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Activation of the Metalloproteinase ADAM17 by the Mechanosensitive Ion Channel Piezo1

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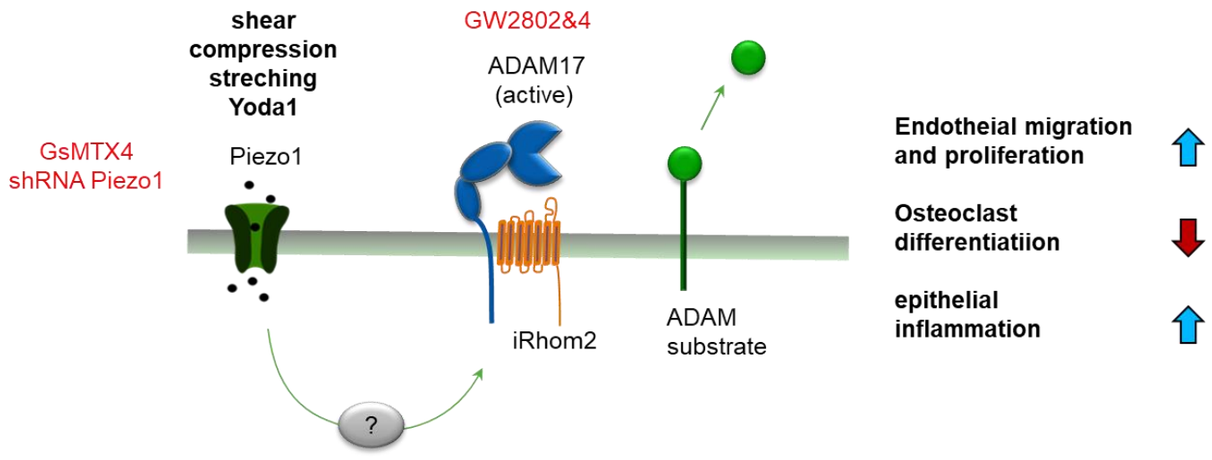
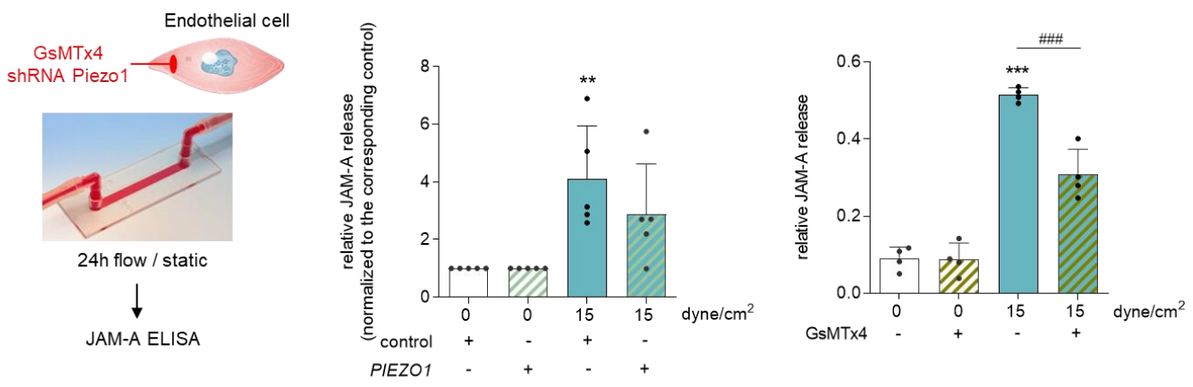
BACKGROUND / AIM

Surface expressed proteases of the ADAM family including ADAM17 are well know to shed mediator molecules, adhesion molecules or receptors from the cell surface and are therefore implicated in various cell and tissue responses. We have demonstrated that mechanical activation of the ion channel Piezo1 can enforce the activity of the metalloproteinase ADAM17 in various cell types. Piezo1 mediated activation was found to promote endothelial cell proliferation and migration (Fig. 1), downregulate osteoclast differentiation (Fig.2) and increase the inflammatory response of keratinocytes (Fig.3). ADAM17 is well known to be regulated via the adapter molecule iRhom2, but it remains unclear how Piezo1 mediated signaling can tune this regulation.



