REVIEW

Mitochondria as target of endocrine-disrupting chemicals: implications for type 2 diabetes

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Abstract

Type 2 diabetes is a chronic, heterogeneous syndrome characterized by insulin resistance and pancreatic β -cell dysfunction or death. Among several environmental factors contributing to type 2 diabetes development, endocrine-disrupting chemicals (EDCs) have been receiving special attention. These chemicals include a wide variety of pollutants, from components of plastic to pesticides, with the ability to modulate endocrine system function. EDCs can affect multiple cellular processes, including some related to energy production and utilization, leading to alterations in energy homeostasis. Mitochondria are primarily implicated in cellular energy conversion, although they also participate in other processes, such as hormone secretion and apoptosis. In fact, mitochondrial dysfunction due to reduced oxidative capacity, impaired lipid oxidation and increased oxidative stress has been linked to insulin resistance and type 2 diabetes. Herein, we review the main mechanisms whereby metabolism-disrupting chemical (MDC), a subclass of EDCs that disturbs energy homeostasis, cause mitochondrial dysfunction, thus contributing to the establishment of insulin resistance and type 2 diabetes. We conclude that MDC-induced mitochondrial dysfunction, which is mainly characterized by perturbations in mitochondrial bioenergetics, biogenesis and dynamics, excessive reactive oxygen species production and activation of the mitochondrial pathway of apoptosis, seems to be a relevant mechanism linking MDCs to type 2 diabetes development.

Key Words

- ▶ endocrine-disrupting chemicals
- ▶ metabolism-disrupting chemical
- ▶ insulin resistance
- ▶ type 2 diabetes
- ▶ mitochondria

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Introduction

Type 2 diabetes (T2D) is a chronic, lifelong condition characterized by hyperglycaemia resulting from persistent insulin resistance (IR) and/or insufficient insulin production due to β -cell dysfunction or death (Prentki & Nolan 2006). T2D is a heterogeneous, multi-factorial syndrome in which genetic predisposition and environmental factors account for its development. Over the last years, a class of chemical

pollutants named endocrine-disrupting chemicals (EDCs) has been associated with several metabolic diseases, including obesity and T2D (Alonso-Magdalena *et al.* 2011, Neel & Sargis 2011, Gore *et al.* 2015, Braun 2016, Heindel *et al.* 2017). This association seems plausible as these chemicals can alter energy metabolism by affecting multiple cellular events in different organelles, including

endoplasmic reticulum (ER) and mitochondria (Meyer *et al.* 2013, Nadal *et al.* 2017, Rajamani *et al.* 2017).

Mitochondria are essential for the normal cellular function in eukaryotic organisms. Although mitochondria are best known as the powerhouse of the cell due to their crucial role in cellular energy production via oxidative phosphorylation (OXPHOS), these organelles are also key players in other critical cellular processes. For instance, mitochondria are implicated in hormone secretion (Chow *et al.* 2017), generation of reactive oxygen species (ROS) (Brand 2016) and cell death (Fulda *et al.* 2010). Such involvement in a wide variety of processes places the mitochondria at the epicenter of many disorders, including aging and metabolic diseases (Fosslien 2001). A growing body of evidence has linked mitochondrial dysfunction to T2D (reviewed in: Patti & Corvera 2010, Szendroedi *et al.* 2011, Gonzalez-Franquesa & Patti 2017, Fex *et al.* 2018). Essentially, alterations in mitochondrial bioenergetics, biogenesis and dynamics, as well as excessive ROS production, can impact metabolic homeostasis, which might contribute to the establishment of IR and, subsequently, T2D (Petersen *et al.* 2003, 2004, Houstis *et al.* 2006, Anderson *et al.* 2009, Jheng *et al.* 2012).

Thus, due to its vital relevance for the proper physiology and survival of eukaryotic cells, it seems logical that pollutants targeting mitochondria would lead to harmful effects, especially on metabolic homeostasis. In fact, the term metabolism-disrupting chemical (MDC) has been recently proposed to refer to a particular class of EDCs that disturbs energy homeostasis and, therefore, affects the susceptibility to metabolic disorders (Heindel *et al.* 2017). Bisphenol A (BPA), chlorpyrifos, tributyltin

and 2,3,7,8-tetrachlorodibenzodioxin (TCDD) are some of the most common MDCs identified up to date.

In this review, we first highlight the recent evidence correlating EDCs with T2D development. We then outline how mitochondria dysfunction in different tissues involved in metabolic homeostasis is linked to IR and T2D development. Finally, we examine the deleterious effects of MDCs on different mitochondrial processes and discuss how MDC-induced mitochondria dysfunction may lead to IR and T2D. Herein, we indicate doses and type of exposure (e.g. perinatal or during adulthood) for most examples cited, as this information is critical for understanding MDCs effects. To contextualize the reader, we provide a table with the reference doses (RfD) provided by the United States Environmental Protection Agency (EPA) (Table 1) as well as two reports providing comprehensive information on EDC biomonitoring data (CDC 2009, CDC 2018).

Introduction to mitochondria

Before discussing the evidence connecting mitochondrial dysfunction to T2DM, and how MDCs affect mitochondria, we first summarize some key mitochondrial processes (Fig. 1).

Bioenergetics

Mitochondria are often recognized as the powerhouse of the cell, as they are responsible for most part of the cellular energy produced. It is in the mitochondria that sugars, proteins and fats are converted into energy in the form

Table 1 Reference doses (RfD) for some MDCs.

Chemical	RfD (mg/kg/day)	Source/Ref
Arsenic	3×10^{-4}	EPA_Arsenic, inorganic; CASRN 7440-38-2
Atrazine	3.5×10^{-2}	EPA_Atrazine; CASRN 1912-24-9
BBP	2×10^{-1}	EPA_Butyl benzyl phthalate; CASRN 85-687
BPA	5×10^{-2}	EPA_Bisphenol A; CASRN 80-05-7
Cadmium	5×10^{-4} (water) 1×10^{-3} (food)	EPA_Cadmium; CASRN 7440-43-9
Chlorpyrifos	Withdrawn	EPA_Chlorpyrifos; CASRN 2921-88-2
DEHP	2×10^{-2}	EPA_Di(2-ethylhexyl)phthalate (DEHP); CASRN 117-81-7
PFOA	2×10^{-5}	EPA_PFOA
PFOS	2×10^{-5}	EPA_PFOS
TCDD	7×10^{-10}	EPA_2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), CASRN 1746-01-6
Tributyltin oxide	3×10^{-4}	EPA_Tributyltin oxide (TBTO); CASRN 5635-9

According to the United States Environmental Protection Agency (EPA), the reference dose is defined as 'an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime'. The readers are also referred to two reports from the Centers for Disease Control and Prevention (CDC) providing comprehensive information on EDC biomonitoring data (CDC 2009, CDC 2018).

BBP, butyl benzyl phthalate; BPA, bisphenol A; CASRN, Chemical Abstracts Service Registry Number; DEHP, di(2-ethylhexyl)phthalate; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Figure 1

Schematic representation of some mitochondrial functions. (A) Mitochondrial bioenergetics. The tricarboxylic acid cycle (TCA), which takes place in the mitochondrial matrix, generates NADH and FADH₂, whose free energy will be used to transport electrons in the electron transport chain (ETC, located in the inner mitochondrial membrane). Most part of the free energy coming from the electron transfer is used to form an electrochemical gradient ($\Delta\psi_m$) that drives the synthesis of ATP by the ATP synthase. Q and c: ubiquinone and cytochrome c, respectively. (B) Mitochondrial dynamics: mitochondrial fusion (left), which generates large, interconnected mitochondrial networks, is mainly governed by the dynamin-related proteins, mitofusins 1 and 2 (MFN1 and MFN2) and optic atrophy 1 (OPA1). On the other hand, mitochondrial fission (right) leads to fragmented, separated mitochondria. This process is regulated by several proteins, including dynamin-related protein 1 (DRP1), mitochondrial fission protein 1 (FIS1), and the mitochondrial fission factor (MFF). (C) Mitochondria ROS generation and antioxidant activity. Due to its redox activity, the ETC generates reactive oxygen species (ROS) as a consequence of electron leak during the oxidative phosphorylation. The figure depicts the main sites of ROS production in the ETC, i.e. complexes I and III. Of note, there are at least 11 different sites linked to ROS production in the mitochondria, such as the α -ketoglutarate dehydrogenase and the glycerol 3-phosphate dehydrogenase. Complexes I and III generate superoxide radical ($O_2^{\cdot-}$), which can be dismutated to hydrogen peroxide (H_2O_2) by the enzymes superoxide dismutase (SOD) 1 (CuZnSOD, located in the intermembrane space) and 2 (MnSOD, located in the mitochondrial matrix). Other antioxidant enzymes, such as catalase (CAT) and glutathione peroxidase (GPx), can decompose H_2O_2 into H_2O and/or O_2 . (D) Mitochondrial pathway of apoptosis. After an apoptotic stimulus, activated BH3-only proteins translocate to mitochondria where inactivate anti-apoptotic BCL-2 proteins and activate pro-apoptotic BAX and BAK. BAX oligomerization in the outer mitochondrial membrane (OMM) leads to OMM permeabilization and release of cytochrome c (c) and SMAC/DIABLO (S) from the intermembrane space into the cytosol. Under certain conditions (e.g. glucose deprivation and ischemia/reperfusion injury), long-lasting opening of the mitochondrial PTP may also contribute to cytochrome c release. In these situations, prolonged PTP opening leads to mitochondrial dysfunction (e.g. depolarization, and inhibition of oxidative phosphorylation and ATP synthesis) and matrix swelling, which, in turn, causes outer mitochondrial membrane rupture and release of pro-apoptotic factors, including cytochrome c (consecutive arrows). Once in the cytosol, cytochrome c drives caspase activation, which will culminate in activation of apoptosis.

of ATP via two metabolic processes, namely tricarboxylic acid cycle (TCA) and OXPHOS. The free energy carried by the coenzymes NADH and flavin adenine dinucleotide (FADH₂) is used to transport electrons in the electron transport chain (ETC), which is composed of four multipolypeptide enzyme complexes (complexes I to IV) and two electron carriers (ubiquinone and cytochrome c). Much of the free energy coming from the electron transfer is used to form an electrochemical gradient that drives the phosphorylation of ADP by the ATP synthase, an event that is coupled to oxygen consumption (chemiosmotic

model proposed by Mitchell 1961). However, part of this energy may be 'lost' due to proton leak, which may result from the return of protons to the matrix independently of the ATP synthase or be catalyzed by specific mitochondrial proteins, such as the adenine nucleotide translocase and the uncoupling proteins (UCPs) (Jastroch *et al.* 2010).

Biogenesis

Mitochondrial biogenesis is a tightly regulated process whereby cells increase their mtDNA content, mitochondrial

mass and activity in response to different physiological conditions.

Under certain physiological or stressful conditions, activation of different signaling cascades culminates with the activation of transcription factors and co-regulators encoded by both nucleus and mitochondria. From the nuclear side, nuclear respiratory factors 1 and 2 (NRF1 and NRF2) are the two major transcription factors, directly modulating the expression of the mitochondrial transcription factor A (TFAM) and transcription factor B proteins (TFBs), two key regulators of the transcription and replication of mtDNA (Gleyzer *et al.* 2005, Scarpulla 2008).

Mitochondrial biogenesis is coordinated by members of the peroxisome proliferator-activated receptor (PPAR) coactivator-1 (PGC-1) family of coactivators, namely PGC-1 α (PPAR γ coactivator-1 α), PGC-1 β (PPAR γ coactivator-1 β) and PRC (PGC-1 related coactivator) (Puigserver *et al.* 1998, Wu *et al.* 1999, Andersson & Scarpulla 2001, Lin *et al.* 2002). PGC-1 α is considered the master regulator of mitochondrial biogenesis, as its activation leads to activation of several transcription factors, such as PPARs, NRF1/NRF2, estrogen-related receptors (ERR α , ERR β , ERR γ) and thyroid hormone receptors (TR α and TR β) (Puigserver & Spiegelman 2003, Scarpulla 2011).

Dynamics

Mitochondria are very dynamic organelles, exhibiting a wide variety of shapes, size and location that can change within a few seconds or minutes (Twig *et al.* 2010, Picard *et al.* 2016). These characteristics are related to active, regulated processes called mitochondrial fission and fusion (also known as mitochondrial dynamics), as well as the ability of mitochondria to build extensive intracellular networks through the formation of a tubular reticulum (Bereiter-Hahn 1990, Scott & Youle 2010, Prasai 2017). A proper control of mitochondrial dynamics is very important for several biological processes, such as regulation of neuronal development (Choi *et al.* 2013, Burté *et al.* 2015, Denton *et al.* 2018), ROS production (Yu *et al.* 2006, Huang *et al.* 2016, Ježek *et al.* 2018) and apoptosis (Frank *et al.* 2001, Olichon *et al.* 2003, Suen *et al.* 2008).

Mitochondrial fission promotes fragmented, separated mitochondria in a process regulated by several proteins, including dynamin-related protein 1 (DRP1), a master regulator of mitochondrial division in eukaryotic cells and mitochondrial fission protein 1 (FIS1). Conversely, mitochondrial fusion generates large, interconnected mitochondrial networks. Three dynamin-related proteins, namely mitofusins 1 and 2 (MFN1 and MFN2),

and optic atrophy 1 (OPA1), mediate mitochondrial fusion in mammals (Suárez-Rivero *et al.* 2016, Williams & Ding 2017). Both processes contribute to keep a healthy pool of mitochondria by actively participating in mitophagy, the mitochondrial quality control process by which damaged or dysfunctional mitochondria are eliminated by selective autophagy (Lemasters 2005, Williams & Ding 2017). The mitophagic process is mainly orchestrated by two main proteins, namely phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) and Parkin (PARK2). More recently, other proteins participating in mitophagy have been identified, including the E3 ubiquitin ligase ariadne RBR E3 ubiquitin protein ligase 1 (ARIH1) and the inner mitochondrial membrane protein, prohibitin 2 (PHB2) (Palikaras & Tavernarakis 2014, Villa *et al.* 2017, Wei *et al.* 2017).

