## **METASTASIS**

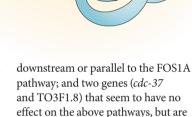
## Pushing on through

Metastasis is a complex process of which we still understand little, but the parallels between metastasis and cell invasion during development can give us some clues. During the development of a connection between uterine cells and vulval cells in the nematode *Caenorhabditis elegans*, one cell, the anchor cell (AC), has to invade through a basement membrane. By identifying genes that regulate this process in *C. elegans*, David Sherwood and colleagues have found new metastasis genes.

Loss of genes that regulate uterine-vulva attachment in *C. elegans* results in two clear phenotypes: protruded vulva (Pvl) and egg-laying defective (Egl). Sherwood and colleagues used the 539 genes identified in previous RNA interference (RNAi) screens that induce these phenotypes to find 99 genes specifically involved in AC invasion through the basement membrane. Focusing on the genes that produced the most severe invasion defects after RNAi-mediated knockdown, they found that members of the cct chaperonin complex and six other genes — mep-1 (a zinc finger transcription factor), lit-1 (an orthologue of nemo-like kinase (NLK)), cdc-37, T03F1.8 (a guanylate kinase) and two uncharacterized genes (cacn-1 and T20B12.1) — were all upregulated in the AC before or during invasion. Vulval cells are known to induce AC invasion and

the authors found that two genes, hbl-1 and unc-62 (orthologues of hunchback and homothorax, respectively), are required for vulval cell development and maturation ahead of AC invasion. Before invasion through the basement membrane occurs, netrin and integrin are known to establish an F-actin-rich invasive membrane in the AC. RNAi silencing of members of the cct complex, hda-1 (a histone deactylase) or mep-1 resulted in an absence of invasive membrane formation, and these genes seem to function independently of netrin and integrin.

Two transcription factors, FOS-1A and EGL-43L, are known to regulate the expression of the zinc metalloproteinase (zmp-1), which is required for basement membrane removal. Loss of five of the genes in the screen resulted in decreased zmp-1 expression, one of which (lit-1) was shown to be regulated by FOS-1A, and loss of cct, hda-1 and mep-1 resulted in reduced levels of FOS-1A and decreased expression of zmp-1. These results indicate that there are three main groups of genes that regulate AC invasion: upstream regulators that control the formation of the invasive AC membrane and removal of the basement membrane through the FOS-1A pathway; genes that are



involved in AC invasion.

Although the human orthologues of some of these genes (FOS, EVI1 (egl-43L), HDA1 and CDC37) are involved in metastasis, the authors also found that CCT5 and NLK could inhibit the ability of human tumour cells to invade a basement membrane, but had no effect on cell proliferation or migration.

These findings add to the evidence that invasion programmes that occur during development are relevant to metastasis, and further analyses of more of the genes identified in this paper should continue to contribute to our understanding of normal and pathological cell invasion.

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