role in many cardiovascular diseases and can be found in cardiac tissue as well as in circulating blood, opening the possibility to use them as diagnostic surrogate markers[16-19]. They were reported alterations in the expression of specific miRNAs in human atherosclerotic plaques which suggest that miRNAs may have an important role in regulating the evolution of atherosclerotic plaque toward instability and rupture[20,21]. Bidzhekov *et al*[22] identified miRNAs co-expressed in plaque tissue and classical monocytes (miR-99b, miR-152), or non-classical monocytes (miR-422a) which serve as therapeutic targets for treating inflammatory vascular diseases. Also, miR-126 is highly expressed in the heart and vasculature of zebrafish[23] and miR-221 positively regulates smooth muscle proliferation and neointimal formation[24,25]. The effects of miR-221 are strengthened by the concurrent upregulation of miR-21 in neointimal lesions[26]. miR-21, which is a ubiquitously expressed prosurvival miRNA, was shown to inhibit PTEN expression under these conditions[26]. Other miRNAs that may also contribute to vessel formation include miR-130a, which is upregulated in endothelial cells during tubulogenesis and facilitates the process by targeting and inhibiting the expression of antiangiogenic transcription factors GAX and HOXA5[27]. In contrast, overexpression of miR-92a in endothelial cells blocked tubulogenesis and was associated with reduced cell migration and adhesion, but did not affect viability or proliferation[28]. On the other hand miRNA-145 has been studied for its therapeutic properties in atherosclerotic disease. It was found that miRNA is abundant in arteries[26] and in differentiated vascular smooth muscle cells[29].

CONCLUSION

Furthermore, it was promoted the idea that MPs represent transport vehicles for a large number of specific miRNAs in circulation[30,31]. Moreover, it was showed that embryonic stem cell-derived MPs contain abundant miRNAs and that they can transfer a subset of miRNAs to mouse embryonic fibroblast *in vitro*[32]. Additionally, MPs released from mesenchymal stem cells protect from acute kidney injury induced by ischaemia reperfusion injury and from subsequent chronic renal damage[33]. Other studies demonstrated that the expression of miRNAs and RNAs in secreted vesicles does not necessarily reflect the intracellular expression of RNAs[34,35]. Hergenreider *et al*[36] suggest that extracellular vesicles from Krüppel-like factor 2 (KLF2)-transduced cells contain a specific combination of miRNAs, including miR-143/145, which mediate the biological properties. Thus, vesicles from KLF2-transduced endothelial cells, but not from controls, reduce atherosclerotic lesion formation *in vivo*, in a miR-143/145-dependent manner and they may provide a promising strategy to combat atherosclerosis. Also, stem cell-derived MPs appear to be naturally equipped to mediate tissue regeneration under certain conditions[37]. Therefore, the extracellular vesicles are considered potent sources of genetic information transfer between mammalian cells and

tissues resulting in both beneficial (cell communication, stem cell plasticity and repair of injured tissues) and potentially detrimental (spread of disease) outcomes[37].

These data open new research perspectives on the use of MPs to transfer miRNAs-based information from stem cells/precursors/cells to target differentiated cells. Further studies on MPs biology and function may help elucidate the exact role that MPs as gene therapy tools.

REFERENCES

1 **Libby P**, Aikawa M. Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. *Nat Med* 2002; **8**: 1257-1262 [PMID: 12411953 DOI: 10.1038/nm1102-1257]

2 **Hansson GK**. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352**: 1685-1695 [PMID: 15843671 DOI: 10.1056/NEJMra043430]

3 **Hristov M**, Weber C. Differential role of monocyte subsets in atherosclerosis. *Thromb Haemost* 2011; **106**: 757-762 [PMID: 21901241 DOI: 10.1160/TH11-07-0500]

4 **Baron M**, Boulanger CM, Staels B, Tailleux A. Cell-derived microparticles in atherosclerosis: biomarkers and targets for pharmacological modulation? *J Cell Mol Med* 2012; **16**: 1365-1376 [PMID: 22050954 DOI: 10.1111/j.1582-4934.2011.01486.x]

5 **Georgescu A**, Alexandru N, Andrei E, Titorencu I, Dragan E, Tarziu C, Ghiorghe S, Badila E, Bartos D, Popov D. Circulating microparticles and endothelial progenitor cells in atherosclerosis: pharmacological effects of irbesartan. *J Thromb Haemost* 2012; **10**: 680-691 [PMID: 22303879 DOI: 10.1111/j.1538-7836.2012.04650.x]

6 **van Doormaal FF**, Kleinjan A, Di Nisio M, Büller HR, Nieuwland R. Cell-derived microvesicles and cancer. *Neth J Med* 2009; **67**: 266-273 [PMID: 19687520]

7 **Hugel B**, Martínez MC, Kunzelmann C, Freyssinet JM. Membrane microparticles: two sides of the coin. *Physiology* (Bethesda) 2005; **20**: 22-27 [PMID: 15653836 DOI: 10.1152/physiol.00029.2004]

