Oral presentation

Development of novel inhibitor with the potential to suppress EGFR activity based upon the crystal structures of human NSDHL

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NSDHL, a crucial enzyme involved in human cholesterol synthesis and the regulation of epidermal growth factor receptor (EGFR) trafficking pathways, has garnered attention as a promising therapeutic target due to its significant implications in cholesterol-related diseases and carcinomas. However, the lack of atomic-level details has impeded the development of pharmacological agents targeting NSDHL. In this study, we presented two X-ray crystal structures of human NSDHL, elucidating the coenzyme-binding site and the distinctive conformational changes upon coenzyme binding in detail. Through structure-based virtual screening and biochemical evaluation, we identified a novel NSDHL inhibitor with suppressive activity against EGFR. Treatment with this potent NSDHL inhibitor enhanced the anti-tumor effect of an EGFR kinase inhibitor in EGFR-driven human cancer cells. These findings collectively provide a solid foundation for the development of therapeutic agents targeting NSDHL-related diseases.

[1] Kim, D-G., Cho, S., Lee, K. Y., Cheon, S. H., Yoon, H. J., Lee, J. Y., Kim, D., Shin, K. S., Koh, C. H., Koo, J. S., Choi, Y., Lee, H. H., Oh, Y. K., Jeong, Y. S., Chung, S. J., Baek, M., Jung, K. Y., Lim, H. J., Kim, H. S., Park, S. J., Lee, J. Y., Lee, S. J. & Lee, B-J. (2021). *Cell Mol Life Sci.* **78**, 207–225.