ROS and oxidative stress

Mitochondria are considered the major source of intracellular ROS, which are mainly produced as consequence of electron leak from the ETC during the OXPHOS. Mitochondria present at least 11 different sites associated with ROS generation; it is generally well accepted that complexes I and III are the two major sites (Brand 2016).

ROS act as a double-edged sword for the cells. Physiological concentrations of ROS act as second messengers in diverse cellular and mitochondrial processes and signaling pathways (Sena & Chandel 2012). Conversely, excessive ROS can react with lipids, nucleic acids (including mtDNA) and proteins, causing oxidative damage and, eventually, cell death (Circu & Aw 2010). To keep ROS levels under control and avoid their potentially detrimental effects, mitochondria have evolved an antioxidant defense composed by non-enzymatic (e.g. ascorbic acid and α -tocopherol) and enzymatic (e.g. catalase and superoxide dismutase, SOD) systems (Sies 1993). Moreover, it has been suggested that UCP2 and UCP3 might be involved in the control of ROS production (Arsenijevic *et al.* 2000, Mailloux & Harper 2011, Pons *et al.* 2015). When antioxidant defenses fail to cope with excessive ROS production, cells undergo oxidative stress, which has been associated with IR and T2DM (Houstis *et al.* 2006, Anderson *et al.* 2009, Tangvarasittichai 2015).

Mitochondria and cell death

Along with their role in energy production, mitochondria are also implicated in several signaling pathways.

For instance, mitochondria play a crucial role in the intrinsic pathway of apoptosis, which requires permeabilization of the outer mitochondrial membrane (OMM). Regulation of OMM permeabilization depends on the balance between anti- and pro-apoptotic B-cell lymphoma 2 (BCL-2) family proteins. This family comprises three groups of proteins: anti-apoptotic (e.g. BCL-2 and BCL-XL), pro-apoptotic (e.g. BAX and BAK) and BH3-only proteins (e.g. PUMA, and BIM) (Youle & Strasser 2008). Upon exposure to cell death stimuli (e.g. DNA damage), BH3-only proteins translocate to mitochondria, where they bind and inactivate anti-apoptotic BCL-2 proteins. Subsequently, BH3-only proteins stimulate BAX and BAK, causing OMM permeabilization and release of pro-apoptotic proteins, such as cytochrome *c* and SMAC/DIABLO, from the intermembrane space. Additionally, long-lasting opening of the mitochondrial permeability transition pore (PTP) also contributes to cytochrome *c* release under certain conditions (e.g. glucose deprivation and ischemia/reperfusion injury). Once in the cytosol, cytochrome *c* binds to the apoptotic protease activating factor 1, leading to the activation of caspase-9 and -3, and, ultimately, apoptosis (Ow *et al.* 2008, Youle & Strasser 2008).

EDCs and T2D

EDCs have been defined by the Endocrine Society as ‘an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action’ (Zoeller *et al.* 2012). The definition includes a great variety of compounds, such as industrial and waste products, plasticizers, flame retardants, pesticides and food additives. Human exposure mainly occurs by ingestion, inhalation and dermal uptake (Gore *et al.* 2015). The current knowledge on the relationship between EDCs and T2D is briefly discussed below and in other comprehensive reviews (Alonso-Magdalena *et al.* 2011, Gore *et al.* 2015, Heindel *et al.* 2017, Mimoto *et al.* 2017, Nadal *et al.* 2017, Lind & Lind 2018).

Although initial concern on EDCs was focused on their capacity to induce reproductive abnormalities, we have learned over the years that these compounds can also exert other detrimental effects. In this regard, an enlarging body of evidence has provided a strong support for the role of EDCs in the etiology of diabetes and other metabolic disorders (Alonso-Magdalena *et al.* 2011, Gore *et al.* 2015, Heindel *et al.* 2017, Nadal *et al.* 2017).

Among them, those with the most conclusive evidence of a diabetogenic role are plasticizers like BPA and phthalates, some persistent organic pollutants (POPs), such as dioxins, polychlorinated biphenyls (PCBs), perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), and dichlorodiphenyltrichloroethane (DDT), as well as some heavy metals, including arsenic and cadmium (Gore *et al.* 2015, Cardenas *et al.* 2017).

Numerous studies conducted in animals have explored the metabolic effects of MDCs at different timing of exposure. In adult animals, several MDCs have been shown to decrease insulin sensitivity and promote glucose intolerance. For instance, BPA exposure (100 µg/kg/day) resulted in postprandial hyperinsulinemia, impaired glucose tolerance and marked IR in mice (Alonso-Magdalena *et al.* 2006) along with defective insulin signaling in liver and muscle (Batista *et al.* 2012). Additionally, BPA exposure (50 µg/kg) diminished hepatic glucokinase activity (Perreault *et al.* 2013). At higher doses (20 and 200 mg/kg/day), BPA also impaired insulin signaling and decreased hepatic glucose oxidation and glycogen content (Jayashree *et al.* 2013). Analogously, the exposure to some PCBs, such as aroclor (0.5, 5, 50 and 500 µg/kg/day), PCB-118 (37.5 mg/kg), PCB-138 (37.5 mg/kg) or PCB-126 (10 µg/kg/day), has been associated to increased body weight gain, IR, hyperinsulinemia and changes in pancreatic α - (decrease) and β -cell (increase) mass (Ruzzin *et al.* 2009, Zhang *et al.* 2015a, Kim *et al.* 2016, Loiola *et al.* 2016). Importantly, complex interactions between diet and PCBs have been reported in the development of metabolic disorders. Thus, aroclor (36 mg/kg/week) exacerbated high-fat diet (HFD)-induced IR (Gray *et al.* 2013), while other PCBs (PCB-77: 50 mg/kg; PCB-126: 1.6 mg/kg) provoked glucose intolerance and impaired insulin sensitivity in obese mice only when there was a switch from HFD to a less caloric diet (Baker *et al.* 2013, 2015).

Cadmium and arsenic may also promote perturbations on glucose handling. Cadmium administration has been shown to promote hyperglycaemia, impaired glucose tolerance and reduced plasma insulin levels (Ithakissios *et al.* 1975, Merali & Singhal 1980, Kanter *et al.* 2003, Edwards & Prozialeck 2009, Trevino *et al.* 2015). Similarly, arsenic (0.05–50 ppm) has been shown to alter glucose tolerance (Paul *et al.* 2011, Huang *et al.* 2015), an effect that was aggravated in diabetic mice (Liu *et al.* 2014) or in the presence of a metabolic stressor (e.g. HFD) (Paul *et al.* 2011).

Increasing attention has been focused on the exposure to MDCs during intrauterine life, which turns

out to be an extremely sensitive period. Several studies have largely demonstrated that maternal exposure to environmental pollutants during development may lead to severe metabolic perturbations. Thus, offspring from mice exposed to BPA (5–5000 µg/kg/day) during pregnancy manifested glucose intolerance, IR as well as alterations on β -cell function and mass (Alonso-Magdalena *et al.* 2010, Angle *et al.* 2013). Impairments on glucose and lipid metabolism were exacerbated when animals were challenged with HFD (Wei *et al.* 2011, García-Arevalo *et al.* 2014) and, in some cases, were accompanied by alterations in the structure of the hypothalamic energy balance circuitry (MacKay *et al.* 2013, 2017). At earlier stages, BPA (10 µg/kg/day and 25 mg/kg/diet) altered pancreas development (García-Arevalo *et al.* 2016, Whitehead *et al.* 2016). In addition, metabolomics studies have demonstrated global changes in metabolism, including energy metabolism and brain function on BPA-exposed pups (0.025, 0.25 and 25 µg/kg/day) (Cabaton *et al.* 2013). Importantly, BPA-induced metabolic disorders can be transmitted to next generation (Li *et al.* 2014, Susiarjo *et al.* 2015, Bansal *et al.* 2017).

Notably, the adverse metabolic outcomes affect not only the offspring but also the mother. BPA-exposed dams (10 and 100 µg/kg/day) developed gestational glucose intolerance and decreased insulin sensitivity (Alonso-Magdalena *et al.* 2010, Susiarjo *et al.* 2015). Although these metabolic perturbations disappeared after parturition, the remission was only temporal and alterations reappeared months later (Alonso-Magdalena *et al.* 2015).

Prenatal exposure to PCB has also been linked to the programming of glucose and energy homeostasis in the offspring. Exposure to PCB-153 (0.09–1406 µg/kg/day) during gestation and lactation resulted in increased glucose levels in the male offspring while, in the female, promoted increased glucagon levels and decreased pancreatic weight (van Esterik *et al.* 2015). In combination with a HFD, PCB exposure provoked hepatic steatosis, alterations in the plasma adipokine profile and increased expression of genes related to lipid biosynthesis (Wahlang *et al.* 2013). Likewise, DDT-exposed offspring (1.7 mg/kg/day) manifested glucose intolerance, hyperinsulinemia, dyslipidemia and impaired thermogenesis (La Merrill *et al.* 2014).

The metabolic effects of di(2-ethylhexyl) phthalate (DEHP) have also been explored. DEHP exposure (1.25 and 6.25 mg/kg/day) throughout gestation and lactation resulted in abnormalities in pancreas development and function, which were reflected by decreased pancreatic β -cell mass and insulin content at the moment of weaning

(Lin *et al.* 2011). When getting older (8–9 weeks of age), DEHP-exposed animals presented elevated glucose levels and impaired glucose and insulin tolerance.

Other persistent compounds, such as PFOS (16, 32 and 64 µM), have been proposed to disrupt pancreas organogenesis (Sant *et al.* 2017). This has been demonstrated to occur in zebrafish while, in rodents, PFOS (0.3 and 3 mg/kg/day) administration during gestational and lactational periods altered glucose metabolism not only in the offspring but also in the mother (Wan *et al.* 2014). Conversely, no changes on glucose tolerance were observed in the PFOA-offspring (3–3000 µg/kg/day), although the animals exhibited alterations in the hepatic structure (van Esterik *et al.* 2016).

Regarding human data, a number of cross-sectional studies have established a link between BPA levels and the incidence of T2D. Representative data from National Health and Nutrition Examination Survey (NHANES) (2003–2004) demonstrated a positive correlation between BPA levels and increased incidence of T2D and cardiovascular disease (Lang *et al.* 2008). Similar results were observed in data pooled across collection years (2003–2004/2005–2006) (Melzer *et al.* 2010). Studies based on NHANES 2003–2008 reported a connection between BPA levels and the incidence of diabetes (Shankar & Teppala 2011) and prediabetes (Sabanayagam *et al.* 2013) independently of traditional diabetes risk factors. BPA has also been linked to the prevalence of IR, hyperinsulinemia and adverse glucose homeostasis (Wang *et al.* 2012, Beydoun *et al.* 2014, Tai & Chen 2016). In children, BPA has been associated to the presence of IR regardless of BMI (Menale *et al.* 2017). Human exposure to some phthalate metabolites has also been associated with elevated fasting glucose and insulin levels, IR, as well as increased prevalence of diabetes in different populations (Svensson *et al.* 2011, James-Todd *et al.* 2012, Lind *et al.* 2012, Kim *et al.* 2013, Trasande *et al.* 2013, Huang *et al.* 2014, Sun *et al.* 2014a, Dales *et al.* 2018).

Besides that, a large number of epidemiological evidence supports the role of different POPs in metabolic disorders. This is the case of some PCBs and organochlorine pesticides that have been correlated with decreased insulin sensitivity and diabetes risk (Wang *et al.* 2008, Lee *et al.* 2010, 2011, Wu *et al.* 2013, Suarez-Lopez *et al.* 2015). Some studies have also evaluated the metabolic consequences of POP exposure in early life. Thus, prenatal exposure to some PCBs has been associated with increased fasting insulin levels in girls at 5 years of age (Tang-Peronard *et al.* 2015), while PCBs and organochlorine exposure has been related to decreased insulin levels

in newborns (Debost-Legrand *et al.* 2016). Regarding perfluorinated compounds (PFCs), PFOA exposure has been linked to elevated diabetes prevalence in adults (He *et al.* 2017) and elderly (Lind *et al.* 2014), while an association between PFOA levels and impaired β -cell function has been observed in adulthood (Domazet *et al.* 2016). Perfluoroalkoxy alkanes exposure during pregnancy was positively related to impaired gestational glucose tolerance (Matilla-Santander *et al.* 2017).

Mitochondria and T2D

Numerous studies have reported mitochondrial alterations in peripheral tissues that play a crucial role in the control of glucose metabolism (Kelley *et al.* 2002, Kusminski & Scherer 2012, Sebastian *et al.* 2012, Supale *et al.* 2012). However, whether those abnormalities are the cause or a consequence of T2D remains unclear. As this subject is outside the scope of the present review, and it has been extensively reviewed elsewhere, the interested reader is referred to some reviews on the topic (Patti & Corvera 2010, Szendroedi *et al.* 2011, Di Meo *et al.* 2017, Gonzalez-Franquesa & Patti 2017, Fex *et al.* 2018).

MDCs and mitochondria

Effects of MDCs on mitochondria have been described since the 1960s. Yet up to date, only a few studies have shown a correlation between MDC-induced mitochondrial dysfunction and IR/T2D. In this section, we discuss those mechanisms.

MDCs and mitochondrial bioenergetics

Numerous studies have reported that MDCs exposure affect mitochondrial bioenergetics, either via direct interaction with mitochondrial proteins or secondary to transcriptional changes (Melnick & Schiller 1982, Moreno & Madeira 1991, Shertzer *et al.* 2006, Walters *et al.* 2009, Carchia *et al.* 2015).

