Inhibition of Volume-Regulated Anion Channel Suppresses Migration of Colorectal Cancer Cells

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Cell volume homeostasis is fundamental to cell functions, including proliferation, migration, and growth. Previous studies have identified LRRC8 (leucine rich repeat containing 8 subunits) as the bona fide volume-regulated anion channel (VRAC, ICl) essential for the regulatory volume decrease in response to cell swelling (ICl, swell). Here we explored the role of LRRC8 in colorectal cancer (CRC) cell migration. Cellular migration of CRC cell lines harboring different KRAS mutations were visualized and quantified, in real-time, with a live cell microscopy in the presence and absence of DCPIB, a selective blocker of VRAC. For CRC cell line derived from cecum, poorly differentiated SNU-C2B (G12D mutant) exhibited faster cellular migration than moderately differentiated NCI-H747 (G13D mutant); cellular migration corroborated increased cell stiffness as measured by magnetic twisting cytometry and faster remodeling of the underlying cytoskeleton (CSK) network as measured by spontaneous tracer motions. For CRC cell line derived from colon, however, HCT-15 harboring G13D mutation migrated faster than SW-480 and SW-837 harboring G12V and G12C mutations, respectively. Interestingly, cellular migrations and the rate of CSK remodeling ranked in order with KRAS mutations (G12D>G13D>G12V>G12C). For all KRAS mutants, DCPIB significantly inhibited cellular migrations. Further work is warranted to investigate the role of LRRC8 on the material properties of CRC. In conclusion, investigating the effect of pharmacologic agents on modulating the cytoskeleton and VRACs may serve as novel therapeutic targets for CRC metastasis. Supported by NIH R25ES020721, P01HL114471, R01HL164404, and R01DK100483 grants.