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Meeting abstract

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Identification of SH3 domain interaction partners of FasL using a human SH3 domain phage display library

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Unlike other members of the tumour necrosis factor superfamily, Fas ligand (CD95L) contains a unique polyproline region (aa 37–70) as part of its N-terminal intracellular tail. We already described several SH3 or WW domain proteins that proved to interact with FasL via this proline-rich domain (PRD). We defined distinct adapter proteins that are involved in the regulation of FasL sorting and trafficking and identified ADAM10 as the FasL sheddase (see [1] for review). Given that ADAM10-mediated ectodomain shedding regulates the surface expression of FasL and that FasL is subsequently released into the cytosol by regulated intramembrane proteolysis (RIPing) through the γ-secretase-like enzyme SPPL2a, we are interested in defining interactions involving the generated intracellular fragment of FasL. Interestingly, so far we failed to co-immunoprecipitate either the FasL N-terminal membrane fragments generated by ADAM10 cleavage or the FasL intracellular remainder generated by SPPL2a activity with previously described interaction partners, while full length FasL was co-immunoprecipitated. From precipitates with a new mAb directed against the intracellular portion of FasL, however, we can readily detect processed FasL in T cell blasts. In order to identify other SH3 domain proteins that potentially (and selectively?) interact with the RIPed FasL PRD, we used a SH3 domain phage display library containing all 288 SH3 domains expressed in humans. We are thus confident to be able to present the complete "SH3 interactome" for the FasL PRD in Weimar. The identification of interactors will give us some hints on the still open function of the intracellular FasL fragments.

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References

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