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GUEST EDITORIAL

The CHOP conundrum: controversial discussion about the role of endoplasmic reticulum stress in hepatotoxicity

Seddik Hammad

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Currently, much effort is invested into the identification of biomarkers for predicting toxicity (Campion et al. 2013; Ireno et al. 2014; Sheng et al. 2014). This field of research is often linked to the establishment of in vitro systems, which recapitulate critical aspects of the in vivo situation (Godoy et al. 2009, 2010, 2013; Mielke et al. 2011; Hengstler et al. 2012, 2014; Hammad 2013; Krug et al. 2013; Nussler and Wildemann 2014; Hammad et al. 2014). For example, biomarkers have been established in hepatocyte (Zellmer et al. 2010; Heise et al. 2012; Schug et al. 2013) or stem cell-derived neuronal (Waldmann et al. 2014) in vitro systems. One particularly intensively studied factor is CHOP, which represents a biomarker of endoplasmic reticulum stress (Marciniak et al. 2004; Dalton et al. 2013). Many chemicals which modify proteins induce endoplasmic reticulum (ER) stress (Cribb et al. 2005; Jang et al. 2011; Ji et al. 2011). When misfolded proteins accumulate in the ER, three sensors are activated: IRE1 alpha, PERK, and ATF6 (Hetz 2012). Upon prolonged ER stress, all three branches of the ER stress response induce transcription of CHOP (Ron and Walter 2007; Tabas and Ron 2011), which induces expression of pro-apoptotic genes (Puthalakath et al. 2007; Li et al. 2009). Numerous studies have reported a pro-apoptotic or pro-damage role of CHOP (Marciniak et al. 2004; Sanchez-Lopez et al. 2013; Teske et al. 2013; Yang et al. 2014; Yoon et al. 2014). Also in the liver, CHOP has been described as a pro-damage factor. Upon administration of acetaminophen, CHOP knockout mice have been reported to show lower levels of liver damage than wild-type animals (Uzi et al. 2013). Therefore, the recently published observation of Godoy and his team that CHOP does not play a pro-damage role in the liver is surprising (Campos et al. 2014). The authors used the well-characterized model of acute hepatotoxicity by carbon tetrachloride (CCl_4), which is known to induce pericentral liver damage (Höhme et al. 2007; Hoehme et al. 2010; Hammad et al. 2014). In their study, CCl_4 caused nuclear translocation of CHOP in the liver (Campos et al. 2014). Importantly, CHOP translocation to the nucleus occurred only in the pericentral compartment of the lobule, the region where CCl_4 induces necrosis. Moreover, pro-apoptotic CHOP-regulated genes were observed, such as upregulated GADD34, TRB3, and EROIL (Campos et al. 2014). This scenario strongly suggests a situation of CCl_4-induced ER stress, where CHOP plays a pro-damage function. However, when Campos and colleagues repeated the experiment in CHOP knockout mice, they observed no major difference compared with wild-type animals. Rather, a trend to slightly more liver damage was seen in the CHOP knockout mice. Since the result was surprising, the experiment was repeated with various doses and exposure periods. However, the provocative negative result was reproduced (Campos et al. 2014). This leads to the question, whether the role of CHOP in hepatotoxicity is more complex than previously expected. It also remains difficult to understand, why CHOP plays a pro-damage role in acetaminophen, but not in CCl_4-induced hepatotoxicity. The current study of Campos et al. (2014) shows that CHOP cannot be accepted as a well-understood pro-damage biomarker of hepatotoxicity.

S. Hammad (✉)
Department of Forensic Medicine and Veterinary Toxicology, Faculty of Veterinary Medicine, South Valley University, Qena 83523, Egypt
e-mail: seddik.hammad@vet.svu.edu.eg

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