ABSTRACT

Metastasising tumours is the main death cause among cancer patients today and tumour blood vessels have been a central target in research of cancer treatment over the last years.

During development the neural cell adhesion molecule (N-CAM) is known to be involved in morphogenesis; regarding cell migration, neurite extension and fasciculation. It was recently shown that N-CAM also has a protective role in tumourigenesis. When deleting N-CAM in a tumour mouse model it started to metastasise.

We have demonstrated that loss of N-CAM cause tumour blood vessels to loose their integrity, change expression pattern of extracellular matrix molecules, and detach pericytes from the endothelium. Further on, these events leads to extended blood vessel leakage and connection of intratumoural cavities with the vasculature, creating a plausible route for isolated cell clusters within the cavities to metastasise. Correlating results were obtained by gain of function experiments, where N-CAM was overexpressed in a fibrosarcoma cell line. Transplanted cells resulted in tumours with increased blood vessel density, improved pericyte recruitment and faster growth. The role of pericytes in metastasis was tested by crossing the tumour mouse model with a transgenic mouse deficient in pericyte integration into the blood vessel wall. We showed that an impaired pericyte attachment to the endothelium alone was enough to initiate metastasis.

N-CAMs effect on pathological angiogenesis was also studied in the retina, using the oxygen induced retinopathy (OIR) model. This system represents the condition present in, e.g. diabetic retinopathy and retinopathy of prematurity (ROP). N-CAM deficient mice generated less pathological angiogenesis, in form of smaller and fewer tufts.

In summary, by using loss- and gain-of function in two independent tumour models, we have shown that N-CAM plays a role in tumour blood vessel integrity crucial in limiting tumour metastasis. Loss of N-CAM also limits pathological angiogenesis in the retina.