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Cell Biology

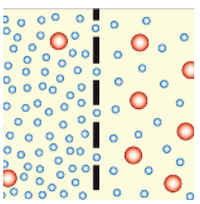
Main finding: Water and ion flux across cell membranes drives motility of cancer cells within confined spaces.

Concept: Aquaporin and Na^+/H^+ pumps concentrate at the leading edge of osmotically locomoting cells.

Impact: Motility based on water permeation represents an alternative to actin/myosin–based locomotion.

AN OSMOTIC ENGINE DRIVES CELL MOTILITY IN TIGHTLY CONFINED SPACES

Metastasizing tumor cells crawl atop other cells and squeeze through narrow channels, or microtracks, in the extracellular matrix (ECM) to reach new tissues. Migration upon two-dimensional surfaces requires actin cytoskeleton polymerization and myosin motor protein contractility, but recent studies have suggested that that confined migration of cancer cells can be actin and myosin independent. Stroka and colleagues hypothesized that cells migrating within a confined environment can generate propulsive force by balancing a net inward flow of ions and water at the cell's leading edge with a net outflow at the trailing edge. The model predicts that ion pumps and water channels in the cell membrane would be spatially biased toward the leading edge, and also that changes to osmolarity in the extracellular environment in front of or behind the cell could affect the velocity or the direction of movement. Consistent with this model, when migration along ECM microtracks was simulated using narrow channels in a microfluidic device, the motility of metastatic



breast cancer cells and mouse sarcoma cells toward a chemoattractant occurred even when actin and myosin contractility was inhibited, but this motility was strongly impaired after knockdown of either the water channel aquaporin 5 (AQP5) or the Na^+/H^+ exchanger NHE1. As the model predicted, both these proteins were distributed in polarized fashion toward the leading edge of migrating cells. Further, hypotonic shock at a cell's leading edge or hypertonic shock at the trailing edge caused changes in cell volume and subsequent reversal in the direction of migration, even when this caused cells to move away from chemotactic signals. These data demonstrate that cell motility within confined environments can be accomplished through an osmotic mechanism despite inhibition of actin polymerization or myosin contractility. ■

Stroka KM, Jiang H, Chen SH, Tong Z, Wirtz D, Sun SX, et al. Water permeation drives tumor cell migration in confined microenvironments. Cell 2014;157:611–23.

Tumor Heterogeneity

Major finding: Distinct subclones within mammary tumors functionally cooperate in a WNT-driven model system.

Concept: *Wnt1*^{low} basal subclones rely on and recruit *Wnt1*^{high} luminal cells to maintain oncogenic signaling.

Impact: Clonal cooperation in human tumors may affect clinical behavior and response to therapeutics.

COOPERATIVE SUBCLONES DRIVE TUMOR MAINTENANCE IN A BREAST CANCER MODEL

Intratumoral heterogeneity is a common feature of many human malignancies, including breast cancer, but its relevance to tumor initiation or maintenance is unclear. To gain insight into the relationship of individual subclones within a tumor, Cleary and colleagues utilized a mouse model system in which mammary tumors are driven by *Wnt1* transgene expression and are characterized by the coexistence of both low *Wnt1*-expressing (*Wnt1*^{low}) basal and high *Wnt1*-expressing (*Wnt1*^{high}) luminal lineages. A subset of *Wnt1*-induced tumors spontaneously acquired somatic *Hras* mutations restricted to the basal cell subtype, suggesting a biclonal configuration; however, both lineages were required for tumor formation in secondary recipients and depended on *Wnt1* expression by luminal cells. In a related mouse model with doxycycline (DOX)-inducible *Wnt1* (iWNT) expression, biclonal mammary tumors regressed upon DOX withdrawal. However, iWNT-derived *Hras*-mutant basal tumor cells transplanted into mice constitutively expressing *Wnt1* only partially regressed upon DOX withdrawal and spontaneously relapsed. In relapsed tumors, host-derived *Hras*–wild-type *Wnt1*^{high} luminal cells were invariably recruited by and intermingled with donor *Wnt1*^{low} *Hras*-mutant basal tumor cells, suggesting that *Hras*-mutant *Wnt1*^{low} donor basal subclones recruited host luminal epithelial cells to serve as a source of WNT1. In the absence of a substitute WNT1 source, DOX-deprived iWNT tumors regressed but frequently relapsed weeks later as DOX-independent tumors, mimicking acquired resistance to targeted therapy. The WNT pathway was reactivated in the majority of DOX-independent tumors, either through mutations that allowed DOX-independent WNT1 transgene expression or through activating mutations in *Ctnnb1*, which encodes the WNT1 downstream effector β-catenin. Taken together, these studies provide evidence for interclonal cooperation during tumor progression that suggests a nonhierarchical mechanism for maintenance of tumor heterogeneity that may inform therapeutic strategies and studies of tumor evolution. ■

Cleary AS, Leonard TL, Gestl SA, Gunther EJ. Tumour cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancer. Nature 2014;508:113–7.

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AACR American Association for Cancer Research

CANCER DISCOVERY

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