Role of Fas Associated Death Domain (FADD) protein in regulation of Apoptosis and Inflammatory Signaling in Cancer

Summary

Fas associated death domain (FADD) is a pivotal signaling component of programmed cell death. Activation of death receptor signaling allows interaction of FADD with procaspase-8/10 to form a death inducing signaling complex (DISC) and further execution of downstream signaling of apoptosis. The death receptor apoptosis is negatively regulated by anti-apoptotic protein cellular FLICE-like inhibitory protein (cFLIP). FADD aids as an adaptor protein and provides a common binding platform to procaspase-8 and cFLIP at the DISC in death receptor signaling. However, cFLIP competitively exclude binding of procaspase-8 with FADD and restricts cascade of apoptosis signaling to promote cell proliferation. The pleiotropic cytokine Tumor Necrosis Factor-α (TNF-α) canonically regulate anti-apoptotic expressions of cIAPs and cFLIP at transcription level by inducing NF-κB signaling. In the present study, the regulatory role of FADD over the activation of NF-κB and $cFLIP_L$ during TNF-α stimulation was explored. Here, it was found that induced expression of FADD progressively interacts with procaspase-8 and preclude cFLIP occupancy from the DISC. FADD turn over the expression of $cFLIP_L$ by activating terminal kinase JNK1 to augment apoptosis. In addition, over expression FADD and knockdown of $cFLIP_L$ challenge the mitochondrial integrity and pulverize the membrane potential by altering the expression of Bcl-2 and cytochrome c to facilitate extrinsic and intrinsic signaling of apoptosis. Moreover, expression of FADD and $cFLIP_L$ determines fate of cell survival or survival by regulating autophagic cell death signaling. Interestingly, FADD regulates the canonical inflammasome activation to restrict the processing and maturation of pro-inflammatory cytokine IL-1β. Thus, FADD has an important role in regulation various cellular signaling to determine fate of cell death or survival. Further, the delivery of FADD protein inside the cell was carried out by using cell permeable peptide (CP) followed b investigation of its apoptotic potential on cancer cells. It was observed that, conjugate of CP-FADD efficiently delivered inside the cells and induces apoptotic cell death. This study provides a novel approach for inducing the apoptosis that may offer a new direction for cancer therapy.