In pancreatic islets, BPA (25 μ g/L) induced mitochondrial swelling and decreased cytochrome *c* oxidase activity and ATP levels (Song *et al.* 2012). This reduction in ATP levels was later confirmed in rat INS-1E cells, and it was associated with a BPA-induced reduction in mitochondrial mass, dissipation of the mitochondrial membrane potential (MMP) and abnormal expression of genes involved in mitochondrial

function (Lin *et al.* 2013). To better understand the mechanisms whereby environmental doses of BPA lead to mitochondrial dysfunction in isolated islets, Carchia and colleagues used a transcriptomic approach, which revealed that 1 nM BPA decreased the expression of 29 genes, some of which were involved in OXPHOS and mitochondrial dysfunction, such as *Uqcrrb*, *Atp1b1* and *Iars* (Carchia *et al.* 2015). Interestingly, these findings were not restricted to *ex vivo* or *in vitro* studies. Pancreatic islets from F1 and F2 adult male mice offspring of mothers exposed to BPA (10 mg/kg/day) presented impaired mitochondrial oxygen consumption and changes in the expression of several mitochondrial genes (Bansal *et al.* 2017). As mitochondria are critical for the regulation of β -cell mass and function (Kaufman *et al.* 2015), mitochondrial dysfunction might be related to BPA-induced β -cell impairment (Alonso-Magdalena *et al.* 2006, Carchia *et al.* 2015, Bansal *et al.* 2017).

Upregulation of *Ucp2* mRNA expression has been found upon BPA exposure (Wei *et al.* 2011, Song *et al.* 2012, Bansal *et al.* 2017). Elevated UCP2 activity might be, at least in part, responsible for the above-mentioned reduction in the MMP and ATP levels, leading to attenuated GSIS, as reported in islets from UCP2-overexpressing animals (Chan *et al.* 1999, 2001). However, it is important to confirm UCP2 expression at protein level before drawing any conclusion, as it has been shown that UCP2 expression is mainly regulated at the translational level (Hurtaud *et al.* 2007).

Multiple cellular processes could be potentially affected by mitochondrial dysfunction in hepatocytes. Augmented hepatic lipid accumulation has been found in adult rats treated with atrazine (30 μ g/kg/day) (Lim *et al.* 2009), BPA (40 μ g/kg/day) (Jiang *et al.* 2014a) and tributyltin (0.1 μ g/kg/day) (Bertuloso *et al.* 2015) and was usually accompanied by reduced activity of mitochondrial proteins (mainly respiratory complexes I and III), MMP and ATP production (Lim *et al.* 2009, Jiang *et al.* 2014a). Studies in hepatocyte cell lines and/or mitochondria isolated from liver suggest that these effects may be direct on mitochondria (Nakagawa & Tayama 2000, Gogvadze *et al.* 2002, Lim *et al.* 2009, Huc *et al.* 2012, Moon *et al.* 2012, Sagarkar *et al.* 2016). Altogether, these studies suggest that intrahepatic lipid accumulation derived from mitochondrial dysfunction might be partially responsible for the IR and glucose intolerance observed in atrazine- and BPA-treated animals (Lim *et al.* 2009, Alonso-Magdalena *et al.* 2010, Wei *et al.* 2011, García-Arevalo *et al.* 2014).

Atrazine exposure also leads to muscle lipid accumulation, reduced mitochondrial respiration and

changes in mitochondrial morphology. Curiously, reduced oxygen consumption rate was not related to changes in the protein expression of several mitochondrial OXPHOS complex subunits (e.g. SDHA and UQCRC2), but rather to direct effects on mitochondrial complex III. Moreover, atrazine-treated rats were insulin resistant and presented low energy expenditure (Lim *et al.* 2009). In L6 myotubes, atrazine treatment (50 and 100 µM) resulted in the downregulation of several genes related to OXPHOS (e.g. *mt-Co3* and *Sdhc*) and mitochondrial biogenesis (e.g. *Tfam*), leading to reduced ATP production (Sagarkar *et al.* 2016). Similar results were observed in cardiac muscle from BPA-treated male rats (50 µg/kg/day). Additionally, BPA-treated animals also presented reduced MMP and activities of mitochondrial complexes I–IV (Jiang *et al.* 2015). Similarly, prenatal exposure to BPA (50 µg/kg/day) downregulated genes related to OXPHOS pathway (e.g. *Cyts*), fatty acid oxidation (e.g. *Acadm* and *Lp1*) and mitochondrial biogenesis (e.g. *Nrf1* and *Ppargc1a*) as well as reduced MMP in heart of neonatal rats (Jiang *et al.* 2014b). TCDD (10 nM) induced mitochondrial dysfunction in C2C12 skeletal myoblasts, leading to dissipation of MMP, reduced levels of mitochondrial genome-coded cytochrome *c* oxidase subunits I and II and increased ROS production (Biswas *et al.* 2008). Despite the lack of more direct evidence on IR and T2D development, the results above are in line with findings in insulin-resistant and/or T2D individuals, in which alterations in muscle mitochondrial capacity and gene expression (e.g. *NRF1*, *SDHC* and *PPARGC1A*), as well as increased intramyocellular lipid accumulation, have been documented (Jacob *et al.* 1999, Patti *et al.* 2003, Petersen *et al.* 2004).

In human adipose-derived stem cells, tributyltin (100 nM) inhibited oxygen consumption (Llobet *et al.* 2015). Similarly, 3T3-L1 adipocytes exposed to BPA (10 nM), 4-nonylphenol (600 pM) and diethylstilbestrol (0.23 pM) exhibited decreased mitochondrial respiration and mitochondria-associated ATP production, as well as reduced glycolytic function (Tsou *et al.* 2017). These effects might be due to direct effects on the activity of mitochondrial proteins and/or modulation of mitochondria biogenesis, which are consistent with the mitochondrial impairment observed in WAT from obese/T2D individuals (Bogacka *et al.* 2005, Choo *et al.* 2006, Dahlman *et al.* 2006, Rong *et al.* 2007).

MDCs and mitochondrial biogenesis

A wide variety of MDCs interfere with mitochondrial biogenesis by modulation of proteins involved in this

process. For instance, livers from rats exposed to sodium arsenite (25 ppm) presented reduced levels of *Nrf1*, *Nrf2* and *Tfam*, and *Ppargc1a* (PGC-1α) and diminished expression and activity of mitochondrial complexes (Prakash & Kumar 2016). In human liver HepG2 cells and C3H10T1/2 mesenchymal stem cells, the plasticizer benzyl butyl phthalate (BBP, 1 nM–50 µM) also downregulated the expression of *NRF1*, *NRF2*, *TFAM* and *PPARGC1A* (Zhang *et al.* 2015b, Zhang & Choudhury 2017). Additionally, levels of sirtuins (SIRT) 1 and 3, two NAD⁺-dependent deacetylases with different roles in the control of mitochondrial biogenesis (Nogueiras *et al.* 2012), were also decreased. Under certain metabolic conditions (e.g. fasting or obesity), SIRT1 and SIRT3 can also impact hepatic gluconeogenesis and fatty acid metabolism (Milne *et al.* 2007, Hirschey *et al.* 2010), pancreatic insulin secretion and viability (Moynihan *et al.* 2005, Caton *et al.* 2013) and fatty acid and glucose metabolism in skeletal muscle and adipose tissue (Picard *et al.* 2004, Jing *et al.* 2011). Hence, downregulation of these proteins may impair metabolic function, leading to metabolic diseases. In fact, some studies have shown that *Sirt1* deletion results in hyperglycaemia and IR (Wang *et al.* 2011), whereas SIRT1 gain-of-function prevents diabetes in mice models (Banks *et al.* 2008). Similarly, *Sirt3*-knockout mice and cultured myoblasts silenced for *Sirt3* exhibited increased oxidative stress and impaired insulin signaling (Jing *et al.* 2011).

Reportedly, hearts from neonatal rats prenatally exposed to BPA (50 µg/kg/day) had decreased expression of mitochondrial biogenesis regulators (PGC-1α, ERRα, ERRγ, PPARα, NRF1 and TFAM) (Jiang *et al.* 2014b). Likewise, long-term exposure to BPA (50 µg/kg/day) induced PGC-1α promoter hypermethylation and reduced *Ppargc1a* expression in heart tissue upon 24 and 48 weeks of treatment (Jiang *et al.* 2015). Interestingly, similar results were found in skeletal muscle from insulin-resistant patients with T2D and obese individuals, where PGC-1α methylation was related to reduced mitochondrial biogenesis (Barrès *et al.* 2009, 2013). Along with decreased PGC-1α expression, BPA-treated animals also displayed reduced levels of *Nrf1*, *Nrf2* and *Tfam*, and some of their target genes, including *Atp5e*, *Atp5o*, *Uqcrc2* and *Uqcrl1*. These data show that BPA-induced perturbations in mitochondrial biogenesis might be, at least partially, responsible for the mitochondrial abnormalities observed in BPA-treated animals, such as reduction in the activity of mitochondrial proteins, depolarized MMP and decreased ATP levels (Lin *et al.* 2013, Jiang *et al.* 2014b, 2015).

Another mechanism by which MDCs may induce mitochondrial perturbations was described in human

trophoblast-like JAR cells treated with 2 nM TCDD (Chen *et al.* 2010). In this study, TCDD exposure decreased mtDNA copy number and increased mtDNA deletions, including a 7599-bp deletion of mtDNA encompassing genes encoding proteins involved in mitochondrial function. In addition, TCDD cells presented reduced MMP, lower ATP levels and increased oxidative stress.

As alterations in the process of mitochondrial biogenesis seem to be involved in the mitochondrial dysfunction observed in insulin-responsive tissues in T2D (Gonzalez-Franquesa & Patti 2017), changes in mitochondrial biogenesis also seem to contribute to EDC-induced IR.

MDCs and mitochondrial dynamics

A growing body of evidence suggests that impairment of mitochondrial dynamics is related to IR and T2D (Yoon *et al.* 2011, Rovira-Llopis *et al.* 2017). Alterations in mitochondrial fission and fusion contribute to mitochondrial dysfunction (Bach *et al.* 2003, Jheng *et al.* 2012, Boutant *et al.* 2017), oxidative and/or ER stress (Yu *et al.* 2006, Sebastian *et al.* 2012, Wang *et al.* 2015) and β -cell apoptosis (Men *et al.* 2009, Molina *et al.* 2009), which, eventually, might lead to impaired glucose homeostasis and IR. In human-induced pluripotent stem cells, exposure to tributyltin (50 nM) or chlorpyrifos (30 μ M) reduced MFN1 expression, leading to mitochondrial fragmentation (Yamada *et al.* 2016, 2017). Chlorpyrifos (25–100 μ M) also caused mitochondrial dysfunction (reduced complex I activity, MMP and ATP levels), increased ROS production and activation of PINK1/Parkin-mediated mitophagy in SH-SH5Y neuroblastoma cells (Dai *et al.* 2015, Park *et al.* 2017). These data correlate with a study showing fragmented mitochondrial network in myocardium of diabetic patients, which was associated with a reduced MFN1 expression in atrial tissue. Additionally, attenuated complex I activity and higher ROS levels were also observed in their atrial myocardium (Montaigne *et al.* 2014).

Cadmium exposure also changes mitochondrial dynamics. Liver from cadmium-treated animals (1–2 mg/kg/day) and L02 hepatocytes (12 μ M) presented excessive mitochondrial fragmentation, which preceded mitochondrial dysfunction. Moreover, cadmium augmented DRP1 expression and its recruitment into mitochondria. These changes in DRP1 expression and recruitment, as well as mitochondrial fragmentation, were associated with disturbances in Ca^{2+} homeostasis (Xu *et al.* 2013). The same group also showed that cadmium-induced DRP1-dependent intense mitochondrial fission and

mitophagy, causing mitochondrial loss and hepatotoxicity. Interestingly, DRP1 inhibition reverted cadmium-induced effects on mitochondria (Pi *et al.* 2013).

Acute exposure to high doses of BPA (25–100 μ M) induced mitochondrial dysfunction and loss, as well as activation of PINK1/Parkin-dependent, AMPK-mediated mitophagy in neuronal cells (Agarwal *et al.* 2015). Similarly, chronic exposure to BPA (40 μ g/kg/day *in vivo*; 100 μ M *in vitro*) increased DRP1-mediated mitochondrial fragmentation in the hippocampus of rat brains and in neuronal stem cells. Interestingly, inhibition of DRP1 reverted BPA-induced mitochondrial dysfunction and fragmentation (Agarwal *et al.* 2016). These findings are in line with observations in differentiated myoblasts, in which palmitate-induced mitochondrial dysfunction, fission and impaired insulin-stimulated glucose uptake were prevented by inhibition of DRP1 using pharmacological and genetic approaches (Jheng *et al.* 2012).

Taken together, these studies suggest that MDC-induced alterations in mitochondrial dynamics might be part of the mechanism by which mitochondrial dysfunction and exacerbated oxidative stress lead to IR. Conversely, it is worth noting that, in most cases, mitophagy acts as a protective mechanism under certain stress response circumstances (Kubli & Gustafsson 2012, Meyer *et al.* 2017). Therefore, mitophagy activation in response to MDCs might be a way to protect against MDC-induced cell injury.

MDCs, ROS and oxidative stress

Due to their ability to impair mitochondrial bioenergetics, it seems reasonable to assume that MDCs also modulate ROS generation. PFCs, especially PFOA and PFOS, induce ROS production likely as a consequence of inhibition of mitochondrial respiratory chain (mainly complexes I and II) (Panaretakis *et al.* 2001, Mashayekhi *et al.* 2015, Shabalina *et al.* 2016). Of note, PFOA effects on ROS production and MMP were reduced by treatment with the antioxidant N-acetylcysteine (Panaretakis *et al.* 2001). More recently, Han and collaborators have shown that livers from rats treated with PFOS (1 or 10 mg/kg) presented augmented ROS levels and diminished antioxidant defense (decreased SOD and catalase activities; lower total GSH and GSH/GSSG ratio) (Han *et al.* 2018). These findings are in line with previous studies showing that HFD increased the H_2O_2 -emitting potential of mitochondria and induced a shift of the cellular redox environment to a more oxidized state in skeletal muscle (Anderson *et al.* 2009). Interestingly, PFOS-induced oxidative stress was associated

with activation of nuclear factor- κ B (NF- κ B) and tumor necrosis factor- α (TNF α), two pathways implicated in IR (Hotamisligil *et al.* 1993, Hotamisligil 1999, Arkan *et al.* 2005, Cai *et al.* 2005).

