CELL MIGRATION

Changing shape

> “cells lacking FAM40B, MST3 or MST4 had reduced extravasation into the lung”

The actomyosin cytoskeleton controls cell shape and migration through connections to the plasma membrane. Many factors involved in this process are known, but the molecular details, as well as how this process influences cancer cell migration, are unclear.

Madsen *et al.* screened for *Drosophila melanogaster* genes involved in the regulation of actin-based cell migration and then analysed 85 human homologues of these genes, as these might be involved in cancer cell migration. Loss of 32 of the 85 genes in human A431 epidermoid carcinoma cells altered the actin cytoskeleton. The authors chose to focus on a group of proteins encoded by these genes — FAM40A, FAM40B and striatin 3 (STRN3) — as they are known to form the striatin-interacting phosphatase and kinase (STRIPAK) complex. Loss of FAM40A and STRN3 increased cortical myosin light chain (MLC) and ERM (ezrin, radixin and moesin) protein phosphorylation, reduced cell area and increased membrane blebbing (a contractile phenotype). Loss of FAM40B had the opposite effect. Similar phenotypes were observed when these proteins were depleted from MDA-MB-231 cells, which have a mesenchymal phenotype, in contrast to epithelial A431 cells.

The STRIPAK complex also contains MST kinases and core protein phosphatase 2A (PP2A) proteins. Depletion of MST3 and/or MST4 in MDA-MB-231 and A431 cells increased cell area and reduced cortical actomyosin, similar to FAM40B depletion. Further experiments showed that MST3 and MST4 are negatively regulated by FAM40A, which enables PP2A to dephosphorylate MST3 and MST4, and that FAM40B is likely to be a competitive inhibitor of FAM40A function.

Computational modelling and subsequent cellular migration assays indicated that loss of FAM40B, MST3 or MST4 led to weak colocalization of the actomyosin contractile machinery and actin linkage to the plasma membrane, and faster migration on 2D substrates. By contrast, cells with loss of FAM40A migrated more slowly in these conditions and had colocalization of the actomyosin network and membrane–actin linkage, which promotes migration in confined environments. This is the type of environment that cells would encounter *in vivo*. Indeed, the authors found that MDA-MB-231 cells lacking FAM40B, MST3 or MST4 had reduced extravasation into the lung following intravenous injection into mice, whereas FAM40A depletion slightly increased lung colonization. Furthermore, MST3 overexpression increased the ability of MDA-MB-231 cells to metastasize to lymph nodes from a primary tumour in the mammary fat pad, and this was decreased if FAM40A was overexpressed.

MST3 and MST4 overexpression was shown to correlate with breast cancer subtypes that are more aggressive, and high MST4 expression indicated worse distant metastasis-free survival. *FAM40B* was also shown to be frequently amplified and mutated in data from The Cancer Genome Atlas, and functional analysis of two of the mutants indicated that they cannot bind to PP2A subunits; therefore, these mutations promote cell contraction.

These data provide some molecular insight into how MST3 and MST4 activity and FAM40B mutations might promote metastatic phenotypes, and increase our understanding of cancer cell migration.

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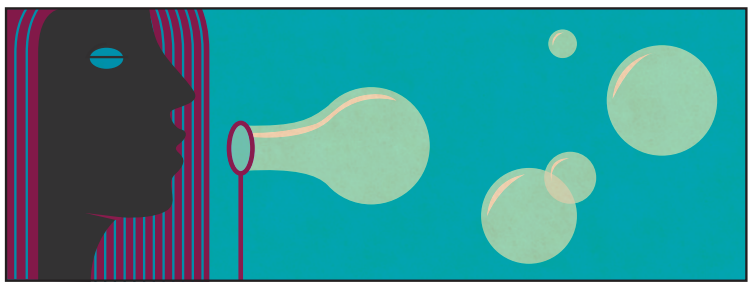
ORIGINAL RESEARCH PAPER Madsen, C. D. *et al.* STRIPAK components determine mode of cancer cell migration and metastasis. *Nature Cell Biol.* **17**, 68–80 (2015)



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