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Modulation of microRNAs by aspirin in cardiovascular disease ☆

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ABSTRACT

Aspirin is among the most widely prescribed drugs in cardiovascular and cerebrovascular diseases for both primary and secondary prevention. The major mechanisms underlying its benefits are the inhibitory effects on platelet activation and prostanoid biosynthesis induced by COX-1 and COX-2 inactivation. MicroRNAs (miRNAs) are newly proposed mediators of the effects of aspirin. In this review, we summarize the evidence on the links between miRNAs and aspirin use in relation to cardiovascular diseases. In addition, we discuss the studies suggesting a possible role for miRNAs as biomarkers of aspirin resistance, a condition during which atherothrombotic events occur despite aspirin use, and which affects a considerable proportion of patients with cardiovascular disease.

Introduction

MicroRNAs (miRNAs) are a class of small non-coding RNAs that post-transcriptionally regulate gene expression by inhibition of mRNA translation or induction of mRNA degradation [1]. These molecules are involved in various physiological and pathological processes, examples being cardiovascular events [2–4], cancer [5–10], diabetes mellitus [11], etc. Platelets are nuclear cellular fragments that originate from megakaryocytopoiesis; despite the absence of genomic DNA and a nucleus, post-transcriptional gene regulation can still occur due to the presence of the necessary spliceosome factors [12,13].

Cyclooxygenase (COX) has two well-known membrane-anchored functional isoenzymes in humans: COX-1 and COX-2. COX-1 are constitutively expressed in most normal tissues while COX-2 is highly induced by proinflammatory mediators. COX-1 is the predominant isoform in normal vessels with constitutive expression in the endothelium and irregular expression in the vascular smooth muscles. On the contrary, COX-2 is not expressed in the majority of normal endothelial or vascular smooth muscle cells while it could be rapidly induced with vascular injury or inflammation. Aspirin is an analgesic and anti-inflammatory drug that works as an irreversible inhibitor of COX-1. COX-1 is the catalytic enzyme of arachidonic acid conversion to prostaglandins G_2, H_2 and subsequently to thromboxane A_2; it is largely found in platelets but is not restricted to that location [14]. Thromboxane A_2 acts as a vasoconstrictor, a proliferative factor for vascular smooth muscle cells and also a platelet aggregator. The COX-1 enzyme inhibition is irreversible and persists for the entire lifespan of the platelets [15]. Aspirin also inhibits COX-2, though to a lesser extent [14].

Besides the irreversible inhibition of COX-1, aspirin acts through other mechanisms in the prevention of cardiovascular disease, such as platelet inactivation by inhibition of P-selectin glycoprotein favoring leukocytes recruitment and rolling, and inhibition of platelet factors and fibrinogen, which favor the development of thrombosis. Aspirin also prevents thrombin formation which is the convertor of fibrinogen to fibrin or influences the quality of fibrin within

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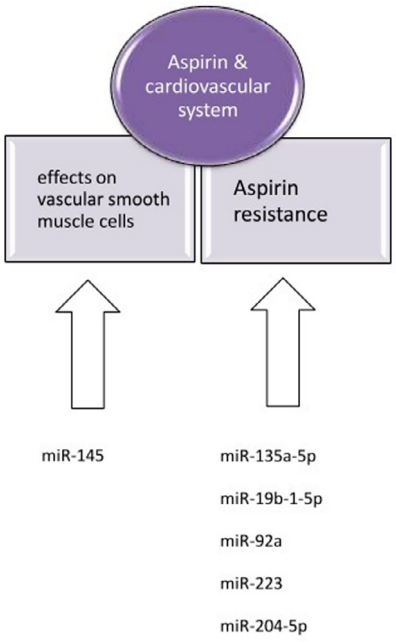

Fig. 1. miRNAs and aspirin in cardiovascular disease.

the thrombus. Increasing the rate of fibrinolysis is another mechanism of action of aspirin that is related to the acetylation of fibrinogen [16]. A pharmacokinetic and pharmacodynamic study of aspirin in 22 healthy volunteers showed almost complete inhibition of platelet function 20 min and 5 min after its administration in oral or intravenous form respectively [17]. There are a few small and heterogenous studies investigating the impact of aspirin on the vascular function and blood pressure in patients with arterial hypertension that are not adequate for drawing reliable conclusions [18]. Further studies are needed to address this issue.

