Regulatory mechanism of miR-223 on platelet reactivity in ischemic stroke patients after clopidogrel treatment

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Abstract

Background: Recent studies have confirmed that microRNA-223 may participate in high-on clopidogrel treatment platelet reactivity. Clopidogrel requires hepatic enzyme metabolic activation to produce its metabolite with pharmacological activity, as a result, there are few researches about platelet reactivity. The aim of the current study is to explore the possible regulatory mechanism between microRNA-223 and platelet reactivity after clopidogrel treatment. Methods: In this study, we established an experimental model of MEG-01 cells treated with clopidogrel and human liver microsomes incubation system, so that the effects of clopidogrel active metabolites on megakaryocytes and platelets can be simulated. The relation of microRNA-223, C/EBP α and P2Y12 was further investigated by both cell experiments and clinical studies. Results: The ratio of platelet P2Y12 expression before and after treatment was significantly higher in Low Responders group (1.14604 vs 0.77097, p=0.031). After treatment at 200 ul/2 ml for 3 and 5 consecutive days, miR-223 expression in MEG-01 cells decreased by 47.3% and 32%, respectively ($p < 0.05$). P2Y12 mRNA expression was 193.4% higher after 3 consecutive days ($p < 0.001$), and significantly lower after 5 consecutive days than that in the negative control group ($p < 0.05$). P2Y12 and C/EBP α protein expression were significantly lower after 5 consecutive days ($p < 0.01$). Conclusions: A negative feedback loop was carried out by clopidogrel active metabolite to recede its inhibition of P2Y12 signal pathway through P2Y12-PI3K/Akt-C/EBP α-miR-223 pathway, which may be excessively activated and play a role in the occurrence of high-on clopidogrel treatment platelet reactivity.

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