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Mena promotes tumor-intrinsic metastasis through ECM remodeling and haptotaxis

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Summary

Oudin and colleagues report a novel and specific function of Mena in mediating directional migration of breast cancer cells towards a fibronectin gradient of increasing concentration. This Mena-mediated haptotactic response depends on the binding of Mena to the $\alpha 5 \beta 1$ integrin receptor, adhesion protein signaling, and FN fibrillogenesis.

Cancer cells use a variety of extracellular matrix (ECM) proteins to navigate in the tumor microenvironment. These directional cues are known as guidance cues and may originate from the cancer cells as well as from the supporting stromal cells. When cancer cells come into contact with these microenvironmental cues, they react by altering their morphology, and migration. An increasing number of studies focus on examining chemotaxis, the process by which cancer cells integrate signals generated through soluble cues to drive cell migration, invasion and metastasis. In addition to chemotaxis, there is a lesser-studied mode of migration in which cells utilize the varying concentration of the underlying ECM as a guidance cue for their directional migration. The process of substrate-bound cue-mediated cell migration is known as haptotaxis. During haptotaxis, cells are guided by gradients of surface-bound ECM proteins, much in the same way cells are guided during chemotaxis. However, it is important to note that although similar, these two forms of cell migration have their own signaling modalities (1, 2). Pioneering work carried out throughout the 80's and 90's by Drs. Leo Furcht, and Lance Liotta demonstrated that in addition to simply being permissive for cancer cell migration, varying concentrations of ECM proteins can act as directional cues (1, 3). These early studies showed that many different ECM proteins, such as laminin, collagen, vitronectin, and thrombospondin, could regulate the directional migration of cancer cells via integrin signaling and adhesion protein phosphorylation.

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Despite these early efforts into understanding the mechanisms that orchestrate haptotaxis, our molecular understanding of haptotaxis and whether cancer cells use haptotaxis to migrate in vivo during metastasis remains very limited.

In an effort to examine haptotaxis during metastasis, a study lead by Dr. Madeleine Oudin from the laboratory of Dr. Frank Gertler analyzed how cancer cell-ECM interactions generate signals and changes in cell behavior and morphology to promote directed cell migration and invasion (4). Specifically, the authors set out to determine how fibronectin, an ECM protein implicated with disease progression and mortality (5), regulates cancer cell haptotaxis and, ultimately, breast cancer metastasis. This study found that Mena^{INV}, an isoform of the adhesion and actin-modulating protein Mena that is associated with aggressive tumors and metastasis (6), interacts with $\alpha 5\beta 1$ integrin (by binding to $\alpha 5$ integrin) to elicit haptotaxis on FN gradients in vitro and in vivo (Figure 1). Using pre-clinical tumor xenograft models and analysis of breast patient samples, the authors describe a previously unappreciated mechanism of metastasis, in which upregulation of Mena and its invasive isoform, Mena^{INV}, endows tumor cells with the ability to migrate up FN gradients and fashion their own pathway towards the bloodstream.

A previous study from the laboratory of Dr. Gertler demonstrated that, in contrast to the other members of the Ena/VASP family, Mena contains a LERER repeat region, which enables Mena to bind to $\alpha 5$ integrin. Moreover, Mena^{INV}, the alternatively spliced and cancer-associated isoform of Mena, contains a unique 19-amino acid inclusion not present in Mena or any of the other members of the Ena/VASP family. Inclusion of the INV sequence is shown to increase sensitivity to EGF (7), as well as increase the association of Mena with $\alpha 5$ -integrin, and in doing so, increasing cancer cell sensitivity towards FN gradients. Since high concentrations of FN are typically found near blood vessels and in metastatic sites (8), the authors speculate that Mena^{INV}-mediated haptotaxis towards FN may promote cancer cell metastasis. Indeed, work presented in the current study, as well as in previous studies, shows that Mena^{INV} is significantly associated with increased tumor recurrence, metastatic mammary tumors, and decreased breast cancer patient survival. Taken together, these data support a unique role of Mena^{INV} in promoting cancer cell chemotaxis and haptotaxis towards tumor microenvironmental cues, thus facilitating tumor invasion and metastasis.

