

EGFR-Dependent Regulated Intramembrane Proteolysis of EpCAM—Letter

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Hsu and colleagues reported on EGF/EGFR-triggered activation of regulated intramembrane proteolysis (RIP) of EpCAM that induces an EMT phenotype (1). This finding is of utmost interest, as it might explain contradicting effects of EpCAM on adhesion, proliferation, and invasion and shed light on EpCAM-based plasticity in cancer progression.

EGF treatment of one endometrial carcinoma line induced a loss of the extracellular domain of EpCAM (EpEX) at the membrane. Treatment of cells with EGFR inhibitor Iressa suggested a dependency of the observed phenotype on EGFR signaling, which however was not further explored. Parallel treatment of cells with γ -secretase inhibitor DAPT counteracted effects of EGF and restored EpEX expression at the membrane of EGFR-positive cells (Fig. 1A; ref. 1).

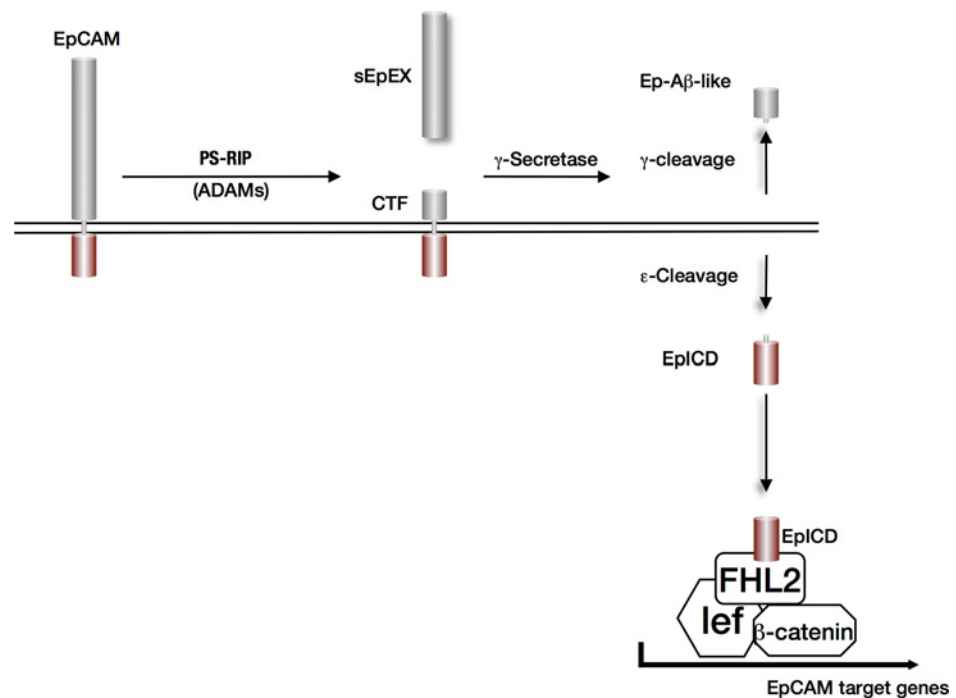
Classically, RIP depends on initial shedding of the substrate's ectodomain by α - (e.g., ADAMs) and/or β -proteases (e.g.,

BACE1). Ectodomain shedding is a commonly accepted prerequisite for subsequent intramembrane cleavage of the resulting C-terminal fragments (CTF) through the action of the γ -secretase complex (see Fig. 1 for schematic representation).

In contrast to the authors' assumption, "stabilization of EpCAM by the inhibition of EpICD cleavage" through γ -secretase inhibitor DAPT should not impact on EpEX shedding, because aforesaid shedding must have preceded EpICD release. Evidence therefore was reported by Maetzel and colleagues in the initial description of EpCAM cleavage (Fig. 2A and B in ref. 2). DAPT treatment inhibited EpICD formation and resulted in the accumulation of EpCAM-CTFs (Fig. 2A), whereas pharmacologic and genetic inhibition of ADAM17 resulted in EpEX, EpCAM-CTF, and EpICD reduction or loss (Figs. 2B and 3). These results have been repeatedly confirmed, for example, by Lin and colleagues, who unquestionably demonstrated a lack of effect of DAPT on EpEX

Figure 1.

Schematic representation of the regulated intramembrane proteolysis of EpCAM. Cleavage of EpCAM is initiated upon shedding of the ectodomain EpEX through ADAM proteases. The resulting CTF is a substrate for the γ -secretase complex. Intramembrane cleavage occurs at gamma sites to release the A β -like fragment and at epsilon sites to release EpICD into the nucleus, where it cooperates with β -catenin and Lef1 to regulate gene transcription.



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formation (Fig. 4E in ref. 3), Schnell and colleagues (Fig. 5C in ref. 4), and Tsaktanis and colleagues (Fig. 1A in ref. 5).

In conclusion, it appears hardly conceivable that inhibition of γ -secretase has any direct effect on EGF/EGFR-mediated shedding of EpEX. Inhibition of ADAMs and BACE1 with small-molecule inhibitors such as TAPI and C3 would have been more informative to address this central mechanistic question of the article, which remains open and further challenged by conflicting reports on enhanced signaling of EGFR in presenilin-deficient cells (6).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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