Chronic exposure to arsenic affects insulin sensitivity in peripheral tissues through multiple mechanisms and signaling pathways (Diaz-Villasenor *et al.* 2007). A recent study showed that arsenic-induced oxidative stress dampened insulin-dependent glucose uptake and GLUT4 expression in adipocytes and myotubes. In this study, arsenic treatment (0.5–2 μ M) downregulated the expression of the mitochondrial oxidative stress response protein SIRT3 and, some SIRT3-target proteins, namely FOXO3a, MnSOD and PGC-1 α (Divya *et al.* 2015). Furthermore, overexpression of SIRT3 or MnSOD partially restored insulin sensitivity in these cells. Curiously, SIRT3 deficiency leads to pronounced oxidative stress and development of IR and metabolic syndrome in mice (Hirschey *et al.* 2011, Jing *et al.* 2011).

ROS play a critical role in pancreatic β -cell dysfunction and death (Evans *et al.* 2003). In general, MDC-induced ROS contributes to β -cell death. In INS-1E cells, BPA (25–100 μ M) increased ROS production and depleted intracellular GSH, which was followed by DNA damage and p53 activation (Xin *et al.* 2014). At 1 nM, BPA-treated islets showed increased ROS levels as well as reduced expression of two ROS-scavenging genes, glutathione peroxidase 3 (*Gpx3*) and superoxide dismutase 2 (*Sod2*), resulting in NF- κ B activation (Carchia *et al.* 2015). In both studies, treatment with N-acetylcysteine partially rescued BPA-induced changes, reinforcing that oxidative stress is part of the mechanism underlying BPA effects on β -cells.

As aforementioned, BPA exposure increases *Ucp2* expression in β -cells. As UCP2 activation protects β -cells from ROS deleterious effects (Chan *et al.* 2004), this increment might be a defensive response against BPA-induced β -cell stress. However, there is no evidence supporting this statement yet.

MDCs and cell death

A common feature of T2D development is the reduction in β -cell mass secondary to increased rates of β -cell death. In this context, exposure to certain metabolic conditions (e.g. chronic hyperglycemia and hyperlipidemia) activates several stress responses that trigger β -cell apoptosis (Cnop *et al.* 2005, Rhodes 2005). Likewise, many MDCs cause β -cell apoptosis via activation of responsive mechanisms known to be associated with β -cell demise in T2D, such as ER and oxidative stress (Lu *et al.* 2011, Chang *et al.* 2013,

Lin *et al.* 2013, Sun *et al.* 2014b, Carchia *et al.* 2015, Suh *et al.* 2017a,b). For instance, INS-1 cells exposed to DEHP (25–625 μ M) presented excessive ROS generation as well as inhibited nuclear factor erythroid 2-related factor 2 (NRF-2)-dependent antioxidant response. Furthermore, DEHP treatment induced Ca²⁺ depletion and activation of ER stress response via PKR-like ER kinase (PERK) pathway. Ultimately, DEHP-induced persistent oxidative and ER stress caused β -cell dysfunction and apoptosis (Sun *et al.* 2014b).

In response to oxidative and ER stress, several mitogen-activated protein kinases (MAPK) involved in cell survival responses are activated (McCubrey *et al.* 2006, Darling & Cook 2014). In β -cells, exposure to arsenic, cadmium or tributyltin resulted in the activation of some MAPK, namely c-Jun N-terminal kinase 1/2 (JNK1/2), extracellular signal-regulated kinases 1/2 (ERK1/2) and p38 (Lu *et al.* 2011, Chang *et al.* 2013, Huang *et al.* 2018). Interestingly, only JNK signaling was directly implicated in apoptosis, which is in agreement with findings suggesting a pro-apoptotic role for JNK1 in β -cells (Marroquí *et al.* 2014, Dos Santos *et al.* 2017).

Several MDCs regulate PTP opening and expression of BCL-2 proteins (Panaretakis *et al.* 2001, Gogvadze *et al.* 2002, Yang *et al.* 2012, Xia *et al.* 2014), though little is known about PTP contribution to β -cell apoptosis. Regarding the modulation of BCL-2 members, available studies show decreased *Bcl2* expression, and either increased (Lin *et al.* 2013, Carchia *et al.* 2015) or unchanged (Lu *et al.* 2011, Chang *et al.* 2013) *Bax* expression. These changes potentiated the BAX/BCL-2 ratio, favoring the pro-apoptotic pathway.

Altogether, some possible mechanisms for MDC-induced, oxidative and ER stress-mediated β -cell apoptosis include (1) induction of the transcription factor C/EBP homologous protein (CHOP), which modulates the expression of some BCL-2 members, such as BCL-2, PUMA and BIM (McCullough *et al.* 2001, Wali *et al.* 2014); (2) JNK1 activation, which activates BAX and BIM by phosphorylation (Kim *et al.* 2006, Marroquí *et al.* 2014), upregulates DP5 and PUMA (Gurzov *et al.* 2009, Cunha *et al.* 2016) and downregulates MCL-1 (Allagnat *et al.* 2011), and (3) activation of proinflammatory pathways, such as NF- κ B and TNF α , which, among other effects, modulate the expression of BCL-2 members (Cnop *et al.* 2005, Gurzov & Eizirik 2011).

Concluding remarks

Besides the great number of studies comprising MDCs and mitochondria, little is known about the relationship between MDC-induced mitochondria dysfunction and

Figure 2

Metabolism-disrupting chemicals-induced mitochondrial dysfunction may lead to insulin resistance and type 2 diabetes. Metabolism-disrupting chemicals (MDCs) can directly or indirectly alter several mitochondrial processes, such as bioenergetics, biogenesis, dynamics and ROS production. As a result, MDC-induced mitochondrial dysfunction may disrupt insulin sensitivity in skeletal muscle, adipose tissue and liver, as well as induce β -cell dysfunction and cell death. Ultimately, these effects may contribute to the mechanism leading to insulin resistance and type 2 diabetes.

IR/T2D, especially in tissues such as skeletal muscle and adipose tissue. In this review, we have summarized some of the effects promoted by MDCs on mitochondria. Essentially, MDC-induced mitochondrial dysfunction is characterized by perturbations in mitochondrial bioenergetics, biogenesis and dynamics, excessive ROS production and activation of the mitochondrial pathway of apoptosis. These alterations might be relevant for insulin-responsive tissues, in which emerging evidence implicate mitochondrial dysfunction as a contributor mechanism linking MDCs to T2D development (Di Meo *et al.* 2017, Fex *et al.* 2018). Furthermore, it is important to keep in mind that humans are exposed to a mixture of MDCs that might affect mitochondrial function and metabolic homeostasis simultaneously, leading to alterations in insulin sensitivity (adipose tissue, skeletal muscle and liver) as well as cell dysfunction and death (pancreatic β -cells) (Fig. 2).

Recent advances in the field of omics will be of great advantage for MDC research. For instance, the use of mitochondriomics technology, which is the study of the properties of mitochondrial DNA, has been suggested to identify molecular ‘fingerprints’ in MDC research (Messerlian *et al.* 2017). Application of mitochondriomics along with other omics technologies (e.g. genomics, transcriptomics and epigenomics), and integration with more classical approaches will certainly strengthen our knowledge of MDC exposome. Nevertheless, we believe it is still too soon to tell whether all these omics-based information will allow us to know if interactions between exposome and genomics will predict a T2D phenotype.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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References

- Agarwal S, Tiwari SK, Seth B, Yadav A, Singh A, Mudawal A, Chauhan LKS, Gupta SK, Choubey V, Tripathi A, *et al.* 2015 Activation of autophagic flux against xenoestrogen bisphenol-A-induced hippocampal neurodegeneration via AMP kinase (AMPK)/mammalian target of rapamycin (mTOR) pathways. *Journal of Biological Chemistry* **290** 21163–21184. (<https://doi.org/10.1074/jbc.M115.648998>)
- Agarwal S, Yadav A, Tiwari SK, Seth B, Chauhan LKS, Khare P, Ray RS & Chaturvedi RK 2016 Dynamin-related protein 1 inhibition mitigates bisphenol A-mediated alterations in mitochondrial dynamics and neural stem cell proliferation and differentiation. *Journal of Biological Chemistry* **291** 15923–15939. (<https://doi.org/10.1074/jbc.M115.709493>)
- Allagnat F, Cunha D, Moore F, Vanderwinden JM, Eizirik DL & Cardozo AK 2011 Mcl-1 downregulation by pro-inflammatory cytokines and palmitate is an early event contributing to B-cell apoptosis. *Cell Death and Differentiation* **18** 328–337. (<https://doi.org/10.1038/cdd.2010.105>)
- Alonso-Magdalena P, Morimoto S, Ripoll C, Fuentes E & Nadal A 2006 The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. *Environmental Health Perspectives* **114** 106–112. (<https://doi.org/10.1289/ehp.8451>)

- Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I & Nadal A 2010 Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environmental Health Perspectives* **118** 1243–1250. (<https://doi.org/10.1289/ehp.1001993>)
- Alonso-Magdalena P, Quesada I & Nadal A 2011 Endocrine disruptors in the etiology of type 2 diabetes mellitus. *Nature Reviews Endocrinology* **7** 346–35356. (<https://doi.org/10.1038/nrendo.2011.56>)
- Alonso-Magdalena P, Garcia-Arevalo M, Quesada I & Nadal A 2015 Bisphenol-A treatment during pregnancy in mice: a new window of susceptibility for the development of diabetes in mothers later in life. *Endocrinology* **156** 1659–1670. (<https://doi.org/10.1210/en.2014-1952>)
- Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, Lin CT, Price JW III, Kang L, Rabinovitch PS, Szeto HH, et al. 2009 Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *Journal of Clinical Investigation* **119** 573–581. (<https://doi.org/10.1172/JCI37048>)
- Andersson U & Scarpulla RC 2001 PGC-1-related coactivator, a novel, serum-inducible coactivator of nuclear respiratory factor 1-dependent transcription in mammalian cells. *Molecular and Cellular Biology* **21** 3738–3749. (<https://doi.org/10.1128/MCB.21.11.3738-3749.2001>)
- Angle BM, Do RP, Ponzi D, Stahlhut RW, Drury BE, Nagel SC, Welshons W V, Besch-Williford CL, Palanza P, Parmigiani S, et al. 2013 Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol A (BPA): evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation. *Reproductive Toxicology* **42** 256–268. (<https://doi.org/10.1016/j.reprotox.2013.07.017>)
- Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J & Karin M 2005 IKK- β links inflammation to obesity-induced insulin resistance. *Nature Medicine* **11** 191–198. (<https://doi.org/10.1038/nm1185>)
- Arsenijevic D, Onuma H, Pecqueur C, Raimbault S, Manning BS, Miroux B, Couplan E, Alves-Guerra MC, Gubern M, Surwit R, et al. 2000 Disruption of the uncoupling protein-2 gene in mice reveals a role in immunity and reactive oxygen species production. *Nature Genetics* **26** 435–439. (<https://doi.org/10.1038/82565>)
- Bach D, Pich S, Soriano FX, Vega N, Baumgartner B, Oriola J, Dugaard JR, Lloberas J, Camps M, Zierath JR, et al. 2003 Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism: a novel regulatory mechanism altered in obesity. *Journal of Biological Chemistry* **278** 17190–17197. (<https://doi.org/10.1074/jbc.M212754200>)
- Baker NA, Karounos M, English V, Fang J, Wei Y, Stromberg A, Sunkara M, Morris AJ, Swanson HI & Cassis LA 2013 Coplanar polychlorinated biphenyls impair glucose homeostasis in lean C57BL/6 mice and mitigate beneficial effects of weight loss on glucose homeostasis in obese mice. *Environmental Health Perspectives* **121** 105–110. (<https://doi.org/10.1289/ehp.1205421>)
- Baker NA, Shoemaker R, English V, Larian N, Sunkara M, Morris AJ, Walker M, Yiannikouris F & Cassis LA 2015 Effects of adipocyte aryl hydrocarbon receptor deficiency on PCB-induced disruption of glucose homeostasis in lean and obese mice. *Environmental Health Perspectives* **123** 944–950. (<https://doi.org/10.1289/ehp.1408594>)
- Banks AS, Kon N, Knight C, Matsumoto M, Gutiérrez-Juárez R, Rossetti L, Gu W & Accili D 2008 SirT1 gain of function increases energy efficiency and prevents diabetes in mice. *Cell Metabolism* **8** 333–341. (<https://doi.org/10.1016/j.cmet.2008.08.014>)
- Bansal A, Rashid C, Xin F, Li C, Polyak E, Duemler A, van der Meer T, Stefaniak M, Wajid S, Doliba N, et al. 2017 Sex- and dose-specific effects of maternal bisphenol A exposure on pancreatic islets of first- and second-generation adult mice offspring. *Environmental Health Perspectives* **125** 097022. (<https://doi.org/10.1289/EHP1674>)
- Barrès R, Osler ME, Yan J, Rune A, Fritz T, Caidahl K, Krook A & Zierath JR 2009 Non-CpG methylation of the PGC-1 α promoter through DNMT3B controls mitochondrial density. *Cell Metabolism* **10** 189–198. (<https://doi.org/10.1016/j.cmet.2009.07.011>)
- Barrès R, Kirchner H, Rasmussen M, Yan J, Kantor FR, Krook A, Näslund E & Zierath JR 2013 Weight loss after gastric bypass surgery in human obesity remodels promoter methylation. *Cell Reports* **3** 1020–1027. (<https://doi.org/10.1016/j.celrep.2013.03.018>)
- Batista TM, Alonso-Magdalena P, Vieira E, Amaral MEC, Cederroth CR, Nef S, Quesada I, Carneiro EM & Nadal A 2012 Short-term treatment with bisphenol-A leads to metabolic abnormalities in adult male mice. *PLoS ONE* **7** e33814. (<https://doi.org/10.1371/journal.pone.0033814>)
- Bereiter-Hahn J 1990 Behavior of mitochondria in the living cell. *International Review of Cytology* **122** 1–63. ([https://doi.org/10.1016/S0074-7696\(08\)61205-X](https://doi.org/10.1016/S0074-7696(08)61205-X))
- Bertuloso BD, Podratz PL, Merlo E, de Araújo JFP, Lima LCF, de Miguel EC, de Souza LN, Gava AL, de Oliveira M, Miranda-Alves L, et al. 2015 Tributyltin chloride leads to adiposity and impairs metabolic functions in the rat liver and pancreas. *Toxicology Letters* **235** 45–59. (<https://doi.org/10.1016/j.toxlet.2015.03.009>)
- Beydoun HA, Khanal S, Zonderman AB & Beydoun MA 2014 Sex differences in the association of urinary bisphenol-A concentration with selected indices of glucose homeostasis among U.S. adults. *Annals of Epidemiology* **24** 90–97. (<https://doi.org/10.1016/j.annepidem.2013.07.014>)
- Biswas G, Srinivasan S, Anandatheerthavarada HK & Avadhani NG 2008 Dioxin-mediated tumor progression through activation of mitochondria-to-nucleus stress signaling. *PNAS* **105** 186–191. (<https://doi.org/10.1073/pnas.0706183104>)
- Bogacka I, Xie H, Bray GA & Smith SR 2005 Pioglitazone induces mitochondrial biogenesis in human subcutaneous adipose tissue in vivo. *Diabetes* **54** 1392–1399. (<https://doi.org/10.2337/diabetes.54.5.1392>)
- Boutant M, Kulkarni SS, Joffraud M, Ratajczak J, Valera-Alberni M, Combe R, Zorzano A & Cantó C 2017 Mfn2 is critical for brown adipose tissue thermogenic function. *EMBO Journal* **36** 1543–1558. (<https://doi.org/10.15252/embj.201694914>)
- Brand MD 2016 Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signaling. *Free Radical Biology and Medicine* **100** 14–31. (<https://doi.org/10.1016/j.freeradbiomed.2016.04.001>)
- Braun JM 2016 Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nature Reviews Endocrinology* **13** 161–173. (<https://doi.org/10.1038/nrendo.2016.186>)
- Burté F, Carelli V, Chinnery PF & Yu-Wai-Man P 2015 Disturbed mitochondrial dynamics and neurodegenerative disorders. *Nature Reviews Neurology* **11** 11–24. (<https://doi.org/10.1038/nrneurol.2014.228>)
- Cabaton NJ, Canlet C, Wadia PR, Tremblay-Franco M, Gautier R, Molina J, Sonnenschein C, Cravedi JP, Rubin BS, Soto AM, et al. 2013 Effects of low doses of bisphenol A on the metabolome of perinatally exposed CD-1 mice. *Environmental Health Perspectives* **121** 586–593. (<https://doi.org/10.1289/ehp.1205588>)
- Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J & Shoelson SE 2005 Local and systemic insulin resistance resulting from hepatic activation of IKK- β and NF- κ B. *Nature Medicine* **11** 183–190. (<https://doi.org/10.1038/nm1166>)
- Carchia E, Porreca I, Almeida PJ, D'Angelo F, Cuomo D, Ceccarelli M, Felice M De, Mallardo M & Ambrosino C 2015 Evaluation of low doses BPA-induced perturbation of glycemia by toxicogenomics points to a primary role of pancreatic islets and to the mechanism of toxicity. *Cell Death and Disease* **6** e1959. (<https://doi.org/10.1038/cddis.2015.319>)
- Cardenas A, Gold DR, Hauser R, Kleinman KP, Hivert MF, Calafat AM, Ye X, Webster TF, Horton ES & Oken E 2017 Plasma concentrations of per- and polyfluoroalkyl substances at baseline and associations with glycemic indicators and diabetes incidence among high-risk

