Author’s response to reviews

Title: Aspirin and P2Y12 inhibition attenuate platelet-induced ovarian cancer cell invasion

Authors:

Niamh Cooke (niamhcooke@rcsi.ie)
Cathy Spillane (clspilla@tcd.ie)
Orla Sheils (OSHEILS@tcd.ie)
John O'Leary (olearyjj@tcd.ie)
Dermot Kenny (dkenny@rcsi.ie)

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Author’s response to reviews: see over
Author's covering letter for initial submission

Title: Aspirin and P2Y12 inhibition attenuate platelet-induced ovarian cancer cell invasion

Authors:

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Comments: see over
Dear Editor,

We have revised our manuscript according to your requirement as outlined below.

1. **Line Numbering**: Line Numbering and page numbering have been added to the manuscript.

2. **Please include a title page at the front of your manuscript file. It should contain, at minimum, the names, institutions, countries and email addresses of all authors, and the full postal address of the submitting author.** Our manuscript already has a title page with detailed author information. In case this was not clear, we have now added an additional title page to include the names, institutions, countries and email addresses of all authors, and the full postal address of the submitting author.

Yours sincerely,

Dr Niamh Cooke

The aim of our study was to determine if the interaction between ovarian cancer cells and platelets can facilitate metastasis in the bloodstream, and if the use of antiplatelet agents effect these interactions. While many studies have shown that platelets play a role in successful hematogenous dissemination, it is unknown if they can drive different metastatic phenotypes in ovarian cancer. Furthermore, in light of accumulation data on the cancer-protective effect of aspirin, the mechanism by which it mediates reduced morbidity, mortality and metastasis remains poorly understood.
In this study we demonstrate that platelet interactions with two metastatic ovarian cancer cell lines are significantly heterogeneous. In comparison to 59M cells, SK-OV-3 cells induced significantly higher levels of both platelet adhesion and activation. In turn, platelets significantly promoted the ability of SK-OV-3 cells to invade, not 59M cells. Morphology and transcriptome analysis indicated that platelets induce an epithelial-to-mesenchymal transition (EMT) phenotype in SK-OV-3 cells, a process known to promote metastasis. Upon further interrogation, we demonstrate that both aspirin and P2Y₁₂ inhibition can abrogate the invasion-promoting properties of platelets on SK-OV-3 cells.

To our knowledge, this is the first study to give an in-depth account of how platelet adhesion to ovarian cancer cells transforms them into an EMT phenotype, both functionally and at a molecular level, which is essential for migration, extravasation and formation of distant metastasis. Moreover, we also demonstrate for the first time that inhibiting platelet function disrupts the critical extravasation step in the cascade of metastatic ovarian cancer. Since this work provides the scientific and clinical community with new and important information regarding the role of platelets in ovarian cancer metastasis, we believe it is of great relevance to the readers of Molecular Cancer, and we request that you would kindly consider it for publication. This report is not under consideration for publication elsewhere and all named authors have agreed to its submission.

Yours sincerely,

Dr Niamh Cooke