CELL MIGRATION

Cytokine cues

The generation of contractile forces in both tumour cells and the surrounding stromal cells is necessary to create a permissive environment for cancer cell migration and metastasis, but the signals controlling actomyosin contractility are not well understood. Chris Marshall's laboratory working on melanoma cell migration and Cedric Gaggioli's laboratory working on carcinoma-associated fibroblasts (CAFs) in squamous cell carcinoma have shown that a cytokine signalling pathway activating the kinase JAK1 is important in both cell types.

Previous work showed that CAFs use contractile force to remodel the extracellular matrix, thereby creating tracks along which cancer cells can migrate as collective strands; this can be blocked by a pan-JAK kinase inhibitor, P6. The authors treated CAFs that were cultured from an oral squamous cell carcinoma (SCC) with isoform-specific JAK inhibitors and found that JAK1 is the crucial isoform. Knockdown of JAK1 by RNA interference (RNAi) in CAFs reduced RHO kinase (ROCK)-dependent phosphorylation of myosin light-chain 2 (MLC2) and prevented invasion of the SCC cell line SCC12 in an organotypic assay. The importance of JAK1 signalling was confined to the CAFs, as SCC12 cells could still invade in the presence of P6 if untreated CAFs were first allowed to remodel the matrix. JAK1 inhibition also reduced MLC2 phosphorylation

and actomyosin contractility in A375M2 melanoma cells, leading to an elongated rather than a rounded amoeboid morphology.

How is JAK1 activated in these cells? RNAi-mediated knockdown of the GP130-IL6ST subunit, which is common to several cytokine receptors, phenocopied JAK1 loss in both CAFs and A375M2 cells, and *in vivo* imaging of A375M2 xenografts indicated that GP130-IL6ST depletion reduced amoeboid motility of the tumour cells. Different cytokines can activate signalling through GP130-IL6ST, and the authors showed that oncostatin M (OSM) was crucial in CAFs, whereas interleukin-6 (IL-6) activated this pathway and increased invasion in several melanoma cell lines.

One consequence of JAK signalling is activation of the signal transducer and activator of transcription (STAT) family of transcription factors. STAT3 phosphorylation required ROCK and JAK activity, and STAT3 depletion reduced MLC2 phosphorylation and the amoeboid morphology of A375M2 cells. STAT3 was also essential for CAF-mediated matrix remodelling and SCC12 cell invasion *in vitro*. Furthermore, gene expression analyses showed that STAT transcriptional networks,

including GP130-IL6ST and other cytokine-signalling components, are activated under conditions of high contractility, suggesting that positive feedback via STAT3-mediated transcription could occur.

Does this pathway operate *in vivo*? Estimation of cell shape in primary melanomas from 85 patients indicated that the cells in the invasive front of the majority of tumours were rounded and had higher levels of phosphorylated STAT3; similar data were observed in A375M2 xenograft tumours. Interestingly, the examination of metastases from 16 patients showed that metastases were most often composed of rounded cells, but some did have an elongated morphology that correlated with lower STAT3 phosphorylation.

It will be interesting to determine to what extent this pathway operates in other tumour types and whether blocking JAK-STAT signalling can prevent metastasis.

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ORIGINAL RESEARCH PAPER Sanz-Moreno, V. *et al.* ROCK and JAK1 signaling cooperate to control actomyosin contractility in tumor cells and stroma. *Cancer Cell* 20, 229–245 (2011)