Besides the COX-dependent mechanisms, COX-independent ones are also involved, and among them miRNAs have received attention in recent years. Therefore, in this review we summarize the data related to miRNAs modulation following aspirin administration as it relates to cardiovascular disease. We also look at the data that address miRNAs as potential diagnostic or even prognostic markers in aspirin resistance (Fig. 1).

Aspirin, miRNA, and cardiovascular disease

In spite of decades of wide administration of low-dose aspirin for primary prevention of atherosclerotic cardiovascular disease, the results of three large randomized controlled primary prevention clinical trials, the ASCEND trial (15,480 participants with diabetes mellitus and no evident cardiovascular disease, with median follow up of 7.4 years) [19], the ARRIVE trial (A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease; 12,546 non-diabetic participants, with median follow up of 5 years) [20], and the ASPREE trial (Aspirin in Reducing Events in the Elderly study; 19,114 participants without known cardiovascular diseases, with median follow up of 4.7 years) [21] revealed a lack of net benefit for aspirin since the elevated risk of bleeding with its use was much higher than the preventive role toward atherosclerotic cardiovascular diseases. This evidence led to the revision of the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, with the following recommendations:

- Low-dose aspirin might be considered for primary prevention of atherosclerotic cardiovascular diseases (ASCVD) in selected higher-risk adults aged 40–70 years who are not at increased bleeding risk.
- Low-dose aspirin should not be administered on a routine basis for primary prevention of ASCVD among adults >70 years.
- Low-dose aspirin should not be administered for primary prevention among adults at any age who are at increased bleeding risk [22].

In addition, the US Food and Drug Administration (FDA) does not recommend aspirin for the primary prevention of heart attacks and strokes for the general population, while its use should be considered limited to those individuals for whom the benefits outweigh the risks [23]. Therefore, aspirin use is supported by strong evidence of overweighing benefits vs potential risks only in the secondary prevention of cardiovascular disease [24].

At present, very few studies are available about the potential role of miRNAs in determining/modulating the effects of aspirin in the prevention of cardiovascular diseases. Among the 532 miRNAs that have been recognized in platelets of healthy humans, the most abundant ones are the members of let-7 family [25].

There are three types of platelet secretory granules including α–granules, dense granules, and lysosomes. Among them, α–granules are the most abundant and necessary for the activity of platelets. Following the activation of platelets, α–granules fuse with the plasma membrane and release their content. Different functional roles, implicated in the pathogenesis of cardiovascular diseases have been identified for platelet α–granules, such as procoagulative and pro-inflammatory effects, and treatments specifically targeting their content release might be used to control these processes [26]. miR-21 may modulate proteins that regulate the release of α-granule from platelets; proteomics analysis of the platelet releasate showed that treatment with antagonists of miR-21 affects the release of α–granule proteins, such as TGF-β1, von Willebrand factor, and fibronectin [27].

Considering the high clinical importance of aspirin in the management of coronary artery disease, we are going to discuss the role of miRNA in diagnostic tests of aspirin resistance along with its role in the proposed mechanisms for aspirin resistance.

Platelet reactivity/ASA resistance

Aspirin resistance is defined as aspirin inability in the reduction of thromboxane A2 production by platelets which causes impaired suppression of platelet activation and aggregation and has been associated with an increased cardiovascular risk. The following mechanisms have been implicated in aspirin resistance: inadequate aspirin dosage or patient compliance, aspirin interactions with drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), genetic polymorphisms, upregulation of thromboxane biosynthesis in non-platelet sources, and increased turnover of platelets. Therefore, different strategies should be used to overcome aspirin resistance based on the type of cause(s). Developing reliable tests is necessary to investigate the potential mechanisms of action and to investigate the efficacy of treatments [28].