8 **Prokopi M**, Pula G, Mayr U, Devue C, Gallagher J, Xiao Q, Boulanger CM, Westwood N, Urbich C, Willeit J, Steiner M, Breuss J, Xu Q, Kiechl S, Mayr M. Proteomic analysis reveals presence of platelet microparticles in endothelial progenitor cell cultures. *Blood* 2009; **114**: 723-732 [PMID: 19369228 DOI: 10.1182/blood-2009-02-205930]

9 **Mause SF**, Weber C. Microparticles: protagonists of a novel communication network for intercellular information exchange. *Circ Res* 2010; **107**: 1047-1057 [PMID: 21030722 DOI: 10.1161/CIRCRESAHA.110.226456]

10 **Georgescu A**, Alexandru N, Popov D, Amuzescu M, Andrei E, Zamfir C, Maniu H, Badila A. Chronic venous insufficiency is associated with elevated level of circulating microparticles. *J Thromb Haemost* 2009; **7**: 1566-1575 [PMID: 19552639 DOI: 10.1111/j.1538-7836.2009.03525.x]

11 **Shantsila E**, Kamphuisen PW, Lip GY. Circulating microparticles in cardiovascular disease: implications for atherogenesis and atherothrombosis. *J Thromb Haemost* 2010; **8**: 2358-2368 [PMID: 20695980 DOI: 10.1111/j.1538-7836.2010.04007.x]

12 **Ratajczak J**, Miekus K, Kucia M, Zhang J, Reca R, Dvorak P, Ratajczak MZ. Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery. *Leukemia* 2006; **20**: 847-856 [PMID: 16453000 DOI: 10.1038/sj.leu.2404132]

13 **Cai X**, Hagedorn CH, Cullen BR. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. *RNA* 2004; **10**: 1957-1966 [PMID: 15525708 DOI: 10.1261/rna.7135204]

14 **Lewis BP**, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* 2005; **120**: 15-20 [PMID: 15652477]

15 **Berezikov E**, Guryev V, van de Belt J, Wienholds E, Plasterk RH, Cuppen E. Phylogenetic shadowing and computational identification of human microRNA genes. *Cell* 2005; **120**: 21-24 [PMID: 15652478]

16 **Gupta SK**, Bang C, Thum T. Circulating microRNAs as biomarkers and potential paracrine mediators of cardiovascular disease. *Circ Cardiovasc Genet* 2010; **3**: 484-488 [PMID: 20959591 DOI: 10.1161/CIRCGENETICS.110.958363]

17 **Bauersachs J**, Thum T. Biogenesis and regulation of cardiovascular microRNAs. *Circ Res* 2011; **109**: 334-347 [PMID: 21778437 DOI: 10.1161/CIRCRESAHA.110.228676]

18 **Fichtlscherer S**, Zeiher AM, Dimmeler S. Circulating microRNAs: biomarkers or mediators of cardiovascular diseases? *Arterioscler Thromb Vasc Biol* 2011; **31**: 2383-2390 [PMID: 22011751 DOI: 10.1161/ATVBAHA.111.226696]

19 **Hartmann D**, Thum T. MicroRNAs and vascular (dys)function. *Vascul Pharmacol* 2011; **55**: 92-105 [PMID: 21802526 DOI: 10.1016/j.vph.2011.07.005]

20 **Cipollone F**, Felicioni L, Sarzani R, Ucchino S, Spigonardo F, Mandolini C, Malatesta S, Bucci M, Mammarella C, Santovito D, de Lutiis F, Marchetti A, Mezzetti A, Buttitta F. A unique microRNA signature associated with plaque instability in humans. *Stroke* 2011; **42**: 2556-2563 [PMID: 21817153 DOI: 10.1161/STROKEAHA.110.597575]

21 **Raitoharju E**, Lyytikäinen LP, Levula M, Oksala N, Mennander A, Tarkka M, Klopp N, Illig T, Kähönen M, Karhunen PJ, Laaksonen R, Lehtimäki T. miR-21, miR-210, miR-34a, and miR-146a/b are up-regulated in human atherosclerotic plaques in the Tampere Vascular Study. *Atherosclerosis* 2011; **219**: 211-217 [PMID: 21820659 DOI: 10.1016/j.atherosclerosis.2011.07.020]

22 **Bidzhekov K**, Gan L, Denecke B, Rostalsky A, Hristov M, Koeppel TA, Zernecke A, Weber C. microRNA expression signatures and parallels between monocyte subsets and atherosclerotic plaque in humans. *Thromb Haemost* 2012; **107**: 619-625 [PMID: 22370758 DOI: 10.1160/TH11-09-0607]

23 **Wienholds E**, Kloosterman WP, Miska E, Alvarez-Saavedra E, Berezikov E, de Bruijn E, Horvitz HR, Kauppinen S, Plasterk RH. MicroRNA expression in zebrafish embryonic development. *Science* 2005; **309**: 310-311 [PMID: 15919954 DOI: 10.1126/science.1114519]