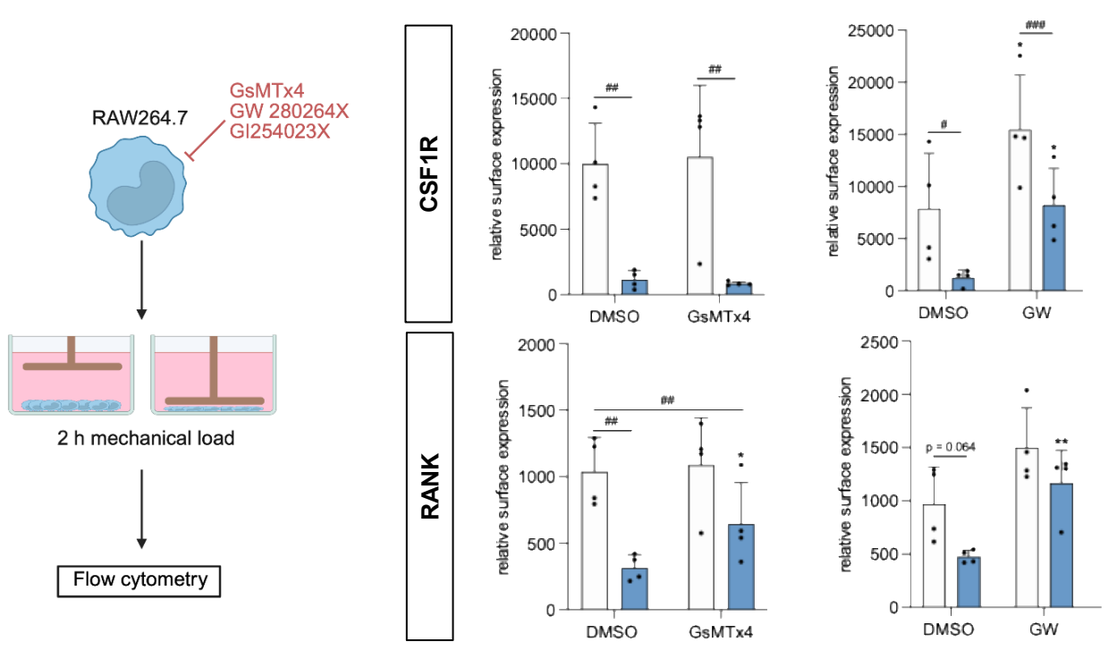
RESULTS

Fig 1:Piezo1 induces ADAM-dependent shedding in endothelial cells exposed to flow (Alessa Pabst et al.)



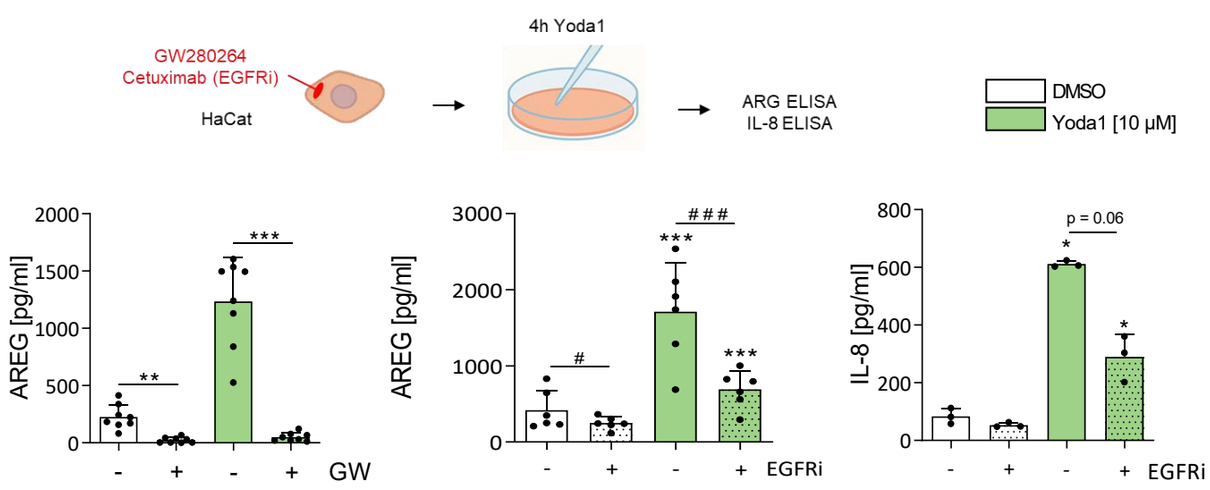
Leading to Increased endothelial migration and proliferation
(Cell. Commun Sigal 2026)

Fig 2: Piezo1-mediated ADAM activation in response to mechanical load reduces expression of osteogenic receptors (Yunus Benli et al.)



