CELL MIGRATION

Follow the leader!

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How tumour cells invade the surrounding tissue remains an open question in cancer biology. While various models exist, a popular concept being the epithelial-to-mesenchymal transition, Erik Sahai and colleagues now provide evidence for an alternative mechanism of epithelial cell invasion that does not involve transition to a mesenchymal state. Instead, squamous cell carcinoma (SCC) cells that retain epithelial characteristics exploit the matrix remodelling ability of nearby mesenchymal cells and follow in their tracks.

Using an organotypic culture model in which SCC cells are grown on a dense matrix, the authors showed that introducing fibroblasts (derived from oral or vulval SCCs) into the culture induced the collective invasion of SCC cells into the underlying matrix, whereby SCC cells invaded in a chain-like manner. The extent of SCC cell invasion depended on the number of fibroblasts introduced. Indeed, close contact with fibroblasts was required for SCC cell invasion, and further analyses showed that fibroblasts led the chains of invading SCC cells.

> “...different cell types within a tumour can cooperate to mediate collective invasion into the surrounding tissue...”

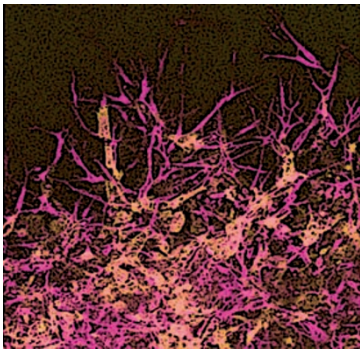

Image of invading fibroblasts leading chains of SCC cells in organotypic culture (colours are artificial). Image courtesy of E. Sahai, Cancer Research UK London Research Institute, London, UK.

The leading fibroblasts appeared to be remodelling the surrounding matrix into tracks, characterized by thick collagen bundles on the sides and an absence of matrix in the centre. So, do the fibroblasts generate these tracks for SCC cells to move through? To answer this question, Sahai and colleagues precultured the organotypic matrix with SCC-derived fibroblasts, and seeded the SCC cells following removal of the fibroblasts. The SCC cells invaded the precultured matrix, indicating that rather than secreting a soluble factor, physical conditioning of the matrix by the fibroblasts promotes SCC cell invasion.

But what is the mechanism that results in these fibroblast-induced tracks? The authors showed that RhoA- and Rho-associated kinase (ROCK)-dependent regulation of actin–myosin interactions was required to induce force-mediated matrix remodelling by the leading fibroblasts. Fibroblasts still invaded the matrix when Rho and ROCK were inhibited, but the SCC cells were unable to follow. Interestingly, only the fibroblasts were affected by Rho and ROCK inhibition, because SCC cells in which ROCK was inhibited continued to invade collectively behind fibroblasts. Next, the authors addressed which integrin family of matrix receptors was involved. Small interfering RNA-mediated depletion of α3 and α5 integrins in the fibroblasts prevented track formation and, hence, collective SCC cell invasion. Conversely, they showed that SCC cells required Cdc42 and its effector kinases MRCKα and MRCKβ (which regulate myosin light chain) to follow invading fibroblasts.

To establish whether this type of invasion is clinically relevant, Sahai and colleagues analysed sections of head and neck SCCs and showed that invading SCC cells were closely associated with fibroblasts within tracks reminiscent of those observed in the organotypic cultures. Using an affinity probe to detect active Rho, they also showed that Rho was active both in stromal fibroblasts and in SCC cells of the tumour, and that the surrounding non-tumour tissue exhibited little activation. Therefore, these findings indicate that different cell types within a tumour can cooperate to mediate collective invasion into the surrounding tissue, with distinct pathways regulating the cytoskeleton and cell adhesion in leading fibroblasts and the SCC cells that follow them.

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ORIGINAL RESEARCH PAPER Gaggioli, C. *et al.* Collective invasion of carcinoma cells is led by fibroblasts; distinct roles for integrins and RhoGTPases in leading and following cells. *Nature Cell Biol.* 25 Nov 2007 (doi: 10.1038/ncb1658)
FURTHER READING Sahai, E. Illuminating the metastatic process. *Nature Rev. Cancer* **7**, 737–749 (2007)