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Commentary

Rhomboids and regulation of receptor tyrosine kinase ligands shedding

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In EBioMedicine, Li and colleagues [4] provide a mechanistic explanation of the role of the human rhomboid family-1 (RHBDF1) in epidermal growth factor receptor (EGFR) activation, in triple negative breast cancer (TNBC). The aberrant activation of EGFR results from increased transcriptional expression, gene amplification, or oncogenic mutations and is implicated in several human cancers. EGFR was the first discovered member of the ErbB family of receptor tyrosine kinases (RTKs). The ErbB family includes three more members, ErbB2/Her2, ErbB3 and ErbB4 which form homo- and heterodimers in the cell surface upon the binding of an EGF family ligand to its cognate receptor. EGF, transforming growth factor α (TGFα), and amphiregulin bind only to EGFR. Neuregulin 1 (NRG1) and NRG2 bind to ErbB3 and ErbB4. Betacellulin, heparin-binding EGF, NRG3, and epiregulin bind to EGFR and ErbB4 [3]. These ligands are initially latent proteins that require a proteolytic process (shedding) to form active growth factors. G protein-coupled receptors (GPCRs) through the activity of a disintegrin and metalloproteinase 17 (ADAM17) enhance the proteolytic release of EGFR ligands and transactivate EGFR. ADAM17, one of the principal mammalian EGFR ligand sheddases, is also known as tumor necrosis factor α-converting enzyme (TACE) [6].

Although EGFR is a well-established treatment target in non-small cell lung cancer (NSCLC), colorectal cancer and head and neck squamous cell carcinoma, in TNBC, where EGFR overexpression is common, EGFR targeted therapies have not yielded significant response rates. RHBDF1, known also as inactive rhomboid protein 1 (iRhom1), is a member of a subfamily of rhomboid-like proteins, located in the endoplasmic reticulum, that lack key catalytic residues, rendering them proteolytically inactive. The first evidence that rhomboid proteases are directly involved in EGFR signaling was when it was reported that rhomboid-like 2 (RHBDL2) cleaves and facilitates EGF secretion and triggers EGFR activation [1]. Since then, it is known that rhomboid proteins like RHBDF1, RHBDD1, and RHBDD2, are highly expressed in human cancers, and are linked with EGFR oncogenic signaling. In head and neck squamous cancer cells, RHBDF1 silencing decreases TGFα secretion and inhibits the GPCR-induced EGFR transactivation [11].

Li et al., have now performed further research on the mechanism of action of RHBDF1 [4]. They have elegantly demonstrated that RHBDF1 promotes the secretion of the EGFR ligand, TGFα, by mediating on the one hand, ADAM17-dependent TGFα shedding, and on the other hand, clathrin-dependent plasma membrane release of pro-TGFα (Fig. 1). Inhibition of RHBDF1 abrogated the GPCR-agonist sphingosine 1-phosphate (S1P)-mediated ADAM17 activation and inhibited the clathrin-coated vesicles uncoating. (Fig. 1). RHBDF1 interacts with auxilin-2, a cofactor of heat shock cognate protein-70 (HSC70) that is directly involved in the uncoating process [4]. Li et al., showed that RHBDF1 inhibition decreased cell migration, proliferation, and invasion in breast cancer cells, in the presence or absence of S1P, indicating that the role of RHBDF1 may be independent of GPCR-dependent EGFR transactivation [4]. Previous work from the same authors has shown that RHBDF1 facilitates the stabilization of the α -subunit of hypoxia-inducible factor-1 (HIF1α) under hypoxia in breast cancer cell lines and its expression is related with shorter progression-free survival in breast cancer patients [9].

The mechanisms of action of RHBDF1 extend much further beyond what is reported in the present study of Jie Li and colleagues [4]. In colorectal cancer, RHBDF1 induces epithelial-to-mesenchymal transition (EMT) through the Wnt/β-catenin pathway [8]. The group of Lu-Yuan Li (senior author in the present study) has related the high expression RHBDF1 to the formation of apicobasal polarity and breast carcinogenesis through interaction with renin–angiotensin system–related C3 botulinum toxin substrate (Rac)1, and cell-division cycle (Cdc)42 [5]. Whether RHBDF1 inhibition is relevant in other EGFR-dependent tumors, aside from breast or head and neck squamous cancer, is uncertain, however, EGFR mutation positive NSCLC is of great interest. We have shown that Yes-associated protein-1 (YAP1) expression and activity is not inhibited upon treatment with EGFR tyrosine kinase inhibitors in EGFR-mutation positive cell lines [2]. Many receptor tyrosine kinases and ligands are transcriptional targets of YAP1. Previous work has shown that GPCR activation by S1P results in YAP1 activation [7]. Exploring the role of RHBDF1 in EGFR-mutation positive NSCLC is intriguing. Until now, no direct or indirect RHBDF1 inhibitors have been described [4]. The proteosome inhibitor bortezomib (Velcade) decreased RHBDF1 protein levels in TNF Receptor Associated Factor 3 (TRAF3)-deficient multiple myelomas [10]. Further research on the RHBDF1 mechanism of action will shed more light on its role in EGFR activation and clarify whether RHBDF1 can be a target to improve current cancer therapeutics.

Disclosure

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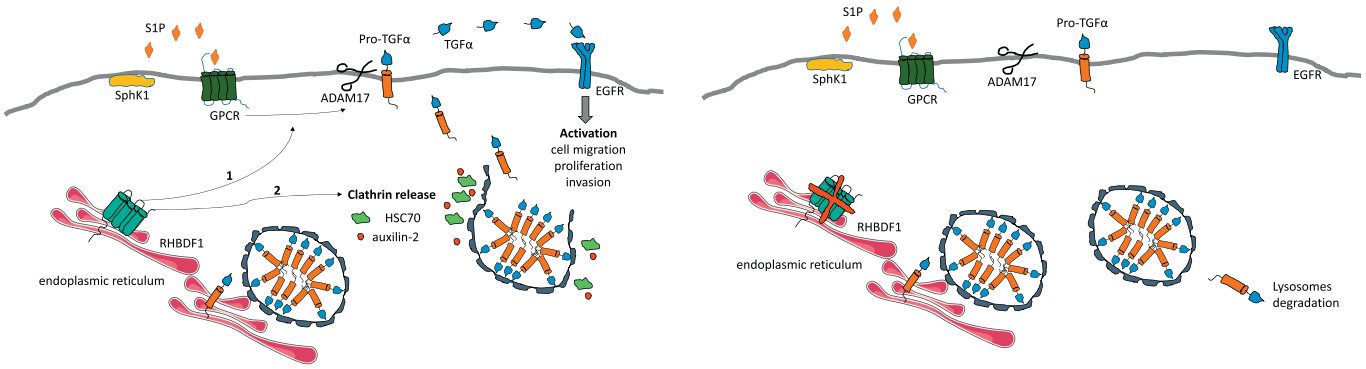

Fig. 1. The role of RHBDF1 in EGFR activation. Active RHBDF1 (left side) promotes the secretion of the EGFR ligand, TGFα, by mediating ADAM17-dependent TGFα shedding (1), and clathrin-dependent plasma membrane release of pro-TGFα (2). When RHBDF1 is not active, then EGFR activation is abrogated (right side).

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