Aspirin resistance is experienced in approximately one fourth of cardiovascular patients [29]. Variability of platelet reactivity among cardiovascular patients treated with antiplatelet drugs such as aspirin is a matter of concern and has been shown to be not only related to inter-individual genetic variations but also to epigenetic factors such as miRNAs. miR-135a-5p and miR-204-5p are two candidate miRNAs that are correlated with platelet reactivity and synergistically affect a group of candidate genes (THBS1, CDC42, CORO1C, SPTBN1, TPM3, GTPBP2, and MAPRE2); these genes were identified via a network biology approach using proteomic and transcriptomic data from two groups of patients, either with extremely high or extremely low platelet reactivity [30]. Another

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Table 1
MiRNAs, cardiovascular disease and platelets.

Regulated miRNA	Cardiovascular disease or event	Target gene	References
miR-45	Ischemia stroke	CD40	[67]
miR-135a-5p and miR-204-5p	Platelet reactivity	THBS1, CDC42, CORO1C, SPTBN1, TPM3, GTPBP2, and MAPRE2	[30]
lower expression of miR-19b-1-5p	Aspirin insensitivity	-	[30]
miR-92a level and platelet distribution width (PDW) assay	Aspirin insensitivity	-	[68]
miR-223	Platelet reactivity	-	[32]
miR-126	Platelet levels altered by aspirin administration	CXCL12, PIK3R2, SPRED1	[30]

group measured sustained platelet aggregation following incubation with indomethacin, a drug that mimics aspirin effect; they reported, a relationship between lower expression of miR-19b-1-5p and aspirin insensitivity and proposed miR-19b-1-5p as a suitable marker for aspirin insensitivity [31].

An association of circulating miR-223 and platelet reactivity has been reported in patients suffering from coronary artery disease who undergo dual antiplatelet therapy with aspirin and clopidogrel [32]. This was a proof-of-concept study for identification of potential platelet miRNAs that could be substitute markers to determine the efficiency of antiplatelet therapy. MiR-126, miR-197, miR-223, miR-24, and miR-21 were discovered by microarray screening as the most highly expressed miRNAs in platelets and platelet microparticles. Among them, a low circulating level of miR-223 was shown to be an independent predictor of poor prognosis associated conditions, such as myocardial infarction, according to the population based study of Bruneck [33], and type 2 diabetes [32,34].

Comparing plasma circulating level of miR-223 quantified by real time PCR between normal-responders and low-responders to antiplatelet therapy with clopidogel and aspirin with troponin-negative non-ST elevation acute coronary syndrome, a decreased level of miR-223, but not other factors (including CYP2C19*2/*3 loss-of-function genotypes, use of calcium channel blockers/proton-pump inhibitors, age, diabetes and smoking), resulted in an independent predictor for responsiveness to antiplatelet therapies [35].

There is an association between overexpression of multidrug resistance protein-4 (MRP4), an ATP binding cassette membrane transporter with active role in extrusion of pharmacological and physiological molecules, and reduction in post by-pass efficacy of aspirin. Using Real time PCR, flow cytometry and western blotting techniques, Giolio et al. reported up-regulation of MRP4and down-regulation of miR-26b in platelets from patients on chronic ASA treatment in comparison with the control group. In addition, miR-26b transfection in platelets was associated with a significant down-regulation of MRP4 expression. Thus, miR-26b seems to be involved in MRP4 modulation and may contribute to ASA resistance [36].

