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EDITORIAL

Current research on cell death mechanisms

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Cell death is one of the key events by which chemicals cause adverse effects. Of course, the relevance of cell death for in vivo toxicity is organ and tissue dependent. For example, hepatotoxic chemicals often reach cytotoxic levels in vivo; adverse effects, such as fibrosis (Godoy et al. 2013; Nussler et al. 2014), are usually observed after cell killing. On the other hand, adverse effects in other organs, e.g., the central nervous system, may be caused by non-cytotoxic concentrations by compromising connectivity of neurons, receptor expression, or neurotransmitter metabolism (van Thriel et al. 2012; Weng et al. 2014; Balmer et al. 2014; Sisnaiske et al. 2014; Waldmann et al. 2014; Krug et al. 2013). Although it is clear that adverse effects can also occur without cell killing by disturbed cell functions, chemicals always have to be considered as critical when close to cytotoxic concentrations are reached in vivo. Therefore, it is not surprising that cell death research and research on factors modifying susceptibility to cell death represent cutting edge topics in toxicology (Indran et al. 2011; Jazirehi et al. 2011; Jiang et al. 1999; Galán et al. 2001; Ambrosio et al. 1993; Aoki et al. 2002; Ashkenazi and Dixit 1998; Barnhart et al. 2003). The most intensively studied and perhaps also most relevant cell death mechanism is apoptosis (Alster et al. 2014; Lopez et al. 2014; Bezler et al. 2012; Ilowski et al. 2011; Godoy et al. 2009). Its morphological features have already been described by Fleming in 1885 as a series of events that include chromatin condensation, membrane surface blebbing, and the breakdown of the cell into apoptotic bodies (Matés et al. 2012; D'Emilio et al. 2010). This strictly defined sequence of events guaranties that cells die in an orderly way in contrast to the chaotic cell death of necrosis (Matés et al. 2008, 2012; Wyllie 2010; Yoo et al. 2009; Hammad et al. 2014; Gabai et al. 2000). This process allows the removal of cells from tissues without inflammation. It plays an important role in embryonic development of organisms and in tissue homeostasis (Morita et al. 2001). When chemicals interfere with the control mechanisms of apoptosis, they may cause cell death at very low concentrations. Therefore, the control mechanisms of pro- and anti-apoptotic factors and their disturbance by chemicals traditionally represent an intensively studied field in toxicology. To give our readers an overview, we summarize key messages from articles about cell death mechanisms published since 2012 (Table 1).

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Table 1 Key messages of publications in the field of cell death mechanisms published in Archives of Toxicology since 2012

Key message	References
Disruptions of ROS/Ca^{2+} play a key role in modulating adaptive and death pathways in response to Cd^{2+} exposure	Thévenod and Lee (2013)
The hepatotoxic mode of action of amphetamines in combination does not deviate from the individual mechanisms	Dias da Silva et al. (2013)
Caffeic acid causes apoptosis b phospholipase c dependent release of Ca^{2+} from the endoplasmic reticulum	Chang et al. (2013)
Autophagy mitigates apoptosis through modulating PI3K/Akt, ERK and JNK signaling	Hsieh et al. (2013)
This review gives an overview of mitochondria-dependent and mitochondria-independent pathways of apoptosis	Sinha et al. (2013)
The cereal mycotoxin zearalenone induces suicidal erythrocyte death by an increase in cytosolic calcium	Jilani and Lang (2013)
The neurotoxicant trimethyltin chloride induces apoptosis by disturbing the balance between NF-kappa B and MAPKs	Qing et al. (2013)
The anti-tubulin agent DPQZ induces apoptosis by RAS/Raf inhibition	Hour et al. (2013)
Micro RNA-210 targets Bcl-2 and induces apoptosis in neuroblastoma cells	Chio et al. (2013)
Beta-ionone initiates apoptosis via PI3K-Akt	Liu et al. (2013)
ABCC1 causes resistance to arsenic compounds	Xu et al. (2013b)
The valproic acid (VPA) analog, (S)-2-pentyl-4-pentynoic acid, is more apoptogenic than valproic acid	Ivanova et al. (2013)
Cytotoxicity of TiO_2 nanoparticles is size dependent	Xiong et al. (2013)
Paraquat activates the Nrf2/HO-1 pathway in the substantia nigra, whereas tert-butylhydroquinone conferees neuroprotection	Li et al. (2012a)
Nanosized copper oxide induces apoptosis by oxidative stress in podocytes	Xu et al. (2013a)
This comprehensive review uptakes the role of oxidative stress in apoptosis and cancer	Matés et al. (2012)
The widely used herbicide paraquat induces apoptosis in alveolar epithelial cells by dysregulation of the Nrf-2 pathway	Chen et al. (2012)
Endosomes and lysosomes play a key role in thallium induced apoptosis	Hanzel et al. (2012)
Arsenic induces apoptosis in myoblasts via reactive oxygen induced ER stress.	Yen et al. (2012)
Intracellular calcium but not the level of reactive oxygen species controls rotenone induced apoptosis in neuronal cells	Swarnkar et al. (2012)
Melatonin prevents nephrotoxicity by restoration of antioxidative enzymes, and antagonization of iNOS and NF-Kappa B	Lee et al. (2012)
Barium inhibits arsenic by modulating JNK 1/2, caspase 3, NF-Kappa B and XIAP	Yajima et al. (2012)
The shape of hydroxyapatite nanoparticles influences cytotoxicity	An et al. (2012)
The anticancer agent polyphyllin D causes apoptosis in erythrocytes by membrane permeabilization and increased intracellular Ca^{2+}	Gao et al. (2012)
Polymorphisms of glutathione S-transferase omega 1-1 may increase the risk of apoptosis related diseases in humans exposed to arsenicals	Escobar-García et al. (2012)
Needle and plate-shaped nanosized hydroxyl-apatite are more cytotoxic than corresponding spherical or rod-shaped nanoparticles	Zhao et al. (2013)
The fungicide ziram induces apoptosis in human T-lymphocytes by the mitochondrial/cytochrome c pathway	Li et al. (2012b)
Apoptosis induced by the Alternaria mycotoxin alternariol in murine hepatoma cells is Ah receptor dependent	Schreck et al. (2012)
Dimethoxycurcumin, a synthetic analog of curcumin includes S-phase arrest and apoptosis in breast cancer cells (MCF 7)	Kunwar et al. (2012)
Stress activated protein kinases can operate independently of P53 by a pathway downstream of caspases	Donauer et al. (2012)
Cocaine induces apoptosis in cultivated proximal tubular epithelial cells of the kidney	Valente et al. (2012)
Inhibition of autophagy protects from pyocyanin induced cell death	McFarland et al. 2012
The flavonoid fisetin induces apoptosis in Hela cells by the caspase-8/caspase-3 pathway	Ying et al. (2012)
2,5-Hexanedione, the main active metabolite of n-hexane, induces apoptosis in human ovarian granulosa cells through Bcl-2, Bax and caspase-3 pathways	Sun et al. (2012)
Salubrinal, an inhibitor of eIF2 alpha dephosphorylation, protects human renal proximal tubular cells from CdCl2 induced apoptosis	Komoike et al. (2012)
Cerium chloride induces apoptosis in mouse hepatocytes	Zhao et al. (2012)

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