This study has demonstrated a critical role of haptotaxis in tumor invasion and metastasis. In the meantime, it also brought out a number of interesting questions regarding to the molecular mechanism regulating haptotaxis. One important aspect to be addressed is the molecular function of Mena^{INV} at $\alpha 5$ integrin-containing adhesions. Specifically, how does Mena^{INV} binding to $\alpha 5$ -integrin sensitize cells to FN gradients? The authors present data supporting the idea that Mena^{INV} couples adhesions to the actin cytoskeleton and, in doing so, elicits actin polymerization downstream of adhesion signaling. However, it remains to be determined whether Mena^{INV} binding to $\alpha 5$ promotes $\alpha 5$ stabilization and/or clustering or whether a FN-mediated clustering of $\alpha 5$ increases Mena^{INV} at adhesions. Because $\alpha 5$ undergoes post-translational cleavage in the extracellular domain to dimerize with $\beta 1$ to form the FN receptor, it would be interesting to determine whether the $\alpha 5\beta 1$ receptor maturation requires Mena binding. Also, if integrins are stabilized and clustered as a result of Mena binding, how is Mena potentiating the phosphorylation of FAK and paxillin as well

as the formation of fibrillar FN (fibrillogenesis)? Does Mena-integrin binding lead to an increase in other adhesion proteins that link the actin cytoskeleton to integrins, such as Talin for example? It would also be interesting to assess the mechanical forces Mena^{INV}-expressing cells exert on the ECM. For example, is there an increase in the mechanical forces exerted by Mena-associated $\alpha 5$ integrins that, in turn, remodel FN into fibrils? Needless to say, future work should go into characterizing the role of Mena at adhesions to provide more mechanistic insight on the role of Mena at focal adhesions. An additional unexplored avenue is whether Mena causes an accumulation of FN by enhancing ECM secretion. Mena^{INV} is known to promote invadopodia-mediated ECM degradation (7), therefore a reduction in FN degradation seems unlikely. Is it possible that there is an increase in ECM secretion through vesicle exocytosis? Fitting with this idea, Mena, through its interaction with profilin, has been shown to mediate vesicle exocytosis (9).

Another important area in understanding haptotaxis is how the polarization of cells is regulated downstream of the Mena- $\alpha 5$ complex to promote directional cell migration. Is haptotaxis-mediated directional migration a Cdc42-driven event? Indeed, Mena function has been implicated downstream of Cdc42 in filopodia formation in fibroblasts (10). Another question is whether the presence of other ECM proteins can mask or potentiate the effect of FN to elicit haptotaxis in cancer cells. Similarly, it would be interesting to assess the role other integrins have in cancer cell haptotaxis. Lastly, because $\alpha 5 \beta 1$ also has a role in promoting angiogenesis, it will be important to elucidate whether $\alpha 5 \beta 1$ orchestrates a scheme in which both the cancer cells and blood vessels are brought together via haptotaxis, thereby enhancing metastasis. Ultimately, understanding how other cues, both soluble and substrate-bound interact to elicit Mena-mediated haptotaxis waits to be elucidated.

This study recalls to our attention the field of haptotaxis in tumor invasion. It will be exciting to uncover additional proteins and mechanisms involved in cancer cell haptotaxis on other tumor-related ECM gradients. The ample amount of data regarding chemotaxis remains to be put into context with the emerging field of haptotaxis, and discerning the mechanisms that distinguish the two is of immediate interest. A relatively recent study on haptotaxis in melanoma cells already suggests that cancer cells use different signaling modalities specifically for haptotaxis, but not chemotaxis (2). More studies are needed to improve our understanding of how the signals generated from soluble and substrate-bound cues are integrated to promote directed cancer cell migration, and metastasis. That being said, with this study, it feels like we are moving in the right direction.

