Prostaglandin E2 promotes the release of angiogenic factors from platelets: role of EP3 receptor

F. Finetti, S. Valentino, M. Ziche, S. Donnini

Dept. of Life Sciences, University of Siena, Via Aldo Moro, 2, 53100 Siena, Italy

Platelets are a natural source of growth factors, cytokines and chemokines that regulate inflammation, angiogenesis, and malignancy. Prostaglandin E2 (PGE2) enhances aggregation of platelets sub-maximally stimulated in vitro. This results from activation of EP3, one of the four PGE2 receptors, which decreases the threshold at which agonists activate platelets to aggregate. We studied whether PGE2 promotes the release of angiogenic factors from platelets and the contribution of EP3 on this PGE2 effect on in vitro platelets isolated from mice wild type (WT) or knockout (KO) for EP3. Platelets collected from WT or KO EP3 mouse were studied using PGE2 at different concentrations, and selective agonists and/or antagonists of the EP receptor subtypes. Angiogenic factors release and function was assayed by western blot, EIA and matrigel assays. Incubation of platelets with PGE2 promoted VEGF, FGF2 and PDGF release. The concentration of growth factors was higher in WT than in EP3 KO platelet releasetes. Similar results were obtained by using PGE2 agonist and/or antagonist. Indeed, the EP3 antagonist significantly inhibited VEGF release from WP platelets incubated with PGE2. Further, incubation of the releasete from WT platelets with endothelial cells promotes pseudocapillary formation, while the releasete from EP3 KO platelets failed to induce pseudocapillary formation. Our findings provide evidence that EP3 modulates angiogenic factor release from platelets in response to PGE2. Because PGE2/EPs signaling pathways can influence the behavior of multiple cell types involved in angiogenesis and cancer, selective targeting of EP3-mediated PGE2 signaling might represent an attractive therapeutic strategy.

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