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METASTASIS

Moved to act

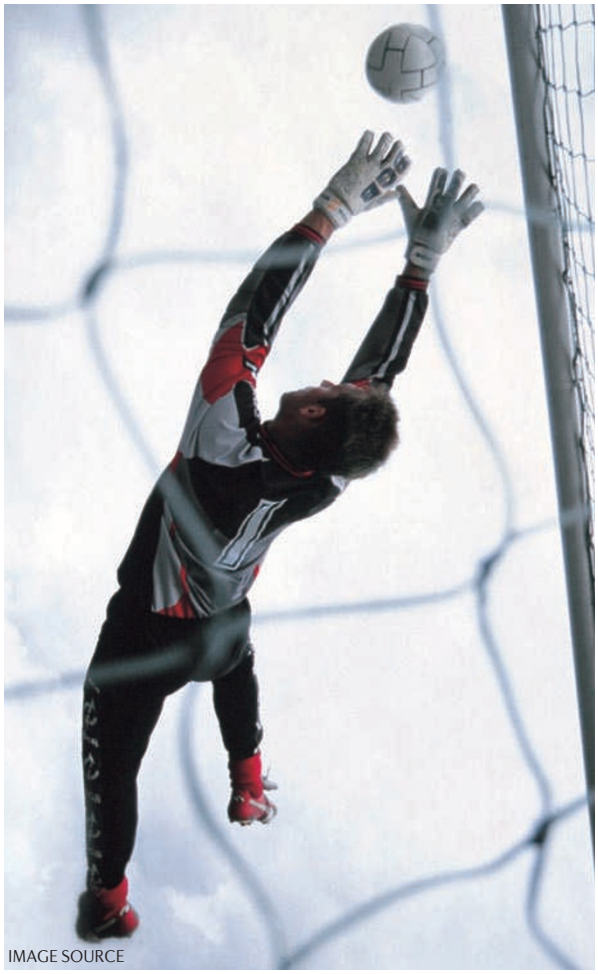

IMAGE SOURCE

The Rho family of small GTPases is known to be important for the regulation of cell motility. A recent paper by Chris Marshall and colleagues published in *Cell* has shown that differential activation of Rac and Rho determines the type of movement that a cell uses.

Individual tumour cells can move either in an amoeboid-like motion, where cells appear rounded, can change direction rapidly and require less proteolytic activity, or as mesenchymal-like cells, which are elongated, show stable polarity in the direction of movement and need to produce proteases in order to migrate through an extracellular matrix. Marshall and colleagues used these morphological differences in a small interfering RNA (siRNA) screen to identify guanidine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) that regulate Rho GTPase function. They screened a melanoma cell line that displays primarily amoeboid movement and found that knockdown of dedicator of cytokinesis 3 (DOCK3) suppressed the appearance of elongated cells. DOCK3 is a Rac GEF, so the authors investigated the function of Rac in converting cells between amoeboid and mesenchymal-like motility. Silencing of *RAC1* led to a loss of elongated cells; moreover, cells infected with a dominant-negative *RAC1* showed only rounded morphology. Further experiments showed that activation of Rac was associated with cellular elongation and mesenchymal-like motility and that this required DOCK3 and a member of the p130^{cas} family of docking proteins, NEDD9, which is encoded by a potential melanoma metastasis gene.

Several results indicated that suppression of Rac activity might be required for amoeboid movement. Activation of ROCK is required for this type of movement, so the authors investigated whether a Rac GAP downstream of ROCK was involved in Rac suppression. An siRNA screen of GAPs showed that inhibition of ARHGAP22 led to elongation of the melanoma cells, and that this was associated with an increase in Rac activity. In agreement with this, the authors found that phosphorylation of myosin light chain (MLC2) through the Rho–ROCK pathway was reduced in elongated cells expressing active RAC1. Further investigation showed that WAVE2, which functions downstream of Rac, mediated the suppression of MLC2 activity. Thus, activation of the NEDD9–DOCK3–Rac pathway promotes mesenchymal-like motility at the expense of amoeboid movement by suppressing MLC2 activation.

How do these findings relate to cancer cell motility and invasion? Importantly, blocking the NEDD9–DOCK3–Rac pathway led to suppression of the mesenchymal-like motility, but cells continued to invade an extracellular matrix using amoeboid movement. To suppress cell motility and invasion both the ROCK–ARHGAP22 and NEDD9–DOCK3–Rac pathways had to be blocked. Furthermore, tail vein injections of mesenchymal-like metastatic melanoma cells expressing siRNAs targeting either DOCK3 or RAC1 showed greater colonization of the lungs than controls, suggesting that amoeboid cell behaviour may be more efficient for establishing metastases.

The authors conclude that the expression levels of NEDD9, DOCK3 and ARHGAP22 are important for determining the mode of movement of melanoma cells and that switching between the two types of motility increases the plasticity of these cells *in vivo*.

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ORIGINAL RESEARCH PAPER Sanz-Moreno, V. *et al.* Rac activation and inactivation control plasticity of tumour cell movement *Cell* **135**, 510–523 (2008)
FURTHER READING Sahai, E. Illuminating the metastatic process. *Nature Rev. Cancer* **7**, 737–749 (2007)