PUBLICATION REVIEW

Impairment of a distinct cancer-associated fibroblast population limits tumour growth and metastasis

Cancer-associated fibroblasts (CAFs) are one of the most plentiful cell types in the diverse tumor microenvironment. There are, however, many subtypes of CAFs that are not easily identified with known biomarkers. There is a need to further study fibroblasts to understand how to mitigate the pro-tumor properties of some subtypes and harness the tumor-suppressive capabilities of others.

To better understand the functional properties of CAFs, this study evaluated the role of a CAF receptor, Endo180, which is predominantly expressed by fibroblasts with little to no expression in tumor cells. Using genetic analysis and a host of analytical methods, they discovered that Endo180 promotes tumor growth and its depletion is associated with impaired contractility and increased fibroblast apoptosis. This study elucidates the role of an important fibroblast marker in tumor survival and metastatic potential.

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Publication highlights:

This study utilized multiple imaging techniques to study different subtypes of fibroblasts and their role in tumor development. Revvity's IVIS® imaging system noninvasively tracked primary and metastatic tumor burden *in vivo*, while the Celigo® and Operetta® provided high resolution images of spheroids and cells, respectively. Findings from each imaging system contributed to the understanding of the role of the CAF receptor Endo180 in the tumor microenvironment.

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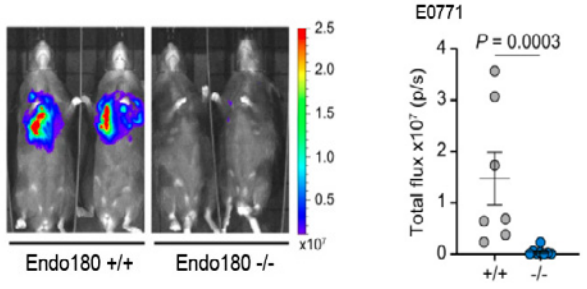

Luciferase expressing syngeneic E0771 mouse mammary carcinoma cells were i.v. injected into Endo180+/+ (WT) and Endo180-/- C57BL/6 mice. *In vivo* bioluminescence imaging was performed after injection of IVISbrite™ D-Luciferin to non-invasively image tumor burden using IVIS optical imaging technology. WT mice developed large macrometastatic lung lesions, while Endo180-/- mice showed impaired tumor growth. Image quantification using Living Image® software validated the *in vivo* observations. These results support the suggestion that Endo180 plays a significant role in supporting metastatic tumor growth.

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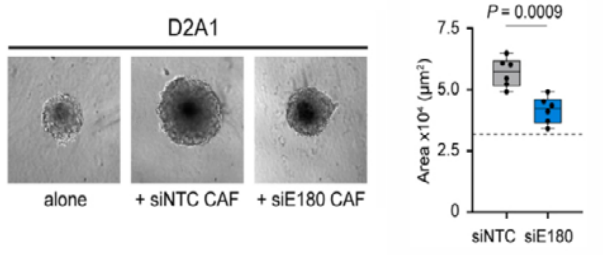
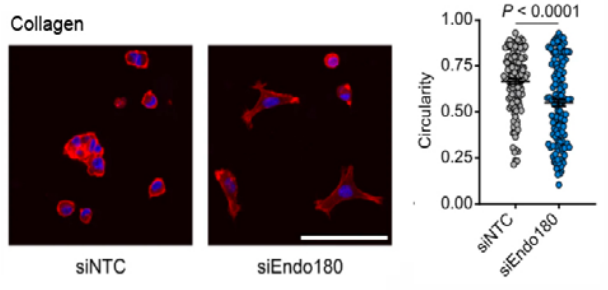


CAFs transfected with either Dharmacon™ non-targeting control siRNA (siNTC) or Endo180-targeting siRNA (siE180) were co-seeded with mouse mammary carcinoma D2A1 cells and spheroid growth was monitored using the plate-based Celigo® Image Cytometer. Representative spheroid images and spheroid area quantification from the Celigo show that admixing D2A1 cells with siE180 CAFs results in significantly impaired spheroid growth as compared to siNTC CAFs.

C



Dharmacon™ siNTC and siE180 CAFs were plated onto collagen-coated soft (2 kPa) hydrogels. Automated imaging using the Operetta® High-Content Analysis System was performed after staining with DAPI and Alexa555-phalloidin, and using ViewPlate™ 96-well black optically clear bottom plates. Cell shapes were analyzed automatically by the Harmony® High-Content Imaging & Analysis Software. The high-content imaging and analysis illustrated the cytoskeletal contraction and rounding of siNTC CAFs as compared to siE180 CAFs, which remained spread.

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