- adults in the diabetes prevention program trial. *Environmental Health Perspectives* **125** 107001. (<https://doi.org/10.1289/EHP1612>)
- Caton PW, Richardson SJ, Kieswich J, Bugliani M, Holland ML, Marchetti P, Morgan NG, Yaqoob MM, Holness MJ & Sugden MC 2013 Sirtuin 3 regulates mouse pancreatic beta cell function and is suppressed in pancreatic islets isolated from human type 2 diabetic patients. *Diabetologia* **56** 1068–1077. (<https://doi.org/10.1007/s00125-013-2851-y>)
- CDC 2009 Fourth national report on human exposure to environmental chemicals. Atlanta, GA, USA: Department of Health and Human Services; Centers for Disease Control and Prevention. (available at: <https://www.cdc.gov/exposurereport/pdf/fourthreport.pdf>)
- CDC 2018 Fourth national report on human exposure to environmental chemicals. Updated Tables, March 2018, Volume One. Atlanta, GA, USA: Department of Health and Human Services; Centers for Disease Control and Prevention. (available at: https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf)
- Chan CB, MacDonald PE, Saleh MC, Johns DC, Marbàn E & Wheeler MB 1999 Overexpression of uncoupling protein 2 inhibits glucose-stimulated insulin secretion from rat islets. *Diabetes* **48** 1482–1486. (<https://doi.org/10.2337/diabetes.48.7.1482>)
- Chan CB, De Leo D, Joseph JW, McQuaid TS, Ha XF, Xu F, Tushima RG, Pennefather PS, Salapatek AMF & Wheeler MB 2001 Increased uncoupling protein-2 levels in beta-cells are associated with impaired glucose-stimulated insulin secretion: mechanism of action. *Diabetes* **50** 1302–1310. (<https://doi.org/10.2337/diabetes.50.6.1302>)
- Chan CB, Saleh MC, Koshkin V & Wheeler MB 2004 Uncoupling protein 2 and islet function. *Diabetes* **53** S136–S142. (<https://doi.org/10.2337/diabetes.53.2007.S136>)
- Chang K-C, Hsu C-C, Liu S-H, Su C-C, Yen C-C, Lee M-J, Chen K-L, Ho T-J, Hung D-Z & Wu C-C 2013 Cadmium induces apoptosis in pancreatic β -cells through a mitochondria-dependent pathway: the role of oxidative stress-mediated c-Jun N-terminal kinase activation. *PLoS One* **8** e54374. (<https://doi.org/10.1371/journal.pone.0054374>)
- Chen SC, Liao TL, Wei YH, Tzeng CR & Kao SH 2010 Endocrine disruptor, dioxin (TCDD)-induced mitochondrial dysfunction and apoptosis in human trophoblast-like JAR cells. *Molecular Human Reproduction* **16** 361–372. (<https://doi.org/10.1093/molehr/gaq004>)
- Choi SY, Kim JY, Kim HW, Cho B, Cho HM, Oppenheim RW, Kim H, Rhyu JJ & Sun W 2013 Drp1-mediated mitochondrial dynamics and survival of developing chick motoneurons during the period of normal programmed cell death. *FASEB Journal* **27** 51–62. (<https://doi.org/10.1096/fj.12-211920>)
- Choo HJ, Kim JH, Kwon OB, Lee CS, Mun JY, Han SS, Yoon YS, Yoon G, Choi KM & Ko YG 2006 Mitochondria are impaired in the adipocytes of type 2 diabetic mice. *Diabetologia* **49** 784–791. (<https://doi.org/10.1007/s00125-006-0170-2>)
- Chow J, Rahman J, Achermann JC, Dattani MT & Rahman S 2017 Mitochondrial disease and endocrine dysfunction. *Nature Reviews Endocrinology* **13** 92–104. (<https://doi.org/10.1038/nrendo.2016.151>)
- Circu ML & Aw TY 2010 Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radical Biology and Medicine* **48** 749–762. (<https://doi.org/10.1016/j.freeradbiomed.2009.12.022>)
- Cnop M, Welsh N, Jonas J-C, Jöns A, Lenzen S & Eizirik DL 2005 Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: many differences, few similarities. *Diabetes* **54** (Supplement 2) S97–S107. (https://doi.org/10.2337/diabetes.54.suppl_2.s97)
- Cunha DA, Cito M, Carlsson PO, Vanderwinden JM, Molkentin JD, Bugliani M, Marchetti P, Eizirik DL & Cnop M 2016 Thrombospondin 1 protects pancreatic β -cells from lipotoxicity via the PERK-NRF2 pathway. *Cell Death and Differentiation* **23** 1995–2006. (<https://doi.org/10.1038/cdd.2016.89>)
- Dahlman I, Forsgren M, Sjogren A, Nordstrom EA, Kaaman M, Naslund E, Attersand A & Arner P 2006 Downregulation of electron transport chain genes in visceral adipose tissue in type 2 diabetes independent of obesity and possibly involving tumor necrosis factor- α . *Diabetes* **55** 1792–1799. (<https://doi.org/10.2337/db05-1421>)
- Dai H, Deng Y, Zhang J, Han H, Zhao M, Li Y, Zhang C, Tian J, Bing G & Zhao L 2015 PINK1/Parkin-mediated mitophagy alleviates chlorpyrifos-induced apoptosis in SH-SY5Y cells. *Toxicology* **334** 72–80. (<https://doi.org/10.1016/j.tox.2015.06.003>)
- Dales RE, Kauri LM & Cakmak S 2018 The associations between phthalate exposure and insulin resistance, beta-cell function and blood glucose control in a population-based sample. *Science of the Total Environment* **612** 1287–1292. (<https://doi.org/10.1016/j.scitotenv.2017.09.009>)
- Darling NJ & Cook SJ 2014 The role of MAPK signalling pathways in the response to endoplasmic reticulum stress. *Biochimica et Biophysica Acta: Molecular Cell Research* **1843** 2150–2163. (<https://doi.org/10.1016/j.bbamcr.2014.01.009>)
- Debost-Legrand A, Warembourg C, Massart C, Chevrier C, Bonvallet N, Monfort C, Rouget F, Bonnet F & Cordier S 2016 Prenatal exposure to persistent organic pollutants and organophosphate pesticides, and markers of glucose metabolism at birth. *Environmental Research* **146** 207–217. (<https://doi.org/10.1016/j.envres.2016.01.005>)
- Denton K, Mou Y, Xu CC, Shah D, Chang J, Blackstone C & Li XJ 2018 Impaired mitochondrial dynamics underlie axonal defects in hereditary spastic paraplegias. *Human Molecular Genetics* **27** 2517–2530. (<https://doi.org/10.1093/hmg/ddy156>)
- Di Meo S, Iossa S & Venditti P 2017 Skeletal muscle insulin resistance: role of mitochondria and other ROS sources. *Journal of Endocrinology* **233** R15–R42. (<https://doi.org/10.1530/JOE-16-0598>)
- Diaz-Villasenor A, Burns AL, Hiriart M, Cebrian ME & Ostrosky-Wegman P 2007 Arsenic-induced alteration in the expression of genes related to type 2 diabetes mellitus. *Toxicology and Applied Pharmacology* **225** 123–133. (<https://doi.org/10.1016/j.taap.2007.08.019>)
- Divya SP, Pratheeshkumar P, Son YO, Roy RV, Hitron JA, Kim D, Dai J, Wang L, Asha P, Huang B, et al. 2015 Adipocytes and myotubes via oxidative stress-regulated mitochondrial sirt3-FOXO3a signaling pathway. *Toxicological Sciences* **146** 290–300. (<https://doi.org/10.1093/toxsci/kfv089>)
- Domazet SL, Grontved A, Timmermann AG, Nielsen F & Jensen TK 2016 Longitudinal associations of exposure to perfluoroalkylated substances in childhood and adolescence and indicators of adiposity and glucose metabolism 6 and 12 years later: the European youth heart study. *Diabetes Care* **39** 1745–1751. (<https://doi.org/10.2337/dc16-0269>)
- Edwards JR & Prozialeck WC 2009 Cadmium, diabetes and chronic kidney disease. *Toxicology and Applied Pharmacology* **238** 289–293.
- Evans JL, Goldfine ID, Maddux BA & Grodsky GM 2003 Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction? *Diabetes* **52** 1–8. (<https://doi.org/10.2337/diabetes.52.1.1>)
- Fex M, Nicholas LM, Vishnu N, Medina A, Sharoyko VV, Nicholls DG, Spégl P MH 2018 The pathogenetic role of β -cell mitochondria in type 2 diabetes. *Journal of Endocrinology* **236** R145–R159. (<https://doi.org/10.1530/JOE-17-0367>)
- Fosslien E 2001 Mitochondrial medicine – molecular pathology of defective oxidative phosphorylation. *Annals of Clinical Laboratory Science* **31** 25–67.
- Frank S, Gaume B, Bergmann-Leitner ES, Leitner WW, Robert EG, Catez F, Smith CL & Youle RJ 2001 The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. *Developmental Cell* **1** 515–525. ([https://doi.org/10.1016/S1534-5807\(01\)00055-7](https://doi.org/10.1016/S1534-5807(01)00055-7))
- Fulda S, Gorman AM, Hori O & Samali A 2010 Cellular stress responses: cell survival and cell death. *International Journal of Cell Biology* **2010** 214074. (<https://doi.org/10.1155/2010/214074>)
- García-Arevalo M, Alonso-Magdalena P, Servitja JM, Boronat-Belda T, Merino B, Villar-Pazos S, Medina-Gomez G, Novials A, Quesada I & Nadal A 2016 Maternal exposure to bisphenol-A during pregnancy increases pancreatic beta-cell growth during early life in male mice

