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METASTASIS

Opposing forces in invasion

> LCRMP1 can enhance metastasis in mice.

Understanding how cancer cells use the actin cytoskeleton to promote migration and invasion may provide insights into metastasis and potential therapeutic targets. Collapsin response mediator protein 1 (CRMP1; also known as DRP1), which has a known role in inducing depolymerization of actin filaments (F-actin) in neurons, has previously been shown to inhibit cancer cell invasion *in vitro* and to predict better outcomes in patients with non-small-cell lung cancer (NSCLC). Hong, Yang and colleagues recently identified a long isoform of CRMP1 (LCRMP1), the expression of which is correlated with poor clinical outcome in NSCLC, and they have now characterized the mechanism behind the differential effects of these two proteins on cancer cell invasion.

The authors first showed that overexpression of LCRMP1 promoted, and conversely that LCRMP1 knockdown inhibited, *in vitro* migration and invasion of NSCLC and renal cell carcinoma cell lines. Both orthotopic injection into the pleural cavity and tail vein injection of NSCLC cells either overexpressing LCRMP1 or with LCRMP1 knocked down confirmed that LCRMP1 can enhance metastasis in mice.

How does LCRMP1 promote cell migration and invasion? Immunofluorescence showed that LCRMP1 colocalized with F-actin. Furthermore, imaging of both fixed and live NSCLC cells showed that LCRMP1 overexpression increased the ratio of F-actin to G-actin (monomers) and induced filopodia formation. The increase in actin filaments and filopodia formation seemed to be a result of LCRMP1 promoting actin nucleation, the first step in F-actin formation, through the Wiskott–Aldrich syndrome protein (WASP) family member WAVE1. The importance of WAVE1 *in vivo* was confirmed by tail vein injection of LCRMP1-overexpressing NSCLC cells with WAVE1 knockdown — these mice had fewer metastatic nodules in the lungs than those injected with cells expressing endogenous levels of WAVE1.

LCRMP1 has 127 additional amino acids in its amino terminus compared with CRMP1, and mutation analysis showed that several conserved amino acids within this region were necessary for filopodia formation. Expression of different levels of each protein in NSCLC cells (as well as a lung squamous cell carcinoma cell line that does not normally express either protein) indicated a dose-dependent effect; invasion increased with increasing LCRMP1 expression and decreased with increasing CRMP1 expression. LCRMP1 and CRMP1 were found in the same complexes by immunoprecipitation, and *in vitro* pull-down assays showed that they could directly bind to each other. Furthermore, CRMP1 seemed to compete with WAVE1 for binding to LCRMP1, which could explain the differential effects of CRMP1 and LCRMP1 on invasion.

Extending their previous findings in patients with NSCLC, the authors showed that the combination of high LCRMP1 and low CRMP1 expression predicted significantly worse overall and disease-free survival compared with low LCRMP1 and high CRMP1 expression. Future studies should clarify whether this could help to stratify patients and whether this pathway can be exploited therapeutically.

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ORIGINAL RESEARCH PAPER Pan, S. H. *et al.* The ability of LCRMP-1 to promote cancer invasion by enhancing filopodia formation is antagonized by CRMP-1. *J. Clin. Invest.* 11 Jul 2011 (doi:10.1172/JCI42975)

FURTHER READING Nürnberg, A., Kitzing, T. & Grosse, R. Nucleating actin for invasion. *Nature Rev. Cancer* **11**, 177–187 (2011)