Highlight report

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EDI3: key enzyme of choline metabolism and a possible link to chronic neurological disorders

The current issue of PNAS reports the discovery and functional characterization of EDI3, a key enzyme of choline metabolism (Stewart et al. 2012). EDI3 cleaves glycerophosphocholine to release choline and glycerol-3-phosphate. This represents a critical step, which provides membrane phospholipids essential for the activation of several signalling pathways. The reaction as such was already known as the “Kennedy pathway”. However, a key enzymatic protein positioned at the start of this pathway remained unidentified—and was now discovered to be EDI3 (Stewart et al. 2012).

The current study of Stewart and colleagues was part of a larger programme aimed at identifying prognostic markers and biomarkers of metastasis in cancer (Schmidt et al. 2008, 2009, 2011, 2012; Kammers et al. 2011; Cadenas et al. 2010, 2011; Petry et al. 2010; Tanner et al. 2006; Brase et al. 2010; Hellwig et al. 2010). EDI3 was shown to be associated with increased metastatic capacity of endometrial carcinomas (Stewart et al. 2012). This effect is mediated by the activation of PKC α which leads to enhanced tumour cell migration. This is certainly of high interest in the field of cancer research and identifies EDI3 as a promising therapeutic target.

However, the focus of Stewart et al. (2012) on tumour biology should not detract from EDI3's possible role in toxicity pathways. Recently, choline metabolism was

reported to be influential in chronic neurological disorders induced by neurotoxic organophosphates (Hou et al. 2009), which are components of pesticides and industrial additives. Exposure to neurotoxic organophosphates leads to acute toxicity, because of the inhibition of acetylcholinesterase (Hou et al. 2009; Solberg and Belkin 1997). However, some organophosphates also compromise choline metabolism by altering the homeostasis of phosphatidylcholine and lysophosphatidylcholine (Hou et al. 2009; Quistad and Casida 2004). Phospholipase B, which cleaves phosphatidylcholine and lysophosphatidylcholine to form glycerophosphocholine, was also suggested as a target of neurotoxic organophosphates. This mechanism appears plausible, since elevated lysophosphatidylcholine is cytotoxic and may lead to demyelination and axonal degeneration (Jean et al. 2002). Herein lies EDI3's potential: Stewart and colleagues have shown that EDI3 activity is linked to intracellular phosphatidic acid and lysophosphatidic acid. Perhaps more importantly, EDI3 uses glycerophosphocholine (GPC) as a substrate and may therefore help the cell to regulate GPC's levels (which is formed from phosphatidylcholine, the most abundant phospholipid). Interestingly, in a human RNA tissue panel, expression levels of EDI3 were highest in brain (Stewart et al. 2012). Since EDI3 recombinant protein is now available, we can now examine its involvement in neurodegenerative disease, in particular its role as a possible target of neurotoxic compounds.

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