

# **Pacsin 2-dependent N-cadherin internalization regulates the migration behaviour of malignant cancer cells**

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Collective cell migration is the coordinated movement of multiple cells connected by cadherin-based adherens junctions and is essential for physiological and pathological processes. Cadherins undergo dynamic intracellular trafficking, and their surface level is determined by a balance between endocytosis, recycling and degradation. However, the regulatory mechanism of cadherin turnover in collective cell migration remains elusive.

In this study, we show that the Bin/amphiphysin/Rvs (BAR) domain protein pacsin 2 (protein kinase C and casein kinase substrate in neurons protein 2) plays an essential role in collective cell migration by regulating N-cadherin (also known as CDH2) endocytosis in human cancer cells. Pacsin 2-depleted cells formed cell–cell contacts enriched with N-cadherin and migrated in a directed manner. Furthermore, pacsin 2-depleted cells showed attenuated internalization of N-cadherin from the cell surface. Interestingly, GST pull-down assays demonstrated that the pacsin 2 SH3 domain binds to the cytoplasmic region of N-cadherin, and expression of an N-cadherin mutant defective in binding to pacsin 2 phenocopied pacsin 2 RNAi cells both in cell contact formation and N-cadherin endocytosis. These data support new insights into a novel endocytic route of N-cadherin in collective cell migration, highlighting pacsin 2 as a possible therapeutic target for cancer metastasis.

**KEY WORDS:** N-cadherin, Pacsin 2, Dynamin 2, Endocytosis, Collective cell migration