Platelet resistance could potentially be identified with a combination of circulating levels of miR-92a and the platelet distribution width (PDW) assay. The arachidonic acid stimulated aggregation test multiplate analyzer (ASPItest) has been widely used to identify aspirin resistance and aspirin responders. The cut-off values for discrimination of these two groups are ≥30 U in the ASPItest, N 11.8 fL in the PDW test, and a relative expression level of 4.5 for miR-92a. A PDW/miR-92a-score using these cut-off values could successfully detect aspirin resistance with the positive and negative predictive values of 88.9% and 95.1%, respectively. Routine laboratory tests in current use for evaluating platelet function suffer from some limitations, including inter-and intra-individual variability, possible inaccuracy due to in vitro and in vivo differences and the need to perform the test within a brief window of 30–120 min post sampling. Therefore, this new method described above could potentially represent an advance for discriminating patients who would benefit from platelet inhibition with aspirin from those who would not [37]. In a validation cohort, both PDW and plasma levels of miR-92a were confirmed to be significantly higher in patients who were aspirin-resistant in comparison to responsive individuals; however, researchers failed to validate the newly developed score as mentioned in the pilot study and the cohort study did not confirm high sensitivity of this score [38]

Two main issues are still to be addressed in validation clinical studies. First, we do not know how to manage the patients who are poor responders to aspirin, and then we do not know if the laboratory monitoring of aspirin therapy is really cost-effective [39].

Endothelial and vascular smooth muscle cells

Aspirin is a drug used both for primary prevention of cerebrovascular and cardiovascular disease [40,41] and also for secondary prevention of recurrent ischemic vascular events [42]. Although these effects are mainly mediated through COX inhibition, miRs are also involved in both aspirin's cardiovascular benefits and aspirin resistance (Table 1).

Abnormal proliferation of vascular smooth muscle cells is one of the pathological features in atherosclerosis, which underlies, among others, ischemic stroke [43,44]. The anti-proliferative and anti-inflammatory effects of aspirin on vascular smooth muscle cells are mediated through inhibition of CD40 mRNA translation by miR-145. This inhibitory effect improves the stability of atherosclerotic plaques. By comparing pre and post aspirin treatment level of miR-145 in 46 ischemic stroke patients, it was revealed that ten days aspirin treatment elevated the level of this miR in peripheral blood mononuclear cells. In addition, this increase in miR-145 and decrease in CD40 expression was more evident in atherosclerotic plaques of aspirin-treated ischemic stroke patients compared to those untreated. In vitro studies reported in vascular smooth muscle cells a significant decrease in IL-6 levels and a significant suppression of cells proliferation and CD40 mRNA expression following aspirin treatment [45]. These effects were reversed when a miR-145 inhibitor was used to suppress the expression of this miRNA. In this study, miR-145 was measured by Real-time PCR after transfection with either miR-145 inhibitor (50, 100, 200 nmol/L) or the miR-145 inhibitor control for 24 h, and the stem loop primers of miR-145 was used to amplify miR-145 in the peripheral blood mononuclear cells from ischemic stroke patients. Furthermore, treatment of ischemic stroke patients with aspirin for 10 days significantly increased the expression of miR-145 in peripheral blood mononuclear cells [45].

Anti-platelet therapy reduces plasma levels of platelet-related miRNAs, including miR-126 and miR-223 [46]. The atheroprotective role of miR-126 has already been recognized. Local CXCL12 (a known mediator of progenitor cell mobilization) induction conferred by miR-126 in endothelial apoptotic bodies may promote atheroprotection, which can be enhanced by miR-126-mediated repression of endothelial vascular cell adhesion molecule-1 expression, thereby limiting inflammatory cell arrest. Recent miRNA profiling studies revealed that circulating levels of vascular-derived

