Aspirin inhibits metastasis in the intravascular phase through the blockade of COX-1-TXA_2 pathway in platelets

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Abstract

Evidence from experimental studies and clinical trials has shown that aspirin reduces the incidence of distant metastases. Aspirin inhibits cyclooxygenase (COX)-1 and COX-2, triggering anti-thrombotic and anti-inflammatory effects, respectively. However, the mechanisms underlying the anti-metastatic effect of aspirin are still largely unknown.

By employing mouse models of experimental and spontaneous metastasis, we have shown that aspirin and a selective COX-1 inhibitor dramatically reduced metastatic lung nodules, an effect that was not replicated by selective inhibition of COX-2. Metastasis was impaired in COX-1 deficient mice as well, suggesting a pivotal role of microenvironmental COX-1 in the metastatic process. In particular, COX-1 activity was essential during the intravascular phase of pulmonary metastasis. Using a model of platelet depletion and re-infusion we identified platelet-derived thromboxane A_2(TXA_2) as the main product of COX-1 responsible for its permissive effect on metastasis. The inhibition of the COX-1-TXA_2 pathway in platelets decreased the aggregation of platelets on tumor cells and was associated with a reduction in endothelial activation, in tumor cell adhesion to the endothelium, in recruitment of metastasis-promoting monocytes/macrophages and in transendothelial migration. Thus, platelet-derived TXA_2 orchestrates the generation of a favorable intravascular metastatic niche that promotes tumor cell seeding and metastasis.

Taken together, our data suggest that COX-1 inhibition in platelets by aspirin is sufficient to exert an anti-metastatic effect and shed a new light on COX-1-TXA_2 signalling in the context of tumor

cell dissemination. From this perspective, TXA_2 might present a more selective therapeutic target for the prevention of metastasis.