- offspring. *Endocrinology* **157** 4158–4171. (<https://doi.org/10.1210/en.2016-1390>)
- García-Arevalo M, Alonso-Magdalena P, Rebelo Dos Santos J, Quesada I, Carneiro EM, Nadal A, García-Arevalo M, Alonso-Magdalena P, Rebelo Dos Santos J, Quesada I, et al. 2014 Exposure to bisphenol-A during pregnancy partially mimics the effects of a high-fat diet altering glucose homeostasis and gene expression in adult male mice. *PLoS ONE* **9** e100214. (<https://doi.org/10.1371/journal.pone.0100214>)
- Gleyzer N, Vercauteren K & Scarpulla RC 2005 Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Molecular and Cellular Biology* **25** 1354–1366. (<https://doi.org/10.1128/MCB.25.4.1354-1366.2005>)
- Gogvadze V, Stridh H, Orenius S & Cotgreave I 2002 Tributyltin causes cytochrome c release from isolated mitochondria by two discrete mechanisms. *Biochemical and Biophysical Research Communications* **292** 904–908. (<https://doi.org/10.1006/bbrc.2002.6679>)
- Gonzalez-Franquesa A & Patti M-E 2017 Insulin resistance and mitochondrial dysfunction. In *Mitochondrial Dynamics in Cardiovascular Medicine*, pp 465–520. Berlin, Germany: Springer. (https://doi.org/10.1007/978-3-319-55330-6_25)
- Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J & Zoeller RT 2015 EDC-2: the Endocrine Society's Second Scientific Statement on endocrine-disrupting chemicals. *Endocrine Reviews* **36** E1–E150. (<https://doi.org/10.1210/er.2015-1010>)
- Gray SL, Shaw AC, Gagne AX & Chan HM 2013 Chronic exposure to PCBs (Aroclor 1254) exacerbates obesity-induced insulin resistance and hyperinsulinemia in mice. *Journal of Toxicology and Environmental Health A* **76** 701–715. (<https://doi.org/10.1080/15287394.2013.796503>)
- Gurzov EN & Eizirik DL 2011 Bcl-2 proteins in diabetes: mitochondrial pathways of β -cell death and dysfunction. *Trends in Cell Biology* **21** 424–431. (<https://doi.org/10.1016/j.tcb.2011.03.001>)
- Gurzov EN, Ortis F, Cunha DA, Gosset G, Li M, Cardozo AK & Eizirik DL 2009 Signaling by IL-1 β +IFN- γ and ER stress converge on DP5/Hrk activation: a novel mechanism for pancreatic beta-cell apoptosis. *Cell Death and Differentiation* **16** 1539–1550. (<https://doi.org/10.1038/cdd.2009.99>)
- Han R, Hu M, Zhong Q, Wan C, Liu L, Li F, Zhang F & Ding W 2018 Perfluorooctane sulphonate induces oxidative hepatic damage via mitochondria-dependent and NF-KB/TNF- α -mediated pathway. *Chemosphere* **191** 1056–1064. (<https://doi.org/10.1016/j.chemosphere.2017.08.070>)
- He X, Liu Y, Xu B, Gu L & Tang W 2017 PFOA is associated with diabetes and metabolic alteration in US men: National Health and Nutrition Examination Survey 2003–2012. *Science of the Total Environment* **625** 566–574. (<https://doi.org/10.1016/j.scitotenv.2017.12.186>)
- Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, et al. 2017 Metabolism disrupting chemicals and metabolic disorders. *Reproductive Toxicology* **68** 3–33. (<https://doi.org/10.1016/j.reprotox.2016.10.001>)
- Hirschey MD, Shimazu T, Goetzman E, Jing E, Schwer B, Lombard DB, Grueter CA, Harris C, Biddinger S, Ilkayeva OR, et al. 2010 SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. *Nature* **464** 121–125. (<https://doi.org/10.1038/nature08778>)
- Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stančáková A, Goetzman E, Lam MM, Schwer B, et al. 2011 SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. *Molecular Cell* **44** 177–190. (<https://doi.org/10.1016/j.molcel.2011.07.019>)
- Hotamisligil GS 1999 Mechanisms of TNF- α -induced insulin resistance. *Experimental and Clinical Endocrinology and Diabetes* **107** 119–125. (<https://doi.org/10.1055/s-0029-1212086>)
- Hotamisligil GS, Shargill NS & Spiegelman BM 1993 Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* **259** 87–91. (<https://doi.org/10.1126/science.7678183>)
- Houstis N, Rosen ED & Lander ES 2006 Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* **440** 944–948. (<https://doi.org/10.1038/nature04634>)
- Huang T, Saxena AR, Isganaitis E & James-Todd T 2014 Gender and racial/ethnic differences in the associations of urinary phthalate metabolites with markers of diabetes risk: National Health and Nutrition Examination Survey 2001–2008. *Environmental Health* **13** 6. (<https://doi.org/10.1186/1476-069X-13-6>)
- Huang CF, Yang CY, Chan DC, Wang CC, Huang KH, Wu CC, Tsai KS, Yang RS & Liu SH 2015 Arsenic exposure and glucose intolerance/insulin resistance in estrogen-deficient female mice. *Environmental Health Perspectives* **123** 1138–1144. (<https://doi.org/10.1289/ehp.1408663>)
- Huang Q, Zhan L, Cao H, Li J, Lyu Y, Guo X, Zhang J, Ji L, Ren T, An J, et al. 2016 Increased mitochondrial fission promotes autophagy and hepatocellular carcinoma cell survival through the ROS-modulated coordinated regulation of the NF κ B and TP53 pathways. *Autophagy* **12** 999–1014. (<https://doi.org/10.1080/15548627.2016.1166318>)
- Huang CF, Yang CY, Tsai JR, Wu CT, Liu SH & Lan KC 2018 Low-dose tributyltin exposure induces an oxidative stress-triggered JNK-related pancreatic β -cell apoptosis and a reversible hypoinsulinemic hyperglycemia in mice. *Scientific Reports* **8** 5734. (<https://doi.org/10.1038/s41598-018-24076-w>)
- Huc L, Lemarié A, Guéraud F & Hélieux-Toussaint C 2012 Low concentrations of bisphenol A induce lipid accumulation mediated by the production of reactive oxygen species in the mitochondria of HepG2 cells. *Toxicology In Vitro* **26** 709–717. (<https://doi.org/10.1016/j.tiv.2012.03.017>)
- Hurtad C, Gelly C, Chen Z, Lévi-Meyrueis C & Bouillaud F 2007 Glutamine stimulates translation of uncoupling protein 2 mRNA. *Cellular and Molecular Life Sciences* **64** 1853–1860. (<https://doi.org/10.1007/s00018-007-7039-5>)
- Ithakissios DS, Ghafghazi T, Mennear JH & Kessler WV. 1975 Effect of multiple doses of cadmium on glucose metabolism and insulin secretion in the rat. *Toxicology and Applied Pharmacology* **31** 143–149. ([https://doi.org/10.1016/0041-008X\(75\)90062-9](https://doi.org/10.1016/0041-008X(75)90062-9))
- Jacob S, Machann J, Rett K, Brechtel K, Volk A, Renn W, Maerker E, Matthaei S, Schick F, Claussen CD, et al. 1999 Association of increased intramyocellular lipid content with insulin resistance in lean nondiabetic offspring of type 2 diabetic subjects. *Diabetes* **48** 1113–1119. (<https://doi.org/10.2337/diabetes.48.5.1113>)
- James-Todd T, Stahlhut R, Meeker JD, Powell SG, Hauser R, Huang T & Rich-Edwards J 2012 Urinary phthalate metabolite concentrations and diabetes among women in the National Health and Nutrition Examination Survey (NHANES) 2001–2008. *Environmental Health Perspectives* **120** 1307–1313. (<https://doi.org/10.1289/ehp.1104717>)
- Jastroch M, Divakaruni AS, Mookerjee S, Treberg JR & Brand MD 2010 Mitochondrial proton and electron leaks. *Essays in Biochemistry* **47** 53–67. (<https://doi.org/10.1042/bse0470053>)
- Jayashree S, Indumathi D, Akilavalli N, Sathish S, Selvaraj J & Balasubramanian K 2013 Effect of Bisphenol-A on insulin signal transduction and glucose oxidation in liver of adult male albino rat. *Environmental Toxicology and Pharmacology* **35** 300–310. (<https://doi.org/10.1016/j.etap.2012.12.016>)
- Ježek J, Cooper KF & Strich R 2018 Reactive oxygen species and mitochondrial dynamics: the yin and yang of mitochondrial dysfunction and cancer progression. *Antioxidants* **7** E13. (<https://doi.org/10.3390/antiox7010013>)
- Jheng H-F, Tsai P-J, Guo S-M, Kuo L-H, Chang C-S, Su I-J, Chang C-R & Tsai Y-S 2012 Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. *Molecular and Cellular Biology* **32** 309–319. (<https://doi.org/10.1128/MCB.05603-11>)

- Jiang Y, Xia W, Zhu Y, Li X, Wang D, Liu J, Chang H, Li G, Xu B, Chen X, et al. 2014a Mitochondrial dysfunction in early life resulted from perinatal bisphenol A exposure contributes to hepatic steatosis in rat offspring. *Toxicology Letters* **228** 85–92. (<https://doi.org/10.1016/j.toxlet.2014.04.013>)
- Jiang Y, Liu J, Li Y, Chang H, Li G, Xu B, Chen X, Li W, Xia W & Xu S 2014b Prenatal exposure to bisphenol A at the reference dose impairs mitochondria in the heart of neonatal rats. *Journal of Applied Toxicology* **34** 1012–1022. (<https://doi.org/10.1002/jat.2924>)
- Jiang Y, Xia W, Yang J, Zhu Y, Chang H, Liu J, Huo W, Xu B, Chen X, Li Y, et al. 2015 BPA-induced DNA hypermethylation of the master mitochondrial gene PGC-1 α contributes to cardiomyopathy in male rats. *Toxicology* **329** 21–31. (<https://doi.org/10.1016/j.tox.2015.01.001>)
- Jing E, Emanuelli B, Hirschey MD, Boucher J, Lee KY, Lombard D, Verdin EM & Kahn CR 2011 Sirtuin-3 (Sirt3) regulates skeletal muscle metabolism and insulin signaling via altered mitochondrial oxidation and reactive oxygen species production. *PNAS* **108** 14608–14613. (<https://doi.org/10.1073/pnas.1111308108>)
- Kanter M, Yoruk M, Koc A, Meral I & Karaca T 2003 Effects of cadmium exposure on morphological aspects of pancreas, weights of fetus and placenta in streptozotocin-induced diabetic pregnant rats. *Biological Trace Element Research* **93** 189–200. (<https://doi.org/10.1385/BTER.93.1-3.189>)
- Kaufman BA, Li C & Soleimanpour SA 2015 Mitochondrial regulation of β -cell function: maintaining the momentum for insulin release. *Molecular Aspects of Medicine* **42** 91–104. (<https://doi.org/10.1016/j.mam.2015.01.004>)
- Kelley DE, He J, Menshikova EV & Ritov VB 2002 Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes* **51** 2944–2950. (<https://doi.org/10.2337/diabetes.51.10.2944>)
- Kim BJ, Ryu SW & Song BJ 2006 JNK- and p38 kinase-mediated phosphorylation of Bax leads to its activation and mitochondrial translocation and to apoptosis of human hepatoma HepG2 cells. *Journal of Biological Chemistry* **281** 21256–21265. (<https://doi.org/10.1074/jbc.M510644200>)
- Kim JH, Park HY, Bae S, Lim YH & Hong YC 2013 Diethylhexyl phthalates is associated with insulin resistance via oxidative stress in the elderly: a panel study. *PLoS ONE* **8** e71392. (<https://doi.org/10.1371/journal.pone.0071392>)
- Kim HY, Kwon WY, Kim YA, Oh YJ, Yoo SH, Lee MH, Bae JY, Kim JM & Yoo YH 2016 Polychlorinated biphenyls exposure-induced insulin resistance is mediated by lipid droplet enlargement through Fsp27. *Archives of Toxicology* **91** 2353–2363. (<https://doi.org/10.1007/s00204-016-1889-2>)
- Kubli DA & Gustafsson ÅB 2012 Mitochondria and mitophagy: the yin and yang of cell death control. *Circulation Research* **111** 1208–1221. (<https://doi.org/10.1161/CIRCRESAHA.112.265819>)
- Kusminski CM & Scherer PE 2012 Mitochondrial dysfunction in white adipose tissue. *Trends in Endocrinology and Metabolism* **23** 435–443. (<https://doi.org/10.1016/j.tem.2012.06.004>)
- La Merrill M, Karey E, Moshier E, Lindtner C, La Frano MR, Newman JW & Buettner C 2014 Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring. *PLoS ONE* **9** e103337. (<https://doi.org/10.1371/journal.pone.0103337>)
- Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB & Melzer D 2008 Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA* **300** 1303–1310. (<https://doi.org/10.1001/jama.300.11.1303>)
- Lee DH, Steffes MW, Sjodin A, Jones RS, Needham LL & Jacobs DR Jr 2010 Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. *Environmental Health Perspectives* **118** 1235–1242. (<https://doi.org/10.1289/ehp.0901480>)
- Lee DH, Lind PM, Jacobs DR Jr, Salihovic S, van Bavel B & Lind L 2011 Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study. *Diabetes Care* **34** 1778–1784. (<https://doi.org/10.2337/dc10-2116>)
- Lemasters JJ 2005 Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging. *Rejuvenation Research* **8** 3–5. (<https://doi.org/10.1089/rej.2005.8.3>)
- Li G, Chang H, Xia W, Mao Z, Li Y & Xu S 2014 F0 maternal BPA exposure induced glucose intolerance of F2 generation through DNA methylation change in Gck. *Toxicology Letters* **228** 192–199. (<https://doi.org/10.1016/j.toxlet.2014.04.012>)
- Lim S, Ahn SY, Song IC, Chung MH, Jang HC, Park KS, Lee KU, Pak YK & Lee HK 2009 Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance. *PLoS ONE* **4** e5186. (<https://doi.org/10.1371/journal.pone.0005186>)
- Lin J, Puigserver P, Donovan J, Tarr P & Spiegelman BM 2002 Peroxisome proliferator-activated receptor gamma coactivator 1beta (PGC-1beta), a novel PGC-1-related transcription coactivator associated with host cell factor. *Journal of Biological Chemistry* **277** 1645–1648. (<https://doi.org/10.1074/jbc.C100631200>)
- Lin Y, Wei J, Li Y, Chen J, Zhou Z, Song L, Wei Z, Lv Z, Chen X, Xia W, et al. 2011 Developmental exposure to di(2-ethylhexyl) phthalate impairs endocrine pancreas and leads to long-term adverse effects on glucose homeostasis in the rat. *American Journal of Physiology: Endocrinology and Metabolism* **301** E527–E538. (<https://doi.org/10.1152/ajpendo.00233.2011>)
- Lin Y, Sun X, Qiu L, Wei J, Huang Q, Fang C, Ye T, Kang M, Shen H & Dong S 2013 Exposure to bisphenol A induces dysfunction of insulin secretion and apoptosis through the damage of mitochondria in rat insulinoma (INS-1) cells. *Cell Death and Disease* **4** e460. (<https://doi.org/10.1038/cddis.2012.206>)
- Lind PM, Zethelius B & Lind L 2012 Circulating levels of phthalate metabolites are associated with prevalent diabetes in the elderly. *Diabetes Care* **35** 1519–1524. (<https://doi.org/10.2337/dc11-2396>)
- Lind L, Zethelius B, Salihovic S, van Bavel B & Lind PM 2014 Circulating levels of perfluoroalkyl substances and prevalent diabetes in the elderly. *Diabetologia* **57** 473–479. (<https://doi.org/10.1007/s00125-013-3126-3>)
- Lind PM & Lind L 2018 Endocrine-disrupting chemicals and risk of diabetes: an evidence-based review. *Diabetologia* **61** 1495–1502. (<https://doi.org/10.1007/s00125-018-4621-3>)
- Liu S, Guo X, Wu B, Yu H, Zhang X & Li M 2014 Arsenic induces diabetic effects through beta-cell dysfunction and increased gluconeogenesis in mice. *Scientific Reports* **4** 6894
- Llobet L, Toivonen JM, Montoya J, Ruiz-Pesini E & López-Gallardo E 2015 Xenobiotics that affect oxidative phosphorylation alter differentiation of human adipose-derived stem cells at concentrations that are found in human blood. *Disease Models and Mechanisms* **8** 1441–1455. (<https://doi.org/10.1242/dmm.021774>)
- Loiola RA, Dos Anjos FM, Shimada AL, Cruz WS, Drewes CC, Rodrigues SF, Cardozo KH, Carvalho VM, Pinto E & Farsky SH 2016 Long-term in vivo polychlorinated biphenyl 126 exposure induces oxidative stress and alters proteomic profile on islets of Langerhans. *Scientific Reports* **6** 27882. (<https://doi.org/10.1038/srep06894>)
- Lu TH, Su CC, Chen YW, Yang CY, Wu CC, Hung DZ, Chen CH, Cheng PW, Liu SH & Huang CF 2011 Arsenic induces pancreatic β -cell apoptosis via the oxidative stress-regulated mitochondria-dependent and endoplasmic reticulum stress-triggered signaling pathways. *Toxicology Letters* **201** 15–26. (<https://doi.org/10.1016/j.toxlet.2010.11.019>)
- MacKay H, Patterson R, Khazall R, Patel S, Tsirlin D & Abizaid A 2013 Organizational effects of perinatal exposure to bisphenol-a and diethylstilbestrol on arcuate nucleus circuitry controlling food intake and energy expenditure in male and female CD-1 mice. *Endocrinology* **154** 1465–1475. (<https://doi.org/10.1210/en.2012-2044>)
- MacKay H, Patterson ZR & Abizaid A 2017 Perinatal exposure to low-dose bisphenol-a disrupts the structural and functional development of the

