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**Crystal Structure of MC159 Reveals Molecular Mechanism of DISC Assembly and FLIP Inhibition.** Jin Kuk Yang, Liwei Wang, Lixin Zheng, Fengyi Wan, Misonara Ahmed, Michael J. Lenardo, Hao Wu, Dept. of Biochemistry, Weill Medical College of Cornell Univ., New York, NY10021, USA.

The death-inducing signaling complex (DISC) comprising Fas, Fas-associated death domain (FADD), and caspase-8/10 is assembled via homotypic associations between death domains (DDs) of Fas and FADD and between death effector domains (DEDs) of FADD and caspase-8/10. Caspase-8/10 and FLICE/caspase-8 inhibitory proteins (FLIPs) that inhibit caspase activation at the DISC level contain tandem DEDs. Here, we report the crystal structure of a viral FLIP, MC159, at 1.2 Å resolution. It reveals a noncanonical fold of DED1, a dumbbell-shaped structure with rigidly associated DEDs and a different mode of interaction in the DD superfamily. Whereas the conserved hydrophobic patch of DED1 interacts with DED2, the corresponding region of DED2 mediates caspase-8 recruitment and contributes to DISC assembly. In contrast, MC159 cooperatively assembles with Fas and FADD via an extensive surface that encompasses the conserved charge triad. This interaction apparently competes with FADD self-association and disrupts higher-order oligomerization required for caspase activation in the DISC.