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METASTASIS

Bringing up the rear

The extent of the requirement for functional migration machinery in tumour dissemination remains unclear. In *Cancer Cell*, James Quigley and colleagues report that blocking the function of the tetraspanin CD151 *in vivo* prevents tumour dissemination by inhibiting migration and access to the vasculature (intravasation) at primary tumour sites.

Tetraspanins are transmembrane proteins that interact with α-integrin subunits and mediate integrin function by regulating cytoplasmic signalling. In this study, injecting anti-CD151 monoclonal antibody (mAb 1A5) into chick embryos or mice bearing human tumours led to a reduction of more than 80% in spontaneous metastasis without having any affect on primary tumour growth.

But how does blocking tetraspanin CD151 interfere with metastasis? The authors first showed that mAb 1A5 treatment both reduced cell migration on different matrices and enhanced focal adhesion formation, suggesting that blocking CD151 inhibits migration by promoting cell–matrix interactions. They then analysed tumour cell behaviour *in vivo* using real-time intravital imaging of individual cells. The authors initially intravenously injected green fluorescent protein-expressing tumour cells with mAb 1A5 to assess whether the anti-CD151 antibody interferes with extravasation. Tumour cells underwent arrest in the vasculature, extravasation and proliferation, but failed to disseminate throughout the stroma. Thus, blocking CD151 does not affect cell extravasation, but does prevent migration within the stroma after departing from the vasculature.

However, inhibition of migration after extravasation would not explain the significant reduction in metastases in animal models, so the authors reasoned that CD151 must be important for cell departure from the primary tumour site. Normally, aggressive metastatic tumours show irregular invasive fronts due to cell migration into the surrounding stroma and along the vasculature. By contrast, antibody-treated tumours had a clearly defined border at the tumour–stroma interface and showed little or no invasion of the surrounding tissue and vasculature. The authors observed that although some residual movement was present, both migration velocity and persistence were reduced within primary tumours, resulting in cells inefficiently moving away from their start position. Furthermore, enhanced single-cell images revealed that although cells moved forward, the rear remained attached to the original location. Interestingly, the loss of CD151 expression has little effect on cell migration *in vivo*, suggesting that mAb 1A5 binding promotes tumour cell immobility. Finally, Quigley and colleagues observed that treating animals with mAb 1A5 prevented tumour cells from entering the vasculature.

This work shows that cell migration is an active contributor to tumour dissemination. Blocking the tetraspanin CD151 prevents de-adhesion at the rear of the cells and prevents motility. It does not affect tumour growth or extravasation, but interferes with two crucial steps in the metastatic cascade: detachment from the primary tumour and intravasation. Inhibition of de-adhesion could therefore be a powerful approach to prevent metastasis.

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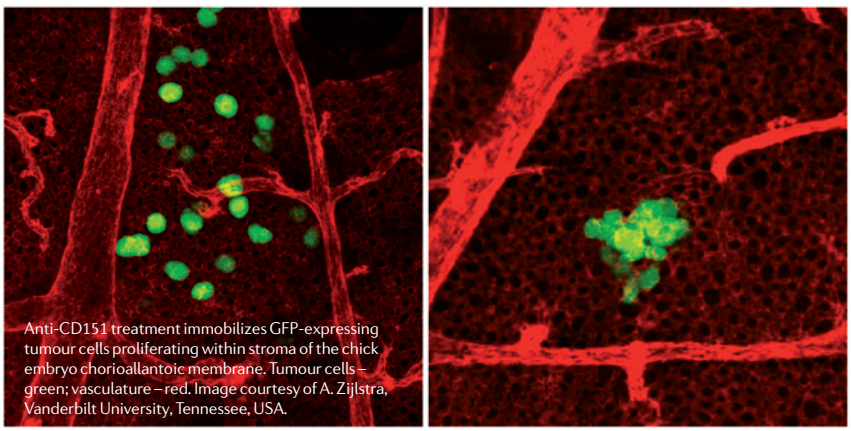
ORIGINAL RESEARCH PAPER Zijlstra, A., Lewis, J., Degryse, B., Stuhlmann, H. and Quigley, J. P. The inhibition of tumor cell intravasation and subsequent metastasis via regulation of *in vivo* tumor cell motility by the tetraspanin CD151. *Cancer Cell* **13**, 221–234 (2008).



Anti-CD151 treatment immobilizes GFP-expressing tumour cells proliferating within stroma of the chick embryo chorioallantoic membrane. Tumour cells – green; vasculature – red. Image courtesy of A. Zijlstra, Vanderbilt University, Tennessee, USA.