A Reverse Genetic Approach to Identify Novel Regulators of Cell Invasive Behavior

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Tumor metastasis by migration through basement membranes, in a process known as cell invasion, contributes to the lethality of cancers. Cell invasion, a conserved behavior found in many developmental processes throughout the Metazoa, is also employed reproductive development in the nematode species, C. elegans. Any defect in the process of vulval morphogenesis can cause malformation of the vulva, resulting in a protruding vulva phenotype (Pvl). Using information from a nematode database and previous studies, twenty-two genes associated with the production of Pvls were selected for individual knockdown via RNA interference (RNAi) and subsequent invasion scoring, which would determine anchor cell invasion as the driving force behind the Pvl. Three of the eight genes yielding Pvls, capg-2, rnr-2 and C23G10.8, showed anchor cell invasion defects as visualized through fluorescence microscopy. Upon further investigation, capg-2, with the greatest defect of 53.8% Pvl penetrance and 58.06% invasion defect penetrance, was associated with the matrix-metalloproteinase pathway of enzymatic membrane breakdown, a process critical to tumor cell migration. Capg-2 was also determined as cell-cycle independent. The suggested dual role is a novel finding directly contrasting the current belief that invasion and proliferation occur simultaneously and suggests the processes to be distinctly regulated. Additionally, a novel C. elegans strain was created, in which green fluorescence of the anchor cell and the underlying vulval precursor cells was engineered into a preexisting strain for improved visualization of the structures, enabling better utilization of the model species to investigate important implications in the inhibition and regulation of cancer metastasis.

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