Title
The adaptor protein SHCA launches cancer invasion

Journal
Journal of Biological Chemistry, 295(31)

ISSN
0021-9258

Authors
Borah, Supriya
Bhowmick, Neil A

Publication Date
2020-07-01

DOI
10.1074/jbc.h120.014283

Peer reviewed

JBC EDITORS' PICK HIGHLIGHT

The adaptor protein SHCA launches cancer invasion

DOI 10.1074/jbc.H120.014283

Supriya Borah[1] **and Neil A. Bhowmick**[1,2,*]

From the [1]*Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA and the* [2]*Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, California, USA*

Edited by Enrique M. De La Cruz

Cancer cell invasion and metastasis rely on invadopodia, important extensions of the cytoskeleton that initiate degradation of the basement membrane that holds a cell in place. Transforming growth factor-β (TGF-β) is well-known to induce breast cancer migration and invasion, but the mechanism by which TGF-β signaling converts into cell motility is not completely understood. A study from Kiepas *et al.* revealed a new TGF-β–dependent role for Src homology/collagen adaptor protein (SHCA) in the initiation of dynamic adhesion complexes involved in the formation of invadopodia. These results highlight new therapeutic opportunities for cancer patients that are not sensitive to HER2 antagonists.

Tumor metastasis, or the spread of cancer cells from an initial locus to other sites, is the primary cause of death in cancer patients. Podosomes and invadopodia enable cell migration in the process of metastasis. Each of these structures requires the interaction of cell-surface proteins, like integrins, with both internal partners, like the actin cytoskeleton, as well as external substrates, like the extracellular matrix (ECM) ligands fibronectin, vitronectin, and collagen subtypes. Internally, actin microfilaments dynamically form larger bundles, called adhesions, with different protein components, such as vinculin, talin, paxillin, and tyrosine-phosphorylated proteins (1); invadopodia adhesions differ slightly in their constituents, containing signaling proteins such as FAK (focal adhesion kinase) and Src (2). Invadopodia use adhesions to create membrane protrusions that degrade the matrix by secreting matrix metalloprotease (MT1-MMP); the resultant remodeling is important for multiple cell types, including macrophage, endothelia, and vascular smooth muscle cells in addition to metastatic cancer cells. A study by Kiepas *et al.* (3) sheds new light on these processes, identifying a role for an unexpected adaptor protein in initiating adhesion formation to support invadopodia function.

Invasive breast cancer serves as a useful model system for studying cancer metastasis. There is specific focus on the oncogene HER2 (ErbB2), a receptor tyrosine kinase in the epidermal growth factor receptor family, because it is amplified and/or overexpressed in 20–30% of invasive breast cancer. Based on the reported role of TGF-β signaling in promoting ErbB2$^+$ lung cancer metastasis (1), it raised a question regarding the roles of the TGF-β/ErbB2 signaling axis in the metastasis process. The SHC adaptor protein (SHCA) is generally known to transmit extracellular signals downstream of receptor tyrosine kinases and is specifically recruited to the phosphorylated tyrosine residues of ErbB2 receptor's cytoplasmic tail. Moreover, this recruitment is essential for enhanced adhesion dynamics and invadopodia formation in ErbB2-positive breast cancer cells in response to TGF-β stimulation (3); the deletion of SHCA completely nullifies this process (4). However, the mechanism behind SHCA-mediated tumor cell metastasis is unclear.

To fill this gap, Kiepas *et al.* (3) explored SHCA's role in migration and invasion by live-cell time-lapse microscopy at the single-cell level. First, consistent with previous reports, the authors confirmed that ErbB2-expressing cells migrated further and faster with enhanced assembly and disassembly of paxillin-containing adhesions in response to TGF-β, whereas cells expressing an ErbB2 variant lacking phosphorylation sites did not (5). This behavior depended on the presence of SHCA and particularly three phosphorylation sites (Tyr-239/Tyr-240 or Tyr-313) previously shown to be associated with mammary tumor expansion and invasion (3, 4).

The authors suspected that the function of SHCA might be linked to adhesions. To test this idea, the authors used protein-proximity assays in ErbB2$^+$ cells treated with TGF-β to look for any binding partners that might indicate whether SHCA is involved in the multitude of protein-protein interactions characteristic of adhesion plaques.

These dynamic adhesions are mediated by both PI3K and MEK/ERK (MAPK), downstream of TGF-β and ErbB2, respectively; however, only PI3K signaling was required for adhesion disassembly. The differential roles for PI3K and MAPK could be interpreted to be due, in part, to their interaction with SHCA signaling. Kiepas *et al.* (3) demonstrated that TGF-β mediated the recruitment and function of lipoma-preferred partner (LPP) to dynamic adhesions in a complex with actin cytoskeleton, such as arpin, paxillin, and talin and (Fig. 1).

Finally, the authors tested whether SHCA's role in adhesion initiation impacted invadopodia function by examining ECM degradation during cell invasion. The findings on the whole demonstrated that SHCA activation is among the first steps in a sequential process of invadopodia formation of the dynamic adhesion assembly complex. Thus, if SHCA activation is interrupted, invadopodia-mediated ECM degradation and movement through the basement membrane could be limited. However, these findings need to be tested in mouse models to determine whether in fact metastasis can be limited by altering SHCA function. Moreover, whereas cell migration can be involved in metastasis, it is neither sufficient nor necessary for metastasis, as cancer cell clusters in circulation are associated with more aggressive disease than when single-cell migration is

* For correspondence: Neil A. Bhowmick, bhowmickn@cshs.org.

