432j Regulation of Apoptosis by Free Fatty Acids and Tnf-α: Role of Double-Stranded RNA-Dependent Protein Kinase (Pkr)

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Different types of free fatty acids (FFAs) have distinct roles in cellular apoptosis: saturated FFAs (e.g. palmitate) have been found to induce apoptosis, while unsaturated FFAs (e.g. oleate) have been found to protect cells from apoptosis induced by other factors such as saturated FFAs (1, 2). Saturated FFA-induced apoptosis has been found to be dependent on the Bcl-2 level (3) and transcription factor, NF-κB, activity (4). Physiologically, high levels of proinflammatory cytokine, tumour necrosis factor α (TNF-α), and saturated FFAs usually appear simultaneously in numerous diseases, such as obesity and diabetes (5, 6). TNF-α has been reported to induce apoptosis by various mechanisms, including down-regulating Bcl-2 protein expression level (7), dephosphorylating Bcl-2 at Ser 87 residue (8), activating NF-κB (3), and phosphorylating eukaryotic initiation factor (eIF2) α (9). Upon auto-phosphorylation and dimerization, PKR, a serine/threonine kinase, is activated and highly involved in phosphorylating eIF2-α (10), activating NF-κB through I-κB kinase complex (IKK) (11), and stimulating protein phosphatase 2A (PP2A) (12), which in turn dephosphorylates Bcl-2 at both serine 70 and 87 residues (13, 14). Given the regulatory roles of PKR in activating NF-κB and phosphorylating Bcl-2 and eIF2-α, we hypothesize that PKR is involved in mediating FFA- and TNF-α-induced apoptosis.

TNF-α-induced PKR activation has been observed in several systems such as articular chondrocytes and U937 cells (15-17), however in our in vitro system (HepG2/C3A cell line), TNF-α was found to decrease the phosphorylation of PKR in both control and palmitate cultures. Saturated FFA (palmitate) also decreased the phosphorylation of PKR while unsaturated FFA (oleate) had no effect on PKR phosphorylation. By inhibiting PKR activity, we found that PKR is required for maintaining the level of Bcl-2 in HepG2/C3A cells. We proposed that PKR is involved in the signaling from FFAs and TNF-α to Bcl-2. In addition, we studied the role of PKR in mediating the phosphorylation of Bcl-2 and eIF-2α, which help transduce the apoptotic signals initiated by FFAs and TNF-α. Our findings suggest a role of PKR in FFA- and TNF-α-induced apoptosis, mediated through the protein level and phosphorylation status of Bcl-2 and eIF-2α.

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