Chemical Inhibition of Prometastatic Lysyl-tRNA Synthetase–Laminin Receptor Interaction

Kim, D.G.; Lee, J.Y.; Kwon, N.H.; Choi, J.W.; Han, J.M.; Kim, K.; Kim, D.; Kang, E.J.; Moon, Y.; Yang, W.S.; Kim, S. (all at Seoul National University, Korea, Medicine); Fang, P.; Guo, M.; Wang, J. (all at Scripps Florida, Cancer Biology); Zhang, Q. (FSU, Chemistry); Young, N.L. (NHMFL, ICR, Biochemistry); Cho, H.Y.; Mushtaq, W.U.; Jeon, Y.H. (all at Korea University, Pharmacy); Kang, H.W.; Joo, J.E.; Hur, Y. (all at Yuan Research Institute, Biochemistry); Kang, W.; Yang, H.; Nam, D.-H. (all at Sungkyunkwan University School of Medicine, Neurosurgery); Lee, M.-S.; Lee, J.W; Rhee, K.H.; Han, B.W.;(all at Seoul National U., Pharmaceutical Sciences); Kim, E.-S.; Moon, A. (both at Duksung Women's University, Pharmacy); Yang, J.S.; Han, G. (both at Yonsei U., Biotechnology); Lee, C. (Korea Institute of Science & Technology, Biochemistry); Wang, M.-W. (Zhangjiang High-Tech Park, Shanghai, Pharmacy)

Summary

Lysyl-tRNA synthetase (KRS), a protein synthesis enzyme in the cytosol, relocates to the plasma membrane after a laminin signal and stabilizes a 67-kDa laminin receptor (67LR) that is implicated in cancer metastasis; however, its potential as an antimetastatic therapeutic target has not been explored. We found that the small compound BC-K-YH16899, which binds KRS, impinged on the interaction of KRS with 67LR and suppressed metastasis in three different mouse models. The compound inhibited the KRS-67LR interaction in two ways. First, it directly blocked the association between KRS and 67LR. Second, it suppressed the dynamic movement of the N-terminal extension of KRS and reduced membrane localization of KRS. However, it did not affect the catalytic activity of KRS. Our results suggest that specific modulation of a cancer-related KRS-67LR interaction may offer a way to control metastasis while avoiding the toxicities associated with inhibition of the normal functions of KRS.

Acknowledgements

A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by National Science Foundation Cooperative Agreement No. DMR-1157490, the State of Florida, and the U.S. Department of Energy. This work was also supported by the Global Frontier Project (grants NRF-M1AXA002-2010-0029785 (S.K.), NRF-M1AXA002-2010-0029765 (Y.H.J.), NRF-2012M3A6A4054271 (J.W.L.) and NRF-2012-054237 (B.W.H.)), the World Class University (grant R31-2008-000-10086-0 (G.H.)), the Proteogenomic Research Program (2012M3A9B9036679 (C.L.))and by the National Research Foundation funded by the Ministry of Education, Science and Technology of Korea (grant ROA-2012-0006262 (A.M.)). This study was also funded by the Ministry for Health and Welfare Affairs of Korea through the Korea Healthcare Technology Research and Development Project (A092255 (D.-H.N.)) and by a grant from Gyeonggi Research Development Program (S.K.). This work was supported in part by grants from the US National Institutes of Health (GM100136 (M.G.)); the US National Science Foundation Division of Materials Research through DMR-11-57490 (A.G. Marshall, Florida State University); by the state of Florida (M.G.) and by a Kimmel Scholar Award for Cancer Research (M.G.). We thank A.G. Marshall for supporting the HDX-MS program and facility, M.-S. Seok (Korea University) for the preparation of the nanodisc and S.W. Lee (Sungkyunkwan University) for X-ray analysis.

References

[1] Kim, D. G., *et al*., Nature Chemical Biology, **10 (1)**, 29-34 (2014).