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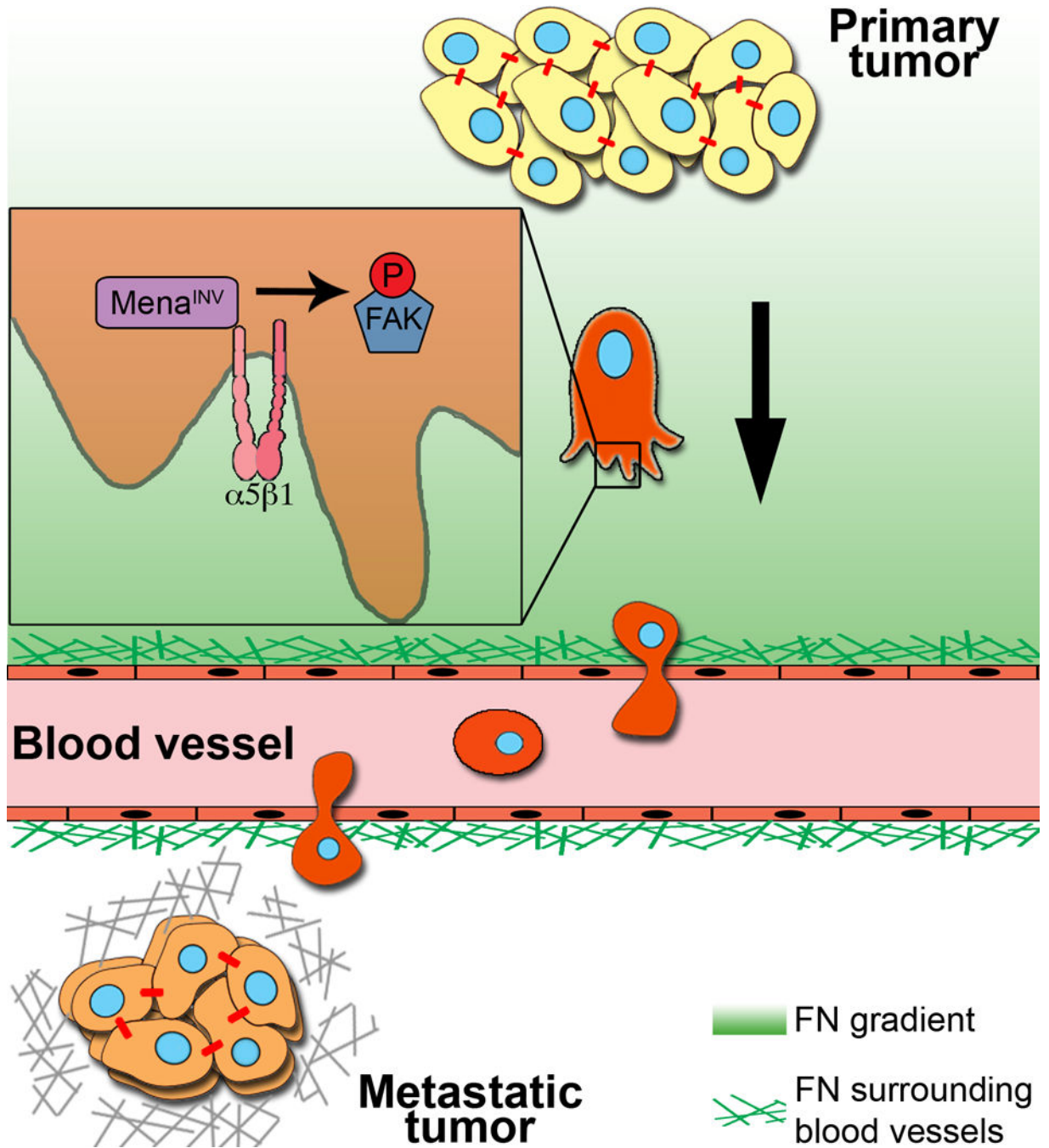


Figure 1. The interaction between Mena and α5β1 integrin regulates cancer cell haptotaxis on FN and leads to metastasis

A tumor-disseminated cancer cell (orange) exhibits haptotactic movement on a gradient of increasing FN concentration (green). The interaction between Mena and α5β1 integrin allows the cancer cell to sense and grow up the FN gradient (vertical arrow) through increased pFAK signaling. Upon reaching FN-enriched blood vessels, the cancer cell undergoes intravasation into the vasculature, and subsequently gives rise to tumor metastasis.