Targeting platelet purinergic signalling as a potential therapeutic approach for cancer

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Platelets(PLT) can interact with circulating cancer cells and contribute to tumor progression and metastasis. The mechanisms involve the induction of phenotypic changes known as epithelial to mesenchymal transition (EMT)(3,4) characterized by the acquisition of mesenchymal markers with the concomitant loss of epithelial ones (e.g. E-cadherin).

We have previously shown that immunodeficient NOD-scid IL2Rγnull mice injected with colon cancer cells (HT29), exposed in vitro to PLT, developed higher degree of metastases compared to mice injected with untreated cells. Aspirin administration reduced metastasis formation(1). Whether other antiplatelet agents, including antagonists of P2Y12 receptor, cause the same efficacy remains to be clarified.

We aimed to evaluate whether the interaction between PLT and HT29 cells in vitro was associated with EMT induction and cancer cell migration and the possible prevention by ticagrelor, an antagonist of P2Y12 receptor for ADP. Another objective was to characterize the expression profile of ATP P2Y and adenosine (ADO) receptors in HT29 cells. In fact, once released ATP and ADP are hydrolysed to AMP and subsequently to ADO by CD39 and CD73 respectively.

In PLT-HT29 cell cocultures we found down-regulation of E-cadherin (evaluated by qPCR and Western blot analysis) in the tumor cells. These changes were associated with enhanced cell migration using Boyden chamber assay. In the presence of ticagrelor (10 ?M), the down-regulation of E-cadherin and cell migration were prevented. Altogether the results suggest the involvement of P2Y12 in platelet-induced malignant phenotype in cancer cells. In order to clarify whether the drug acts only on the platelet receptor or affects also the purinergic receptors in HT29 cells, we characterized their expression in the cancer cells by reverse transcriptase polymerase chain reaction (RT-PCR).

HT29 cells expressed a wide array of metabotropic purinergic receptors including ATP P2Y1,2,4,12,13. These results suggest that ticagrelor may act not only by affecting the signalling of P2Y12 expressed on platelets but also in cancer cells. Moreover, we have found that HT29 cells also express CD73, which might lead to the accumulation of ADO into the extracellular milieu. Also, we detected the expression of ADO A1, A2a and A2b receptor types in HT29 cells.

In conclusion, P2Y12 antagonists may have anti-tumorigenic effect by preventing the cross-talk between PLT and cancer cells. Moreover, we have identified the expression of different purinergic receptors in cancer cells. Further investigation is necessary to clarify their contribution to cancer development and progression thus opening the way to additional therapeutics for a more effective combined anticancer strategy.

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