True Death Effector Domain Assembly for Activating Procaspase-8

Su-Chang Lin¹, Chao-Yu Yang¹, Li-Chung Hsu³, Yu-Chih Lo²

¹ Genomics Research Center, Academia Sinica, Taipei 11529, Taiwan, ² Department of Biotechnology and Bioindustry Sciences, College of Bioscience and Biotechnology, National Cheng Kung University, Tainan 70101, Taiwan, ³ Institute of Molecular Medicine, College of Medicine, National Taiwan University, Taipei 10002, Taiwan

Email of communicating tomlin@gate.sinica.edu.tw

Keywords: Apoptosis, Procaspase-8, Complex assembly

In cells upon activation of the death receptor, procaspase-8 is activated after it is recruited to the receptor complex by interacting with FADD via homotypic death effector domain (DED)-DED interaction. Procaspase-8 activation is regulated by c-FLIP also via their DED-DED interaction and together they play a critical role to determine cell survival and death in development, tissue homeostasis, and immune responses. Notably, the assembly mechanism is complicated because they use the death effector domain to assemble a multiprotein, oligomeric complex, presumably via an unknown helical assembly. In addition, the assembly mechanism is complicated also because FADD contains a single death effector domain, whereas both procaspase-8 and c-FLIP contain a tandem death effector domain. Due to bad behaviors of the death effector domains when overexpressed in the solution, it is hard to reconstitute the complex and to obtain its high-resolution structure and therefore previous publications were not able to reveal their assembly mechanism. Here we report the structure of the death effector domain complex, which reveal the true assembling mechanism of the death effector domain for elucidating the activating mechanism of procaspase-8.