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METASTASIS

Exit this way

> tumour cell-activated platelets secrete adenine nucleotides, which … induce the opening of the endothelial barrier

Tumour cell-mediated activation of platelets is known to correlate with metastatic potential but the mechanisms through which the promotion of metastasis by activated platelets occurs are unknown.

Activated platelets secrete both α-granules and dense granules, and it has been suggested that factors stored in these granules might facilitate metastasis. So, Offermanns and colleagues investigated whether these platelet-derived granules facilitate the extravasation of disseminated tumour cells through the endothelium. They showed that tumour cell migration through endothelial cells in an *in vitro* assay was dependent on secreted factors from platelets, which were activated by co-incubation with various tumour cell lines. Further investigation revealed that platelet-derived adenine nucleotides, which are stored in dense granules, were responsible for this effect and that they also resulted in the opening of the endothelial barrier (through the loss of junctional contacts). Next, the authors made use of a transgenic mouse model, MUNC13-4-deficient mice, which have platelets that are unable to secrete dense granules. They found that subcutaneous injection of B16 melanoma and Lewis lung carcinoma (LLC1) cells into these mice resulted in the formation of primary tumours to the same extent as in wild-type mice but that the number of metastases was significantly reduced in MUNC13-4-deficient mice. Numbers of metastases were also significantly reduced when these cells were injected into the tail vein of MUNC13-4-deficient mice.

How do adenine nucleotides secreted from platelets promote transendothelial migration of disseminated tumour cells? The authors looked at purine nucleotide receptors expressed by endothelial cells and found that knockdown of P2Y purinoceptor 2 (P2Y2) in endothelial cells prevented the platelet-induced transendothelial migration of tumour cells and increased permeability of the endothelium *in vitro*. Moreover, tail vein injection of labelled dextran and B16 cells revealed that extravasation into the lung parenchyma of dextran followed by B16 cells was prevented in both MUNC13-4-deficient and P2Y2-deficient mice. P2Y2 loss also significantly reduced the numbers of lung metastases formed by tail vein injection of LLC1 cells and B16 cells.

Therefore, Schumacher, Strilic *et al*. have shown that tumour cell-activated platelets secrete adenine nucleotides, which engage P2Y2 signalling in endothelial cells and induce the opening of the endothelial barrier. This allows tumour cell extravasation and thus promotes metastasis.

Gemma K. Alderton

ORIGINAL RESEARCH PAPER Schumacher, D. *et al.* Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor. *Cancer Cell* **24**, 130–137 (2013)

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