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Non-apoptotic role of CD95 in lupus and its disruption using a small peptide

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The death receptor CD95 (also known as Fas) plays a pivotal role in immune surveillance and immune tolerance. Interaction of CD95 with its ligand, CD95L, leads to the formation of a molecular complex named death inducing signaling complex (DISC), which orchestrates the implementation of a caspase-driven apoptotic signaling pathway. CD95L is a transmembrane protein that can be cleaved by metalloprotease. Unlike membrane-bound CD95L, metalloprotease-cleaved CD95L (cl-CD95L) fails to trigger DISC formation and rather promotes cell migration through the induction of a PI3K/calcium (Ca^{2+}) cue *(Tauzin, PLoS Biol, 2011 & Malleter, Cancer Res, 2013)*.

We demonstrated that the concentration of cl-CD95L is correlated with the severity of the pathology in systemic lupus erythematosus (SLE) patients. This soluble CD95L is able to enhance extravasation of activated T cells, a cellular phenomenon contributing to the accumulation of lymphocytes in inflamed tissues through the formation of an unconventional CD95-containing receptosome termed the motility-inducing signaling complex (MISC). Formation of this complex is instrumental in evoking a Ca^{2+} response. By selectively interfering with this CD95-mediated Ca^{2+} signal using a cell-penetrating peptide, we prevented *in vitro* and *in vivo* endothelial transmigration of T lymphocytes. In conclusion, our study provides novel insights into the cellular and molecular mechanisms by which cl-CD95L contributes to SLE pathogenesis. Moreover, neutralizing the CD95/CD95L signaling pathway may turn out to be a future therapeutic approach in the treatment of SLE.