24 **Davis BN**, Hilyard AC, Nguyen PH, Lagna G, Hata A. Induction of microRNA-221 by platelet-derived growth factor signaling is critical for modulation of vascular smooth muscle phenotype. *J Biol Chem* 2009; **284**: 3728-3738 [PMID: 19088079 DOI: 10.1074/jbc.M808788200]

25 **Liu X**, Cheng Y, Zhang S, Lin Y, Yang J, Zhang C. A necessary role of miR-221 and miR-222 in vascular smooth muscle cell proliferation and neointimal hyperplasia. *Circ Res* 2009; **104**: 476-487 [PMID: 19150885 DOI: 10.1161/CIRCRESAHA.108.185363]

26 **Ji R**, Cheng Y, Yue J, Yang J, Liu X, Chen H, Dean DB, Zhang C. MicroRNA expression signature and antisense-mediated depletion reveal an essential role of MicroRNA in vascular neointimal lesion formation. *Circ Res* 2007; **100**: 1579-1588 [PMID: 17478730 DOI: 10.1161/CIRCRESAHA.106.141986]

27 **Chen Y**, Gorski DH. Regulation of angiogenesis through a microRNA (miR-130a) that down-regulates antiangiogenic homeobox genes GAX and HOXA5. *Blood* 2008; **111**: 1217-1226 [PMID: 17957028 DOI: 10.1182/blood-2007-07-104133]

28 **Bonauer A**, Carmona G, Iwasaki M, Mione M, Koyanagi M, Fischer A, Burchfield J, Fox H, Doebele C, Ohtani K, Chavakis E, Potente M, Tjwa M, Urbich C, Zeiher AM, Dimmeler S. MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice. *Science* 2009; **324**: 1710-1713 [PMID: 19460962 DOI: 10.1126/science.1174381]

29 **Cheng Y**, Liu X, Yang J, Lin Y, Xu DZ, Lu Q, Deitch EA, Huo Y, Delphin ES, Zhang C. MicroRNA-145, a novel smooth muscle cell phenotypic marker and modulator, controls vas-

cular neointimal lesion formation. *Circ Res* 2009; **105**: 158-166 [PMID: 19542014 DOI: 10.1161/CIRCRESAHA.109.197517]

30 **Shi MA**, Shi GP. Intracellular delivery strategies for microRNAs and potential therapies for human cardiovascular diseases. *Sci Signal* 2010; **3**: pe40 [PMID: 21045204 DOI: 10.1126/scisignal.3146pe40]

31 **Diehl P**, Fricke A, Sander L, Stamm J, Bassler N, Htun N, Ziemann M, Helbing T, El-Osta A, Jowett JB, Peter K. Microparticles: major transport vehicles for distinct microRNAs in circulation. *Cardiovasc Res* 2012; **93**: 633-644 [PMID: 22258631 DOI: 10.1093/cvr/cvs007]

32 **Yuan A**, Farber EL, Rapoport AL, Tejada D, Deniskin R, Akhmedov NB, Farber DB. Transfer of microRNAs by embryonic stem cell microvesicles. *PLoS One* 2009; **4**: e4722 [PMID: 19266099 DOI: 10.1371/journal.pone.0004722]

33 **Gatti S**, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, Tetta C, Camussi G. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. *Nephrol Dial Transplant* 2011; **26**: 1474-1483 [PMID: 21324974 DOI: 10.1093/ndt/gfr015]

34 **Zhang Y**, Liu D, Chen X, Li J, Li L, Bian Z, Sun F, Lu J, Yin Y, Cai X, Sun Q, Wang K, Ba Y, Wang Q, Wang D, Yang J, Liu P, Xu T, Yan Q, Zhang J, Zen K, Zhang CY. Secreted monocytic miR-150 enhances targeted endothelial cell migration. *Mol Cell* 2010; **39**: 133-144 [PMID: 20603081 DOI: 10.1016/j.molcel.2010.06.010]

35 **Valadi H**, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol* 2007; **9**: 654-659 [PMID: 17486113 DOI: 10.1038/ncb1596]

36 **Hergenreider E**, Heydt S, Tréguer K, Boettger T, Horrevoets AJ, Zeiher AM, Scheffer MP, Frangakis AS, Yin X, Mayr M, Braun T, Urbich C, Boon RA, Dimmeler S. Atheroprotective communication between endothelial cells and smooth muscle cells through miRNAs. *Nat Cell Biol* 2012; **14**: 249-256 [PMID: 22327366 DOI: 10.1038/ncb2441]

37 **Lee Y**, El Andaloussi S, Wood MJ. Exosomes and microvesicles: extracellular vesicles for genetic information transfer and gene therapy. *Hum Mol Genet* 2012; **21**: R125-R134 [PMID: 22872698 DOI: 10.1093/hmg/dds317]

P- Reviewer Qin XB **S- Editor** Zhai HH
L- Editor A **E- Editor** Zheng XM