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Meeting abstract

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# Analysis of knockout/knockin mice that express a mutant FasL lacking the intracellular domain

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Fas ligand (FasL; CD178; CD95L) is a type II transmembrane protein belonging to the tumour necrosis factor family; its binding to the Fas receptor (CD95; APO-1) triggers apoptosis in the receptor-bearing cell. Signalling through this pathway plays a pivotal role during the immune response and in immune system homeostasis. Similar to other TNF family members, the intracellular domain has been reported to transmit signals to the inside of the FasL-bearing cell (reverse signalling). Recently, we identified the proteases ADAM10 and SPPL2a as molecules important for the processing of FasL. Protease cleavage releases the intracellular domain, which then is able to translocate to the nucleus and to repress reporter gene activity. To study the physiological importance of FasL reverse signalling in vivo, we established knockout/knockin mice with a FasL deletion mutant that lacks the intracellular portion (FasLDeltaIntra). Co-culture experiments confirmed that the truncated FasL protein is still capable of inducing apoptosis in Fas-sensitive cells. Preliminary immune histochemistry data suggest that, in contrast to published data, the absence of the intracellular FasL domain does not alter the intracellular FasL localization in activated T cells. We are currently investigating signalling and proliferative capacities of T cells derived from homozygous FasLDeltaIntra mice to validate a co-stimulatory role of FasL reverse signalling.