Leading to suppression of osteoclast differentiation (see poster)

Fig. 3:Piezo1-mediated ADAM activation in keratinocytes induces EGFR dependent IL-8 expression (Christoph Knobloch et al.)



Leading to enhancement of epithelial inflammation (see poster)

Fig 4: ERK1/2 is activated via Piezo1 and binds to iRhom2
(Christine Lux et al.)

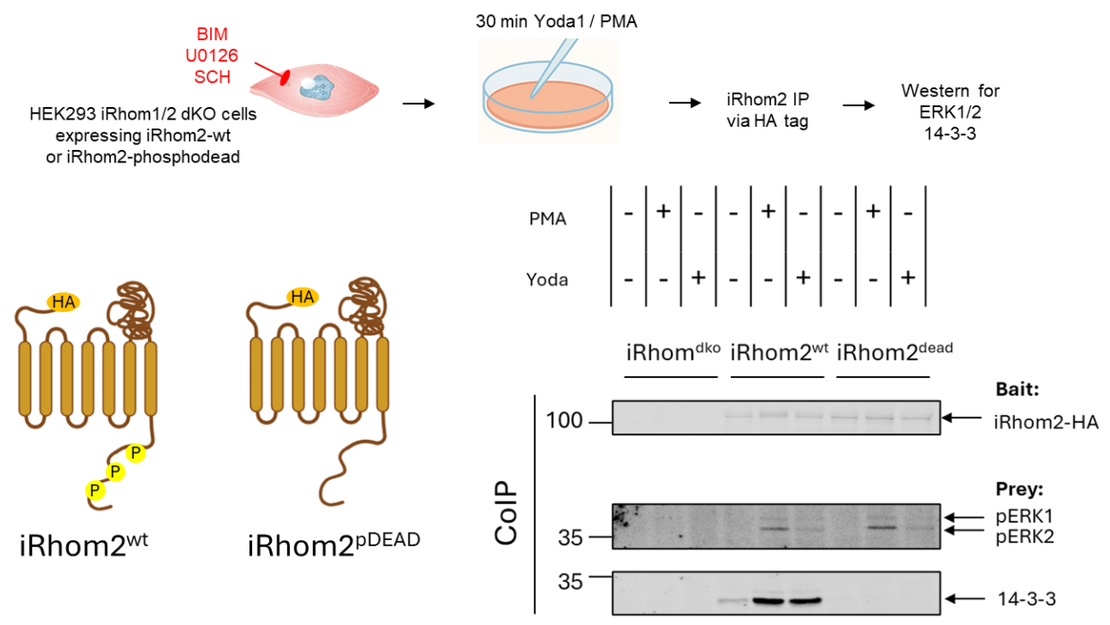


Fig. 5: ERK1/2 activity induces 14-3-3 protein binding to iRhom2

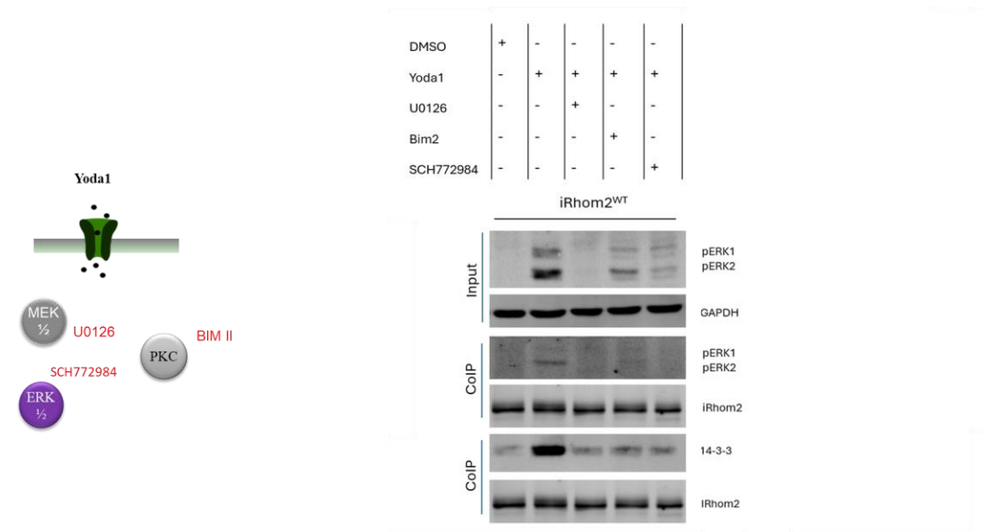
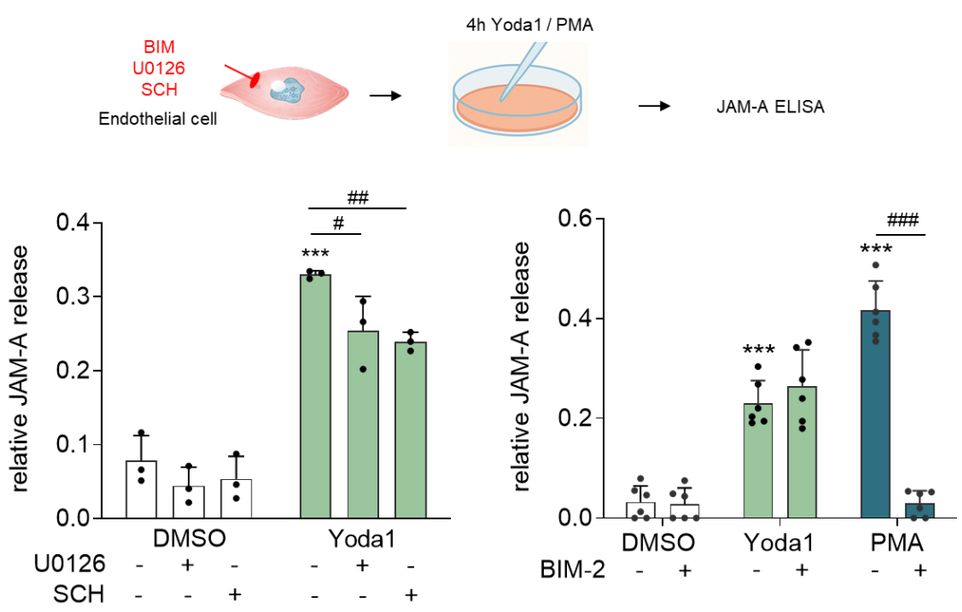


Fig. 6: Piezo1 induced endothelial JAM-A release Is slightly reduced by ERK1/2 inhibition but not by PKC inhibition (Alessa Pabst et al.)



SUMMARY / PROPOSED MODEL

Cell stimulation with the Piezo1 agonist Yoda1 or the PKC agonist PMA leads to activation of several kinases including ERK1/2. In coprecipitation studies with transfected HEK293 cells ERK1/2 associates with tagged iRhom2. Bound ERK1/2 is phosphorylated when cells are stimulated with Yoda1 or PMA (Fig .4). This is linked to increased binding of iRhom2 to 14-3-3 protein which is known to strongly depend on phosphorylation of the target proteins. Removal of potential phosphorylation sites in the iRhom2 N-terminus abrogates 14-3-3 binding but does not affect ERK1/2 binding. Inhibition of ERK1/2 kinase abrogates 14-3-3 protein binding (Fig .5). Yoda1 treatment of endothelial cells induced ERK1/ 2 phosphorylation and ADAM17 activation as measured in terms of JAM-A or TNFR shedding. This response could be suppressed in part by the ERK1/2 inhibitor (Fig.6) The data indicate that the ERK1/2 pathway modulates the ADAM17 adapter iRhom2 but is not sufficient to explain ADAM17 regulation in response to Piezo1 signaling.