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miRNAs, including miR-126, were reduced in individuals with CAD [47]. miR-223 has been used to categorize patients as 'responder' and 'non-responder' to the clopidogrel, which is a P2Y12 inhibitor [48]. In an interesting study, the correlation of plasma miRNA levels with platelet function was studied in 125 patients who had a past 30 days history of acute coronary syndrome [49]. Among the identified miRNAs with next-generation sequencing of small RNAs in plasma, miR-126 and miR-223 showed the greatest dependency on platelets [49]. Platelet aggregation was reduced in mice with inhibited miR-126 and this miR affects both directly and indirectly the expression of ADAM9, a predicted and experimentally confirmed target of miR-126 that acts as an accelerator of the adhesion of platelets to collagen [49]. Given the function of ADAM9 as a protease of the ADAM family, it may alter the platelet response by cleaving membrane proteins and also by the expression of P2Y12 receptor that plays an important role in platelet reactivity [49]. However, there is concern that antiplatelet drugs like aspirin and lipid-lowering medications like statins may affect the profile of circulating miRNAs [50,11]. For example, aspirin has been shown to suppress the release of miR-126 following ex vivo activation of platelets [51].

When considering the use of miR-126 as a proposed biomarker for endothelial dysfunction in type 2 diabetes (DM2) and coronary artery disease (CAD), the fact that this miRNA is abundant not only in endothelial cells but also in platelets must be taken into account. Both in vitro and in vivo activation of platelets, with the resultant confounding effect on the plasma level of miR-126, could be impacted by aspirin administration, especially in pathophysiological conditions associated with platelet activation like T2DM [46]. Moreover, de Boer and colleagues revealed the contribution of platelets to the plasma pool of miR-126 in patients with T2DM and the effect of aspirin treatment on this factor. Both platelet inhibition and reduction in miR-126 levels were observed following aspirin administration. This finding suggested that a major part of circulating miR-126 is produced by platelets. Therefore, in pathological states associated with platelet hyper-reactivity such as in T2DM, aspirin may cause reduced levels of circulating miR-126. Hence, the use of platelet inhibitors such as aspirin should be considered as a confounding parameter in any diagnostic application of plasma miR-126 concentrations [52].

In order to determine the possible association between miRNA levels and clinical outcome in patients with acute CAD, large cohort studies with prolonged follow-up are necessary.

Resolvins and lipoxins

Lipoxins and resolvins are anti-inflammatory and inflammatory-resolving lipid mediators, respectively. They are among the first mediators identified that actively promote the resolution of inflammation [53].

Lipoxins are lipoxygenase interaction products that are synthesized from arachidonic acid by three major routes. In the first one, taking place in platelets, 12-Lo lipoxygenase converts leukotriene A4 to lipoxins [54]; in the second route, in neutrophils, erythrocytes and reticulocytes, 5-LO lipoxygenase and 15-LO lipoxygenase, respectively, act in series to convert arachidonic acid to lipoxin A and lipoxin B.4, the third route, is aspirin dependent and generates aspirin-triggered lipoxin (ATL) and 15 epi-lipoxin B4 [55]. It has been proved that local anti-inflammatory actions of low-dose aspirin in healthy individuals is mediated through ATL generation [55,56].

Acetylation of COX-2 following aspirin administration leads to epilipoxins formation and also aspirin could amplify epi–lipoxins formation by nitrosylation of statin-induced COX-2 [57,58]. Resolvins are specialized lipid mediators that promote the resolution of acute inflammation and could be divided into two classes, the E-series resolvins (RvE1, RvE2, and RvE3) which synthetized from eicosapentaenoic acid and the D series resolvins (RvD1–RvD6) derived from docosaesaenoic acid. RvD1 regulates miRNAs target genes with roles in the human immune system, and is associated with resolution of acute inflammation [59]. It has been shown that RvD1 selectively interacts with receptors ALX/FPR2 and GPR32; the administration of RvD1 in ALX/FPR2 transgenic mice significantly up-regulated miR-208a, which then downregulated PDCD4, a proinflammatory regulatory protein acting both as an IL-10 inhibitor and a promoter of the NF-κB pathway [59]. This effect was also accompanied by upregulation of 5-lipoxygenase and regulation of leukotriene B4 production, both of which are targets of miR-219 [59].

