Inhibition of cyclooxygenase-1-dependent signaling between platelets and HT29 colon cancer cells by aspirin prevents upregulation of Twist-1 and repression of E-cadherin

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Twist-1 plays a key role in epithelial-mesenchymal transition (EMT) and metastasis by repressing E-cadherin-mediated cell-cell adhesion and inducing mesenchymal markers and cell motility (Kalluri et al., 2009). Prostaglandin(PG)E_2 signaling mediates EMT and cell migration/invasion (Dovizio et al. 2013). We aimed to address the hypothesis that:(i)tumor cell/platelet cross-talk induces PGE_2 release which may play a role in Twist-1 mRNA up-regulation and E-cadherin mRNA down-regulation, and (ii) selective inhibition of platelet-dependent PGE_2 by aspirin may affect these changes in gene expression. Co-cultures with human colon carcinoma cells (HT29) and platelets were performed for 20 h. In some experiments, platelets were pretreated with aspirin(300 microM), to completely suppress cyclooxygenase(COX)-1 activity. HT29 expressed PGE_2 receptors(i.e.,EP1, EP2 and EP4, but not EP3 and thromboxaneA_2 receptor). Exogenous PGE_2(1.5 ng/ml) added to HT29 cells induced a significant increase of Twist-1 mRNA and down-regulation of E-cadherin mRNA. In platelet-HT29 co-cultures, PGE_2 release(1.3$\pm$0.1ng/ml) was higher than in platelets and HT29 cultured alone. In co-cultures, HT29 mRNA levels of Twist-1 were significantly increased by 4-fold while E-cadherin mRNA levels were significantly reduced by 42% versus HT29 cultured alone. Aspirin pre-treatment of platelets prevented the changes of Twist-1 and E-cadherin mRNA levels in HT29 cells and they were rescued by the addition of PGE_2. In conclusion, selective inhibition of platelet COX-1-dependent PGE_2 by aspirin prevented enhanced expression of Twist-1 and down-regulation of E-cadherin caused in HT29 by platelet interaction. These results open the way to study in animal models and patients the role of this mechanism in the anti-metastatic effect of low-dose aspirin detected in clinical trials.

References

Kalluri R, Weinberg RA (2009) *J Clin Invest.***119:** 1420-8.
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