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EDITORIAL

miRNA and platelet genetic machinery

Pedro C Redondo

Pedro C Redondo, Department of Physiology, Institute of Molecular Pathology Biomarkers, University of Extremadura, Caceres 10003, Spain

ORCID number: Pedro C Redondo (0000-0002-2067-2627).

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Corresponding author to: Pedro C Redondo, PhD, Academic Research, Professor, Department of Physiology, Institute of Molecular Pathology Biomarkers, University of Extremadura, Plaza de Caldereros, s/n., Caceres 10003, Spain. pcr@unex.es
Telephone: +34-927-257106
Fax: +34-927-257110

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Abstract

Platelets are responsible for blood haemostasis. Although anucleate, a complete translational machinery has been found in platelets, which is responsible for new protein generation. Recently, the role of miRNAs in platelets has started to become apparent. In this editorial I highlight this topic in the hope that other scientists may be attracted to work in this area to aid a more complete understanding of protein regulation in platelets and its impact on platelet function.

Key words: Platelets; Thrombosis; Platelet agonists; miRNA

Core tip: miRNAs have been recently identified as a mechanism for regulating protein content in several cell types including platelets. In fact, certain miRNAs have been recently associated with some platelet-related pathologies. Moreover, changes in the miRNAs expression profiles have been evidenced in platelet activated by certain agonists. So, future researches will be needed to provide more information regarding platelet miRNAs in order to be used as an alternative therapy to the nowadays antiplatelet drugs.

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INTRODUCTION

Platelets, though anucleate, are the main cells involved in haemostasis, since they produce or store many molecules that are released once they are activated. Platelet activation results in blood clotting, mainly through the interconnection of two different processes: the extrinsic and intrinsic pathways of the coagulation mechanism. The resulting blood clot requires the generation of a fibrin net that, together with the spread platelets, avoids the loss of other blood cells from the

damaged blood vessel.

The fact that platelets are derived from megakaryocyte fragmentation, together with the lack of positive 4',6-diamidino-2-phenylindole staining, lead to the incorrect conclusion that platelets have a poor translational machinery[1,2]. Therefore, early papers claimed that these cells were unable to produce new proteins. However, more recent work has demonstrated changes in mRNA and proteins in mature platelets, even over short time periods, similar to those found in nucleated cells[3-5]. The discovery of platelet microparticles, circulating small fragments derived from platelets that contain important regulatory factors, has further increased interest in this area. Platelet derived microparticles have been proposed to play a role in the transport of mRNA to other cells[6]. miRNA associated with platelet microparticles has been proposed as a regulatory pathway, or crosstalk mechanism, between platelets and other surrounding cells, such as monocytes and endothelial cells[7-9].

Another important issue is the regulatory effect of miRNA on platelet physiology. Since their discovery in nematodes in 2000[10], these small DNA fragments, derived from non-coding segments of DNA, have been shown to be an important mechanism of gene regulation. Polymerase Ⅱ generates long RNA transcripts (called primary RNA) that are cleaved by a protein complex known as a microprocessor (resulting from the association of RNase Ⅲ and DGCR8). After primary RNA is transported to the cytosol of cells, it is further processed by RNase Ⅲ, DICER and argonaute proteins. Finally, mature miRNAs associate with the complementary 3' untranslated regions of the target RNA, which results in a decrease in target protein expression[11]. Interestingly, the inhibitory effect of the miRNA changes with time and it is specific to a particular tissue, so it is possible to find different functions of a particular miRNA depending of the tissue and the pathology investigated.

Nowadays, there is a robust body of evidence concerning the presence and relevance of miRNA in platelet function and platelet-associated pathologies. Some important investigations and results are described below.

During platelet synthesis and maturation, miRNA 125b appears to regulate the initial phases of megakaryocyte maturation by targeting the cyclin-dependent kinase inhibitor p19 INK4D[12]. Interestingly, a cluster of three miRNAs (miRNA 23a/27a/24 2) counteracts miRNA 125b in platelet maturation from *in vitro* cultured megakaryocytes[13].

miRNAs have also been reported to regulate the expression of proteins involved in the function of mature circulating platelets. For example, artificial downregulation of miRNA 126 in murine platelets leads to reduced ADAM9 and P2Y12 receptor expression[14]. Furthermore, in stored human platelets, miRNA 320c has recently been reported to regulate platelet function by impairing RAP1 activation. RAP1 is regulated by CalDAG-GEFI and is involved in membrane expression of integrins downstream of the activation of ITAM- and G-coupled receptors[15]. Additionally, stored platelets exhibit apoptotic-like events. In fact, as early as the third day of storage, these cells exhibit a reduction of antiapoptotic Bcl-X_L that is associated with an increase in proapoptotic Bak. miRNA let-7b has a 3'-UTR binding region for the *Bcl-x*$_L$ gene, resulting in down-regulation of Bcl-X_L expression, and during platelet storage this miRNA shows increased expression[16]. The latter may be a relevant field for future study since it may help to improve the survival time of haematopoietic cell precursors, so prolonging the availability and efficiency of transfusion.

It is worth mentioning that miRNA may affect protein expression over very short time periods. In a recent publication, the authors listed around 72 miRNAs that are overexpressed and bind to argonaute proteins, and around 30-40 that are silenced in response to the platelet physiological agonist, thrombin. miRNA 27b, which showed reduced expression upon thrombin stimulation, downregulated thrombospondin-1 activity. Thrombospondin-1 is an important protein that participates in the mechanism of angiogenesis regulated by platelets[17].

Finally, the role of miRNAs in the progression of certain illnesses has recently been revealed. For example, in patients suffering essential thrombocytosis, a pool of miRNAs were found to be altered (miR-9, miRNA 490 5p, miRNA 490 3p, miRNA 182, miRNA 34a, miRNA 196b, miRNA 34b*, miRNA 181a 2*). The alteration in these miRNAs, together with a set of mRNA (CAV2, LAPTM4B, TIMP1, PKIG, WASF1, MMP1, ERVH-4, NME4, HSD17B12) and certain point mutations at the gene level, facilitates the progression of this chronic myeloproliferative disorder that leads to elevated platelet production, which may result in stroke, heart attack and the formation of blood clots in patients[18]. In diabetes mellitus patients, miRNA 223, miRNA 126, miRNA 197, miRNA 191, miRNA 21, miRNA 150, miRNA 155, miRNA 140, miRNA 96, miRNA 98 may be involved in the appearance of cardiovascular complications as reported recently[19]. miRNA alteration was also found in the background of primary immune thrombocytopenia[20]. Interestingly, not only may altered miRNA be responsible for the appearance of certain thrombotic illnesses, but also their own expression may be affected by surgical procedures, as was found in patients following cardiopulmonary bypass[21,22]. In these patients, overexpression of miRNAs 10b and 96 was found, and these changes resulted in a reduction in glycoprotein 1b and vesicle-associated membrane protein 8 at both the mRNA and protein level. This has been linked to impaired platelet function associated with the bypass surgery[22].

CONCLUSION

The available evidence in the literature points to an important role for miRNAs in platelet function, as well as in the regulation that platelets exert over surrounding cells. Further investigations of platelet miRNAs are required in order to fully understand the platelet signalling pathways that involve these molecules. Finally, it is possible that the production of anti-miRNAs (antagomirs) will become a promising research area for the prevention of thrombotic diseases.

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