News Release

Title

ROR1 is required for sustained caveolae formation and survival of EGFR-tyrosine kinase-resistant lung cancers

Key Points

- ROR1 functions as a scaffold of cavin-1 and caveolin-1 (CAV1), two essential structural components of caveolae at the plasma membrane, consequently sustaining caveolae formation and prosurvival signaling towards AKT through multiple receptor tyrosine kinases.
- ROR1 inhibition can overcome EGFR-tyrosine kinase inhibitor resistance due to bypass signaling via diverse receptor tyrosine kinases.
- ROR1 thus appears to be an attractive molecular target for this devastating cancer.

Summary

Professor Takashi Takahashi and Designated Assistant Professor Tomoya Yamaguchi at Molecular Carcinogenesis in Nagoya University Graduate School of Medicine (Dean: Masahide, M.D., Ph.D.) have identified an unanticipated function of ROR1, a receptor tyrosine kinase (RTK), as a scaffold of cavin-1 and caveolin-1 (CAV1), two essential structural components of caveolae. ROR1 facilitates the interactions of cavin-1 and CAV1 at the plasma membrane, thereby preventing the lysosomal degradation of CAV1. Consequently, this uncovered ROR1 function sustains caveolae structures and prosurvival signaling towards AKT through multiple RTKs. The present findings thus provide mechanistic insight into how ROR1 inhibition can overcome EGFR-tyrosine kinase inhibitor (TKI) resistance due to bypass signaling via diverse RTKs such as MET and IGF-IR, which is currently a major clinical obstacle in the EGFR-TKI treatment of lung adenocarcinoma patients. Considering its onco-embryonic expression, inhibition of the scaffold function of ROR1 in patients with lung adenocarcinoma is an attractive approach for improved treatment of this devastating cancer.

This work was published in *Nature Communications* on [date].

Research Background

We previously identified ROR1 as a target for transcriptional activation via the lineage-survival oncogene NKX2-1/TTF-1 in lung adenocarcinoma, and ROR1 was also found to sustain PI3K-AKT signaling. It was further noted that ROR1 knockdown effectively overcame the EGFR-TKI resistance conferred by HGF-mediated bypass signaling through MET.

Research Results

In this study, we aimed to elucidate how ROR1 sustains signaling for multiple RTKs in NSCLCs. We consequently discovered an unanticipated function of this RTK. We found that ROR1 functions as a scaffold protein of cavin-1 and CAV1, two essential structural components

of caveolae, a function that in turn sustains caveolae formation and prosurvival signaling through multiple RTKs in NSCLC cells. ROR1 maintained CAV1 expression by preventing its lysosome-dependent degradation, as well as consequential caveolae formation, which in turn sustains prosurvival signaling towards AKT from multiple RTKs such as EGFR, MET and IGF-IR. Inhibition of prosurvival signaling arising from a broad spectrum of RTKs can therefore be attained through the disruption of caveolae structures by inhibiting ROR1; the scaffold function of ROR1 is therefore an attractive target for overcoming EGFR-TKI resistance due to bypass signaling.

Research Summary and Future Perspective

The ROR1 receptor tyrosine kinase possesses an unanticipated function as a scaffold protein of cavin-1 and CAV1, which in turn sustains caveolae formation and prosurvival signaling onto AKT through multiple RTKs in lung cancers. Novel therapeutic strategies to inhibit the scaffold function of ROR1 and thereby attack the cancer's "Achilles heel" may prove effective against this devastating cancer.

Publication

Yamaguchi T, Lu C, Ida L, Yanagisawa K, Usukura J, Cheng J, Hotta N, Shimada Y, Isomura H, Suzuki M, Fujimoto T, Takahashi T. ROR1 sustains caveolae and survival signaling as a scaffold of cavin-1 and caveolin-1. *Nature Communications*; Jan. 4, 2016.

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http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2015/ROR1_20160105jp.pdf