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ANGIOGENESIS

Sneaky switch

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URLs
MMP9
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=4318
VEGF
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7422

Solid tumours contain both transformed cells and non-neoplastic cell types such as macrophages and neutrophils, which have been shown to increase the invasive and metastatic properties of tumour cells and to promote tumour growth. Now, Douglas Hanahan and colleagues have shown that tumour formation in a transgenic mouse model of multistage carcinogenesis is promoted by tumour-infiltrating neutrophils that activate angiogenesis.

RIP1–Tag2 mice, which express the simian virus 40 (SV40) large T antigen (Tag) under the control of the rat insulin promoter 1 (RIP1), develop angiogenic dysplasias and, subsequently, tumours of the pancreatic islets. Previous studies showed that an important trigger of angiogenesis in this model is matrix metalloproteinase 9 (MMP9), which seems to function by increasing the availability of the pro-angiogenic vascular endothelial growth factor (VEGF). However, in this model the tumour cells do not express MMP9.

So, to identify the non-tumour cells that express MMP9, the authors compared normal and neoplastic pancreatic tissues using double-label immunohistochemical staining of MMP9 and leukocyte cell-specific markers. Neutrophils were the only MMP9-positive cells found within islet lesions, and were therefore the prime candidates for MMP9-mediated activation of angiogenesis. The next step was to show the functional involvement of neutrophils *in vivo*.

Giving a neutrophil-depleting antibody to young RIP1–Tag2 mice, in which neutrophil infiltration and angiogenic switching occurs in hyperplastic lesions, halved the number of angiogenic islets compared with mice that received a nonspecific antibody. This effect was similar to either administering an MMP9 inhibitor or deleting the *Mmp9* gene, which indicates that neutrophils are the main cell type responsible for angiogenic switching. Antibody-mediated neutrophil depletion reduced the presence of VEGF–VEGF receptor complexes on the endothelial cells of angiogenic islets by sevenfold, consistent with the expected molecular mechanism of switching.

These findings show that infiltrating neutrophils have a key role in switching on angiogenesis during the early stages of pancreatic tumour development. Establishing whether neutrophils have a similar role in the early progression of other animal and human tumours and identifying the mechanisms that sustain angiogenesis after it has been switched on are important next steps.

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ORIGINAL RESEARCH PAPER Nozawa, H. *et al.* Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis. *Proc. Natl Acad. Sci. USA* **103**, 12493–12498 (2006)