These two miRs are both endogenously expressed in resident peritoneal cells. Overexpression of miR-208a in human macrophages is accompanied by IL-10 upregulation [60]. The role of miRNAs in modulating the cardiovascular effects of aspirin through resolvins or lipoxins warrants study by further research.

ADP receptor antagonists

Ticlopidine, clopidogrel, and prasugrel are antagonists of the P2Y12 platelet adenosine diphosphate (ADP) receptor. ADP P2Y12 is one of the genes regulated by miR-223, a miRNA abundant in platelets, and also a key target of antiplatelet therapy. The circulating level of this miR has been reported to be inversely associated with major cardiovascular events in patients with CAD receiving antiplatelet treatment [61]. In a study by Ambrose et al., washed platelets from healthy subjects were stimulated with specific agonists of the receptors for collagen (glycoprotein VI (GPVI), thrombin (PAR1/PAR4) or ADP (P2Y1/P2Y12)) and then assessed the profile of microRNAs using TaqMan microRNA microarray cards. They showed that following the activation of platelets, the release of 46 miRNAs was stimulated with all agonists. miR-223-3p with a role in myeloid linage development and anti-inflammatory effects was the most abundant among these microRNAs and ADP was shown to play an important role in the release of microRNAs [62].

Significant inter-individual variability in pharmacokinetics exists among patients with a past myocardial infarction or stroke who receive clopidogrel, one of the most commonly used drugs for the secondary prevention of atherothrombotic events. About 1/3 of these patients receive no benefit from Clopidogrel; genetic variability in intestinal drug efflux through permeability glycoproteins (P-gp) and in metabolizing enzymes such as the cytochrome P450 (CYP) which converts inactive pro-drug to the active thiol metabolite are possible underlying causes. Aspirin, commonly co-administered with clopidogrel, decreases the bioavailability of clopidogrel by decreasing oral absorption and inducing intestinal permeability P-gp expression. The effect of aspirin administration on the pharmacokinetics of clopidogrel was investigated in 18 healthy volunteers with CYP2C19 and PON1 genotypes of cytochrome P450, an important metabolizing enzyme affecting the bioactivation of absorbed clopidogrel [63]. An increase (up to 7.67-fold) in the expression of miR-27a was found after aspirin administration [63]. MiR-27a is known to upregulate the expression of P-gp protein by inhibiting transcriptional factors such as phospholipase C/Raf/mitogen-activated protein kinase pathway or the C-terminal-binding protein 1 [64]. After coadministration with low dose of aspirin (2 and 4 weeks of once-daily 100-mg aspirin administration), the antithrombotic efficacy of clopidogrel was not decreased [65]. Aspirin significantly increased the level of plasma miR-27a, which peaked at 1 week after once-daily administration [64].

Among six miRNAs that were screened by high-throughput illumina sequencing in the plasma of patients with CAD undergoing coronary angiography and antiplatelet therapy with clopidogrel

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and aspirin, a high level of miR-142 resulted in an independent risk factor of major adverse cardiovascular events [66]. This result was subsequently validated in 1230 patients with CAD, thus suggesting miR-142 as a potential predictive marker in patients with pre-existent cardiovascular diseases [66].

Future directions

By clarifying the modulating effect of aspirin on miRNAs in the primary and secondary prevention of cardiovascular diseases, a better comprehension of the possible contributors to success or failure of aspirin treatment might be recognized and used to identify patients who benefit greatly from this therapy. Another topic worth studying is the possible use of miRNAs as a fast, reliable method of identification of patients with aspirin resistance.

Conclusion

MiRNAs play an important role in platelet function. Platelets make a substantial contribution to the circulating miRNA pool. Some miRNAs have been identified as antiplatelet. However, the potential confounding effects of the antiplatelet therapy should be considered when interpreting the findings of case–control studies evaluating circulating miRNAs in cardiovascular disease. Furthermore, miRNAs could be used as in vivo biomarkers when assessing platelet responses rather than the current ex vivo ones. At present, only few studies are available on the interactions between miRNAs and aspirin and further investigations are required.

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