C1orf116, an unnamed gene of as-yet unknown function, is a putative prostate cancer metastasis suppressor that inhibits the migratory phenotype of would-be metastatic cells

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Prostate cancer metastasis is lethal and incurable and will contribute to the death of ~29,000 men in 2018. Lethal metastases are the end-result of a cancer cell that escapes the primary tumor, travels through the vasculature, and eventually invades and colonizes a secondary site. Thus, in order for a cancer cell to metastasize from the primary tumor, it must *move*. Understanding the mechanisms that govern this critical event, the epithelial-mesenchymal transition (EMT), would provide valuable insight into the early steps of the metastatic cascade. Using a multi-study gene expression discovery analysis, we previously identified C1orf116 as a novel candidate driver of EMT (doi: 10.1186/s12885-017-3413-3). C1orf116 is highly conserved through bony vertebrates and is widely expressed in human tissues, but it has not been described in any normal or disease state. We found that C1orf116 expression is decreased in PCa patients who suffer a biochemical recurrence (GenomeDx Decipher GRID database). Strikingly, higher C1orf116 expression is also associated with increased recurrence free survival in PCa patients (Project Betastasis). This clinical data clearly support a biologically meaningful role for C1orf116 in restricting metastasis. We overexpressed C1orf116 in otherwise C1orf116^{low} PC3 cells (PC3-oe). PC3-oe cells demonstrated distinctive cobblestone epithelial cellular morphology. Correspondingly, PC3-oe cultures showed increased epithelial marker expression (including OVOL1, CDH1, ESRP), indicating that C1orf116 expression was sufficient to induce an epithelial transition. Conversely, transient siRNA-mediated knock down of C1orf116 expression in C1orf116^{high} C42b cells led to decreased expression of epithelial markers. Interestingly, C1orf116 overexpression reduced local cellular motility (individual cell tracking and scratch closure assay). Cellular motility is influenced by multiple mechanisms including cytoskeletal dynamics and cell-cell adhesion. Interestingly, we found that C1orf116 localizes to the cytoskeleton and to margins of cell-cell contacts. PC3-oe cells showed reduced cytoskeletal stiffness and cell traction forces, consistent with the cytoskeletal remodeling characteristics of less-motile cells. We also found that PC3-oe had increased expression of tight junction complexes (including ZO1, ZO2, ZO3). Taken together, our data implicate C1orf116 as a novel metastasis suppressor in prostate cancer that acts by restricting movement of would-be metastatic cells and promotes epithelial cell phenotype.

Conflicts of Interest: none

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