Cologne Cell Death Club Seminar

SFB 1403 CELL DEATH IN IMMUNITY, INFLAMMATION AND DISEASE

University of Cologne

Speaker: Marion MacFarlane
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Information about the MacFarlane Laboratory

Title: "Molecular Architecture of FADD:Caspase-8 Signalling Complexes – from assembly to co-ordinated control of Life/Death Decisions"

Tuesday 29.06.2021 at 1 pm
Please register here to receive the Zoom login data:
https://uni-koeln.zoom.us/meeting/register/tJAudeytpjMjG9HmtbMD06KF2pPNK_VitFS1

Abstract:
Caspase-8, a key regulator of cell fate, is recruited/activated within large multiprotein signalling platforms including the Death-Inducing Signalling Complex (DISC), Necrosome and Ripoptosome. The best characterized of these, the DISC, is critical for initiation of death receptor-induced apoptosis; consequently, its formation and activation must be tightly regulated. Recruitment of Procaspase-8 to the adaptor molecule FADD is mediated via Death Effector Domain (DED) interactions. Subsequently, multiple Procaspase-8 molecules are required to interact via their tandem DEDs to form a helical Caspase-8-activating chain (Dickens et al. 2012 Mol. Cell; Schleich et al. 2012 Mol. Cell). c-FLIP isoforms, which are key regulators of procaspase-8 activation, are recruited to the complex via a co-operative/hierarchical binding mechanism involving Procaspase-8 (Hughes et al. 2016 Mol. Cell; Horn et al. 2017 Cell Rep). The ratio of c-FLIPL/S to Procaspase-8 is a critical regulator of Caspase-8 dimerization/activation within tDED oligomers and crucially defines how c-FLIP isoforms differentially control cell fate, predicting that c-FLIPS blocks Caspase-8 activation by somehow disrupting tDED triple helix assembly. Now, using negative-stain Electron Microscopy (EM) and Cryo-EM, we have visualized for the first time the 3D structural architecture of FADD:Caspase-8 complexes. Further investigation, including nano-gold immunolabelling, has confirmed the LC-MS/MS-determined stoichiometry of the FADD:Caspase-8 Complex and provided new information on the domain architecture of active Caspase-8 catalytic dimer, as well as its regulation by key tDED regulators (e.g. c-FLIP). Our data provide important novel insights into co-ordinated control of life/death decisions by FADD:Caspase-8 signalling platforms including the DISC, Necrosome and Ripoptosome (Fox et al. 2021 Nat Commun).

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