




Terapie antipiastriniche e gestione delle complicanze

# PLATELET MIR-144-5P REGULATES COX-1/2 EXPRESSION AND MODULATES ASPIRIN RESPONSE IN PATIENTS WITH CARDIOMETABOLIC RISK

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**Background and Aims.** Interindividual variability in response to low-dose aspirin (ASA) contributes to residual platelet activation and thrombotic risk. Platelet microRNAs (miRNAs) may modulate ASA pharmacodynamics, but mechanistic insights remain limited. To investigate whether platelet miR-144-5p regulates cyclooxygenase (COX)-1/2 expression and modulates ASA response in cardiometabolic patients.

**Methods.** Two hundred ASA-treated patients were stratified into tertiles of serum thromboxane $B_2$ ($sTXB_2$) slope, an ex vivo marker of COX-1 recovery. Platelet and extracellular vesicle miR-144-5p levels were quantified by RT-qPCR and correlated with biochemical and clinical variables. Functional studies were performed in megakaryocytic (DAMI) and endothelial (HUVEC) cells transfected with miR-144-5p mimics or inhibitors to assess COX-1/2 regulation.

**Results.** Patients with poor ASA response (3rd tertile of $sTXB_2$ slope) exhibited reduced platelet miR-144-5p ($p=0.027$) and higher COX-1 mRNA/protein levels ($p\leq0.027$), whereas miR-144-5p was enriched in platelet-derived extracellular vesicles. Platelet miR-144-5p was inversely correlated with $sTXB_2$ ($\rho=-0.235$, $p=0.007$) and COX-1/2 mRNA expression. In DAMI (human megakaryocyte) cells, ASA exposure upregulated miR-144-5p cells; in addition, miR-144-5p overexpression suppressed, and inhibition enhanced, COX-1 protein levels. Similar effects were observed in HUVECs, where miR-144-5p downregulated both COX-1 and COX-2. Among our patients, platelet miR-144-5p were lower in those with obesity, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease, conditions known to affect aspirin response.

**Conclusions.** Platelet miR-144-5p directly regulates COX-1/2 expression and contributes to interindividual variability in ASA response. Low platelet miR-144-5p identifies patients with accelerated COX-1 recovery and residual thromboxane generation, providing a mechanistic basis for precision antiplatelet therapy and potential miRNA-targeted interventions.