- hypothalamic feeding circuitry. *Endocrinology* **158** 768–777. (<https://doi.org/10.1210/en.2016-1718>)
- Mailloux RJ & Harper M-E 2011 Uncoupling proteins and the control of mitochondrial reactive oxygen species production. *Free Radical Biology and Medicine* **51** 1106–1115. (<https://doi.org/10.1016/j.freeradbiomed.2011.06.022>)
- Marroquí L, Santin I, Dos Santos RS, Marselli L, Marchetti P & Eizirik DL 2014 BACH2, a candidate risk gene for type 1 diabetes, regulates apoptosis in pancreatic β -cells via JNK1 modulation and crosstalk with the candidate gene PTPN2. *Diabetes* **63** 2516–2527. (<https://doi.org/10.2337/db13-1443>)
- Mashayekhi V, Tehrani KHME, Hashemzaei M, Tabrizian K, Shahraki J & Hosseini M-J 2015 Mechanistic approach for the toxic effects of perfluorooctanoic acid on isolated rat liver and brain mitochondria. *Human and Experimental Toxicology* **34** 985–996. (<https://doi.org/10.1177/0960327114565492>)
- Matilla-Santander N, Valvi D, Lopez-Espinosa MJ, Manzano-Salgado CB, Ballester F, Ibarluzea J, Santa-Marina L, Schettgen T, Guxens M, Sunyer J, et al. 2017 Exposure to perfluoroalkyl substances and metabolic outcomes in pregnant women: evidence from the Spanish INMA Birth Cohorts. *Environmental Health Perspectives* **125** 117004. (<https://doi.org/10.1289/EHP1062>)
- McCubrey JA, LaHair MM & Franklin RA 2006 Reactive oxygen species-induced activation of the MAP kinase signaling pathways. *Antioxidants and Redox Signaling* **8** 1775–1789. (<https://doi.org/10.1089/ars.2006.8.1775>)
- McCullough KD, Martindale JL, Klotz L-O, Aw T-Y & Holbrook NJ 2001 Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state. *Molecular and Cellular Biology* **21** 1249–1259. (<https://doi.org/10.1128/MCB.21.4.1249-1259.2001>)
- Melnick RL & Schiller CM 1982 Mitochondrial toxicity of phthalate esters. *Environmental Health Perspectives* **45** 51–56. (<https://doi.org/10.1289/ehp.824551>)
- Melzer D, Rice NE, Lewis C, Henley WE & Galloway TS 2010 Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. *PLoS ONE* **5** e8673. (<https://doi.org/10.1371/journal.pone.0008673>)
- Men X, Wang H, Li M, Cai H, Xu S, Zhang W, Xu Y, Ye L, Yang W, Wollheim CB, et al. 2009 Dynamin-related protein 1 mediates high glucose induced pancreatic beta cell apoptosis. *International Journal of Biochemistry and Cell Biology* **41** 879–890. (<https://doi.org/10.1016/j.biocel.2008.08.031>)
- Menale C, Grandone A, Nicolucci C, Cirillo G, Crispi S, Di Sessa A, Marzuillo P, Rossi S, Mita DG, Perrone L, et al. 2017 Bisphenol A is associated with insulin resistance and modulates adiponectin and resistin gene expression in obese children. *Pediatric Obesity* **12** 380–387. (<https://doi.org/10.1111/ijpo.12154>)
- Merali Z & Singhal RL 1980 Diabetogenic effects of chronic oral cadmium administration to neonatal rats. *British Journal of Pharmacology* **69** 151–157. (<https://doi.org/10.1111/j.1476-5381.1980.tb10895.x>)
- Messerlian C, Martinez RM, Hauser R & Baccarelli AA 2017 ‘Omics’ and endocrine-disrupting chemicals – new paths forward. *Nature Reviews Endocrinology* **13** 740–748. (<https://doi.org/10.1038/nrendo.2017.81>)
- Meyer JN, Leung MCK, Rooney JP, Sendoe A, Hengartner MO, Kisby GE & Bess AS 2013 Mitochondria as a target of environmental toxicants. *Toxicological Sciences* **134** 1–17. (<https://doi.org/10.1093/toxsci/kft102>)
- Meyer JN, Leuthner TC & Luz AL 2017 Mitochondrial fusion, fission, and mitochondrial toxicity. *Toxicology* **391** 42–53. (<https://doi.org/10.1016/j.tox.2017.07.019>)
- Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, Jin L, Boss O, Perni RB, Vu CB, et al. 2007 Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. *Nature* **450** 712–716. (<https://doi.org/10.1038/nature06261>)
- Mimoto MS, Nadal A & Sargis RM 2017 Polluted pathways: mechanisms of metabolic disruption by endocrine disrupting chemicals. *Current Environmental Health Reports* **4** 208–222. (<https://doi.org/10.1007/s40572-017-0137-0>)
- Mitchell P 1961 Coupling of phosphorylation to electron and hydrogen transfer by a chemi osmotic type of mechanism. *Nature* **191** 145–191. (<https://doi.org/10.1038/191144a0>)
- Molina AJA, Wikstrom JD, Stiles L, Las G, Mohamed H, Elorza A, Walzer G, Twig G, Katz S, Corkey BE, et al. 2009 Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. *Diabetes* **58** 2303–2315. (<https://doi.org/10.2337/db07-1781>)
- Montaigne D, Marechal X, Coisne A, Debry N, Modine T, Fayad G, Potelle C, El Arid JM, Mouton S, Sebti Y, et al. 2014 Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circulation* **130** 554–564. (<https://doi.org/10.1161/CIRCULATIONAHA.113.008476>)
- Moon MK, Kim MJ, Jung IK, Koo Y Do, Ann HY, Lee KJ, Kim SH, Yoon YC, Cho BJ, Park KS, et al. 2012 Bisphenol A impairs mitochondrial function in the liver at doses below the no observed adverse effect level. *Journal of Korean Medical Science* **27** 644–652. (<https://doi.org/10.3346/jkms.2012.27.6.644>)
- Moreno AJM & Madeira VMC 1991 Mitochondrial bioenergetics as affected by DDT. *Biochimica et Biophysica Acta: Bioenergetics* **1060** 166–174. ([https://doi.org/10.1016/S0005-2728\(09\)91004-0](https://doi.org/10.1016/S0005-2728(09)91004-0))
- Moynihan KA, Grimm AA, Plueger MM, Bernal-Mizrachi E, Ford E, Cras-Méneur C, Permutt MA & Imai SI 2005 Increased dosage of mammalian Sir2 in pancreatic β cells enhances glucose-stimulated insulin secretion in mice. *Cell Metabolism* **2** 105–117. (<https://doi.org/10.1016/j.cmet.2005.07.001>)
- Nadal A, Quesada I, Tudurí E, Nogueiras R & Alonso-Magdalena P 2017 Endocrine-disrupting chemicals and the regulation of energy balance. *Nature Reviews Endocrinology* **13** 536–546. (<https://doi.org/10.1038/nrendo.2017.51>)
- Nakagawa Y & Tayama S 2000 Metabolism and cytotoxicity of bisphenol A and other bisphenols in isolated rat hepatocytes. *Archives of Toxicology* **74** 99–105. (<https://doi.org/10.1007/s002040050659>)
- Neel BA & Sargis RM 2011 The paradox of progress: environmental disruption of metabolism and the diabetes epidemic. *Diabetes* **60** 1838–1848. (<https://doi.org/10.2337/db11-0153>)
- Nogueiras R, Habegger KM, Chaudhary N, Finan B, Banks AS, Dietrich MO, Horvath TL, Sinclair DA, Pfluger PT & Tschope MH 2012 Sirtuin 1 and Sirtuin 3: physiological modulators of metabolism. *Physiological Reviews* **92** 1479–1514. (<https://doi.org/10.1152/physrev.00022.2011>)
- Olichon A, Baricault L, Gas N, Guillou E, Valette A, Belenguer P & Lenaers G 2003 Loss of OPA1 perturbs the mitochondrial inner membrane structure and integrity, leading to cytochrome c release and apoptosis. *Journal of Biological Chemistry* **278** 7743–7746. (<https://doi.org/10.1074/jbc.C200677200>)
- Ow YLP, Green DR, Hao Z & Mak TW 2008 Cytochrome c: functions beyond respiration. *Nature Reviews Molecular Cell Biology* **9** 532–542. (<https://doi.org/10.1038/nrm2434>)
- Palikaras K & Tavernarakis N 2014 Mitochondrial homeostasis: the interplay between mitophagy and mitochondrial biogenesis. *Experimental Gerontology* **56** 182–188. (<https://doi.org/10.1016/j.exger.2014.01.021>)
- Panaretakis T, Shabalina IG, Grandér D, Shoshan MC & Depierre JW 2001 Reactive oxygen species and mitochondria mediate the induction of apoptosis in human hepatoma HepG2 cells by the rodent peroxisome proliferator and hepatocarcinogen, perfluorooctanoic acid. *Toxicology and Applied Pharmacology* **173** 56–64. (<https://doi.org/10.1006/taap.2001.9159>)
- Park JH, Ko J, Park YS, Park J, Hwang J & Koh HC 2017 Clearance of damaged mitochondria through PINK1 stabilization by JNK and ERK MAPK signaling in chlorpyrifos-treated neuroblastoma cells. *Molecular Neurobiology* **54** 1844–1857. (<https://doi.org/10.1007/s12035-016-9753-1>)