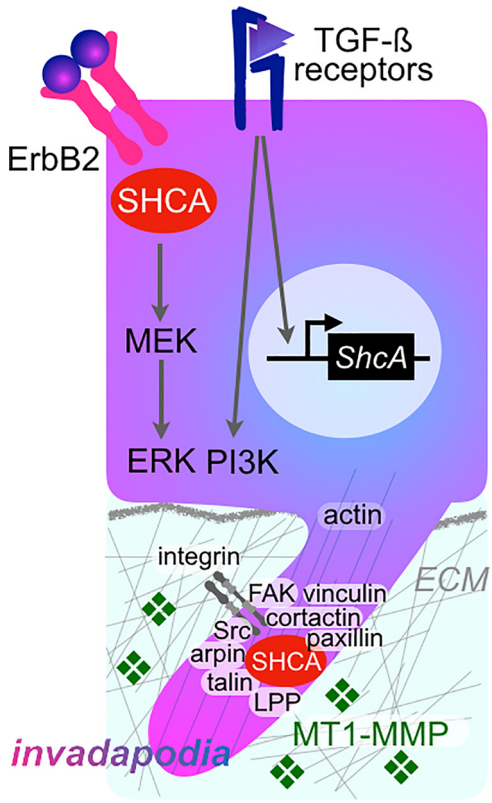

Figure 1. SHCA promotes the formation of dynamic adhesions as part of invadopodia formation in response to TGFβ in ErbB2-expressing cells. *ShcA* expression is induced by TGF-β signaling, and ErbB2 activates SHCA through phosphorylation. The combination of PI3K and MEK/ERK signaling contributes to the development of dynamic adhesions nucleated by SHCA and the critical recruitment of LPP at the integrin/focal adhesion complex. Invadopodia generation involves actin reorganization and matrix metalloprotease (MT1-MMP, *green squares*)–mediated basement membrane degradation. Migration is achieved through the generation of multiple dynamic adhesion complexes such as the single one illustrated.

detected. It is not clear whether such cell clusters require the same dynamic adhesion steps as migrating single cells. As integrin interaction with the extracellular space (mechanosensing) is required for both modes of migration, the impact of SHCA function may be broader than indicated by the single-cell *in vitro* studies in Kiepas *et al.* (3).

Accumulating data would suggest that SHCA is an Achilles' heel in tumor migration and a viable therapeutic target. ErbB2 inhibitors (HER2 antagonists) have a significant impact on breast cancer patients with ErbB2 amplification but do not have a broader impact on migration for other cancers. The identification of TGF-β's role in SHCA signaling and adhesion initiation provides an explanation as to why ErbB2 treatment alone has had limited efficacy in blocking metastasis. Combination therapies including SHCA targeting might enable intervention in breast, head and neck, prostate, fibrosarcoma, and melanoma invasive cancer cell lines, where invadopodia are also present (6). Finally, the role of invadopodia in both cancer and inflammatory cells would suggest that SHCA may even play a part in recruitment of immune infiltrates. Thus, limiting SHCA *in vivo* may negatively impact immune surveillance. These issues need to be addressed through further studies.

Conflict of interest—The authors declare that they have no conflicts of interest with the contents of this article.

Abbreviations—The abbreviations used are: ECM, extracellular matrix; SHCA, Src homology/collagen adaptor protein; PI3K, phosphatidylinositol 3-kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; ERK, extracellular signal–regulated kinase; MAPK, mitogen-activated protein kinase; TGF-β, transforming growth factor-β.

References

1. Geiger, B., Bershadsky, A., Pankov, R., and Yamada, K. M. (2001) Transmembrane crosstalk between the extracellular matrix–cytoskeleton crosstalk. *Nat. Rev. Mol. Cell Biol.* **2,** 793–805 CrossRef Medline
2. Linder, S. (2007) The matrix corroded: podosomes and invadopodia in extracellular matrix degradation. *Trends Cell Biol.* **17,** 107–117 CrossRef
3. Kiepas, A., Voorand, E., Senecal, J., Ahn, R., Annis, M. G., Jacquet, K., Tali, G., Bisson, N., Ursini-Siegel, J., Siegel, P. M., and Brown, C. M. (2020) The SHCA adapter protein cooperates with lipoma-preferred partner in the regulation of adhesion dynamics and invadopodia formation. *J. Biol. Chem.* **295,** 10535–10559 CrossRef Medline
4. Ursini-Siegel, J., Hardy, W. R., Zuo, D., Lam, S. H., Sanguin-Gendreau, V., Cardiff, R. D., Pawson, T., and Muller, W. J. (2008) ShcA signalling is essential for tumour progression in mouse models of human breast cancer. *EMBO J.* **27,** 910–920 CrossRef Medline
5. Wang, S. E., Xiang, B., Zent, R., Quaranta, V., Pozzi, A., and Arteaga, C. L. (2009) Transforming growth factor β induces clustering of HER2 and integrins by activating Src-focal adhesion kinase and receptor association to the cytoskeleton. *Cancer Res.* **69,** 475–482 CrossRef Medline
6. Yamaguchi, H. (2012) Pathological roles of invadopodia in cancer invasion and metastasis. *Eur. J. Cell Biol.* **91,** 902–907 CrossRef Medline