- Patti M-E & Corvera S 2010 The role of mitochondria in the pathogenesis of type 2 diabetes. *Endocrine Reviews* **31** 364–395. (<https://doi.org/10.1210/er.2009-0027>)
- Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, *et al.* 2003 Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of PGC1 and NRF1. *PNAS* **100** 8466–8471. (<https://doi.org/10.1073/pnas.1032913100>)
- Paul DS, Walton FS, Saunders RJ & Styblo M 2011 Characterization of the impaired glucose homeostasis produced in C57BL/6 mice by chronic exposure to arsenic and high-fat diet. *Environmental Health Perspectives* **119** 1104–1109. (<https://doi.org/10.1289/ehp.1003324>)
- Perreault L, McCurdy C, Kerege AA, Houck J, Faerch K & Bergman BC 2013 Bisphenol A impairs hepatic glucose sensing in C57BL/6 male mice. *PLoS One* **8** e69991. (<https://doi.org/10.1371/journal.pone.0069991>)
- Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW & Shulman GI 2003 Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* **300** 1140–1142. (<https://doi.org/10.1126/science.1082889>)
- Petersen KF, Dufour S, Befroy D, Garcia R & Shulman GI 2004 Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *New England Journal of Medicine* **350** 664–671. (<https://doi.org/10.1056/NEJMoa031314>)
- Pi H, Xu S, Zhang L, Guo P, Li Y, Xie J, Tian L, He M, Lu Y, Li M, *et al.* 2013 Dynamin 1-like-dependent mitochondrial fission initiates overactive mitophagy in the hepatotoxicity of cadmium. *Autophagy* **9** 1780–1800. (<https://doi.org/10.4161/auto.25665>)
- Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, De Oliveira RM, Leid M, McBurney MW & Guarente L 2004 Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR- γ . *Nature* **429** 771–776. (<https://doi.org/10.1038/nature02583>)
- Picard M, Wallace DC & Burrelle Y 2016 The rise of mitochondria in medicine. *Mitochondrion* **30** 105–116. (<https://doi.org/10.1016/j.mito.2016.07.003>)
- Pons DG, Nadal-Serrano M, Torrens-Mas M, Valle A, Oliver J & Roca P 2015 UCP2 inhibition sensitizes breast cancer cells to therapeutic agents by increasing oxidative stress. *Free Radical Biology and Medicine* **86** 67–77. (<https://doi.org/10.1016/j.freeradbiomed.2015.04.032>)
- Prakash C & Kumar V 2016 Chronic arsenic exposure-induced oxidative stress is mediated by decreased mitochondrial biogenesis in rat liver. *Biological Trace Element Research* **173** 87–95. (<https://doi.org/10.1007/s12011-016-0622-6>)
- Prasai K 2017 Regulation of mitochondrial structure and function by protein import: a current review. *Pathophysiology* **24** 107–122. (<https://doi.org/10.1016/j.pathophys.2017.03.001>)
- Prentki M & Nolan CJ 2006 Islet beta cell failure in type 2 diabetes. *Journal of Clinical Investigation* **116** 1802–1812. (<https://doi.org/10.1172/JCI29103>)
- Puigserver P & Spiegelman BM 2003 Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator. *Endocrine Reviews* **24** 78–90. (<https://doi.org/10.1210/er.2002-0012>)
- Puigserver P, Wu Z, Park CW, Graves R, Wright M & Spiegelman BM 1998 A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* **92** 829–839. ([https://doi.org/10.1016/S0092-8674\(00\)81410-5](https://doi.org/10.1016/S0092-8674(00)81410-5))
- Rajamani U, Gross AR, Ocampo C, Andres AM, Gottlieb RA & Sareen D 2017 Endocrine disruptors induce perturbations in endoplasmic reticulum and mitochondria of human pluripotent stem cell derivatives. *Nature Communications* **8** 219. (<https://doi.org/10.1038/s41467-017-00254-8>)
- Rhodes CJ 2005 Type 2 diabetes – a matter of beta-cell life and death? *Science* **307** 380–384. (<https://doi.org/10.1126/science.1104345>)
- Rong JX, Qiu Y, Hansen MK, Zhu L, Zhang V, Xie M, Okamoto Y, Mattie MD, Higashiyama H, Asano S, *et al.* 2007 Adipose mitochondrial biogenesis is suppressed in db/db and high-fat diet-fed mice and improved by rosiglitazone. *Diabetes* **56** 1751–1760. (<https://doi.org/10.2337/db06-1135>)
- Rovira-Llopis S, Bañuls C, Diaz-Morales N, Hernandez-Mijares A, Rocha M & Victor VM 2017 Mitochondrial dynamics in type 2 diabetes: pathophysiological implications. *Redox Biology* **11** 637–645. (<https://doi.org/10.1016/j.redox.2017.01.013>)
- Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock EJ, Lillefosse H, Ma T, Pesenti S, Sonne SB, Marstrand TT, *et al.* 2009 Persistent organic pollutant exposure leads to insulin resistance syndrome. *Environmental Health Perspectives* **118** 465–471. (<https://doi.org/10.1289/ehp.0901321>)
- Sabanayagam C, Teppala S & Shankar A 2013 Relationship between urinary bisphenol A levels and prediabetes among subjects free of diabetes. *Acta Diabetologica* **50** 625–631. (<https://doi.org/10.1007/s00592-013-0472-z>)
- Sagarkar S, Gandhi D, Devi Ss, Sakharkar A & Kapley A 2016 Atrazine exposure causes mitochondrial toxicity in liver and muscle cell lines. *Indian Journal of Pharmacology* **48** 200. (<https://doi.org/10.4103/0253-7613.178842>)
- Sant KE, Jacobs HM, Borofski KA, Moss JB & Timme-Laragy AR 2017 Embryonic exposures to perfluorooctanesulfonic acid (PFOS) disrupt pancreatic organogenesis in the zebrafish, *Danio rerio*. *Environmental Pollution* **220** 807–817. (<https://doi.org/10.1016/j.envpol.2016.10.057>)
- Dos Santos RS, Marroqui L, Grieco FA, Marselli L, Suleiman M, Henz SR, Marchetti P, Wernersson R & Eizirik DL 2017 Protective role of complement C3 against cytokine-mediated β -cell apoptosis. *Endocrinology* **158** 2503–2521. (<https://doi.org/10.1210/en.2017-00104>)
- Scarpulla RC 2008 Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiological Reviews* **88** 611–638. (<https://doi.org/10.1152/physrev.00025.2007>)
- Scarpulla RC 2011 Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. *Biochimica et Biophysica Acta* **1813** 1269–1278. (<https://doi.org/10.1016/j.bbamcr.2010.09.019>)
- Scott I & Youle RJ 2010 Mitochondrial fission and fusion. *Essays in Biochemistry* **47** 85–98. (<https://doi.org/10.1042/bse0470085>)
- Sebastian D, Hernandez-Alvarez MI, Segales J, Sorianoello E, Munoz JP, Sala D, Waget A, Liesa M, Paz JC, Gopalacharyulu P, *et al.* 2012 Mitofusin 2 (Mfn2) links mitochondrial and endoplasmic reticulum function with insulin signaling and is essential for normal glucose homeostasis. *PNAS* **109** 5523–5528. (<https://doi.org/10.1073/pnas.1108220109>)
- Sena LA & Chandel NS 2012 Physiological roles of mitochondrial reactive oxygen species. *Molecular Cell* **48** 158–166. (<https://doi.org/10.1016/j.molcel.2012.09.025>)
- Shabalina IG, Kalinovich A V., Cannon B & Nedergaard J 2016 Metabolically inert perfluorinated fatty acids directly activate uncoupling protein 1 in brown-fat mitochondria. *Archives of Toxicology* **90** 1117–1128. (<https://doi.org/10.1007/s00204-015-1535-4>)
- Shankar A & Teppala S 2011 Relationship between urinary bisphenol A levels and diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism* **96** 3822–3826. (<https://doi.org/10.1210/jc.2011-1682>)
- Shertzer HG, Genter MB, Shen D, Nebert DW, Chen Y & Dalton TP 2006 TCDD decreases ATP levels and increases reactive oxygen production through changes in mitochondrial F0F1-ATP synthase and ubiquinone. *Toxicology and Applied Pharmacology* **217** 363–374. (<https://doi.org/10.1016/j.taap.2006.09.014>)
- Sies H 1993 Strategies of antioxidant defense. *European Journal of Biochemistry* **215** 213–219. (<https://doi.org/10.1111/j.1432-1033.1993.tb18025.x>)
- Song L, Xia W, Zhou Z, Li Y, Lin Y, Wei J, Wei Z, Xu B, Shen J, Li W, *et al.* 2012 Low-level phenolic estrogen pollutants impair islet morphology and β -cell function in isolated rat islets. *Journal of Endocrinology* **215** 303–311. (<https://doi.org/10.1530/JOE-12-0219>)

- Suarez-Lopez JR, Lee DH, Porta M, Steffes MW & Jacobs DR Jr 2015 Persistent organic pollutants in young adults and changes in glucose related metabolism over a 23-year follow-up. *Environmental Research* **137** 485–494. (<https://doi.org/10.1016/j.envres.2014.11.001>)
- Suárez-Rivero J, Villanueva-Paz M, de la Cruz-Ojeda P, de la Mata M, Cotán D, Oropesa-Avila M, de Laveria I, Álvarez-Córdoba M, Luzón-Hidalgo R & Sánchez-Alcázar J 2016 Mitochondrial dynamics in mitochondrial diseases. *Diseases* **5** 1. (<https://doi.org/10.3390/diseases5010001>)
- Suen DF, Norris KL & Youle RJ 2008 Mitochondrial dynamics and apoptosis. *Genes and Development* **22** 1577–1590. (<https://doi.org/10.1101/gad.1658508>)
- Suh KS, Choi EM, Rhee SY, Oh S, Kim SW, Pak YK, Choe W, Ha J & Chon S 2017a Tetrabromobisphenol A induces cellular damages in pancreatic β -cells in vitro. *Journal of Environmental Science and Health: Part A Toxic/Hazardous Substances and Environmental Engineering* **52** 624–631. (<https://doi.org/10.1080/10934529.2017.1294964>)
- Suh KS, Choi EM, Kim YJ, Hong SM, Park SY, Rhee SY, Oh S, Kim SW, Pak YK, Choe W, et al. 2017b Perfluorooctanoic acid induces oxidative damage and mitochondrial dysfunction in pancreatic β -cells. *Molecular Medicine Reports* **15** 3871–3878. (<https://doi.org/10.3892/mmr.2017.6452>)
- Sun Q, Cornelis MC, Townsend MK, Tobias DK, Eliassen AH, Franke AA, Hauser R & Hu FB 2014a Association of urinary concentrations of bisphenol A and phthalate metabolites with risk of type 2 diabetes: a prospective investigation in the Nurses' Health Study (NHS) and NHSII cohorts. *Environmental Health Perspectives* **122** 616–623. (<https://doi.org/10.1289/ehp.1307201>)
- Sun X, Lin Y, Huang Q, Shi J, Qiu L, Kang M, Chen Y, Fang C, Ye T & Dong S 2014b Di(2-ethylhexyl) phthalate-induced apoptosis in rat INS-1 cells is dependent on activation of endoplasmic reticulum stress and suppression of antioxidant protection. *Journal of Cellular and Molecular Medicine* **19** 581–594. (<https://doi.org/10.1111/jcmm.12409>)
- Supale S, Li N, Brun T & Maechler P 2012 Mitochondrial dysfunction in pancreatic beta cells. *Trends in Endocrinology and Metabolism* **23** 477–487. (<https://doi.org/10.1016/j.tem.2012.06.002>)
- Susiarjo M, Xin F, Bansal A, Stefaniak M, Li C, Simmons RA & Bartolomei MS 2015 Bisphenol A exposure disrupts metabolic health across multiple generations in the mouse. *Endocrinology* **156** 2049–2058. (<https://doi.org/10.1210/en.2014-2027>)
- Svensson K, Hernandez-Ramirez RU, Burguete-Garcia A, Cebrian ME, Calafat AM, Needham LL, Claudio L & Lopez-Carrillo L 2011 Phthalate exposure associated with self-reported diabetes among Mexican women. *Environmental Research* **111** 792–796. (<https://doi.org/10.1016/j.envres.2011.05.015>)
- Szendroedi J, Phielix E & Roden M 2011 The role of mitochondria in insulin resistance and type 2 diabetes mellitus. *Nature Reviews Endocrinology* **8** 92–103. (<https://doi.org/10.1038/nrendo.2011.138>)
- Tai X & Chen Y 2016 Urinary bisphenol A concentrations positively associated with glycated hemoglobin and other indicators of diabetes in Canadian men. *Environmental Research* **147** 172–178. (<https://doi.org/10.1016/j.envres.2016.02.006>)
- Tang-Peronard JL, Heitmann BL, Jensen TK, Vinggaard AM, Madsbad S, Steuerwald U, Grandjean P, Weihe P, Nielsen F & Andersen HR 2015 Prenatal exposure to persistent organochlorine pollutants is associated with high insulin levels in 5-year-old girls. *Environmental Research* **142** 407–413. (<https://doi.org/10.1016/j.envres.2015.07.009>)
- Tangvarasittichai S 2015 Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. *World Journal of Diabetes* **6** 456–480. (<https://doi.org/10.4239/wjcd.v6.i3.456>)
- Trasande L, Spanier AJ, Sathyanarayana S, Attina TM & Blustein J 2013 Urinary phthalates and increased insulin resistance in adolescents. *Pediatrics* **132** e646–e655. (<https://doi.org/10.1542/peds.2012-4022>)
- Trevino S, Waalkes MP, Flores Hernandez JA, Leon-Chavez BA, Aguilar-Alonso P & Brambila E 2015 Chronic cadmium exposure in rats produces pancreatic impairment and insulin resistance in multiple peripheral tissues. *Archives of Biochemistry and Biophysics* **583** 27–35. (<https://doi.org/10.1016/j.abb.2015.07.010>)
- Tsou TC, Yeh SC, Hsu JW & Tsai FY 2017 Estrogenic chemicals at body burden levels attenuate energy metabolism in 3T3-L1 adipocytes. *Journal of Applied Toxicology* **37** 1537–1546. (<https://doi.org/10.1002/jat.3508>)
- Twig G, Liu X, Liesa M, Wikstrom JD, Molina AJ a, Las G, Yaniv G, Hajnóczky G & Shirihai OS 2010 Biophysical properties of mitochondrial fusion events in pancreatic beta-cells and cardiac cells unravel potential control mechanisms of its selectivity. *American Journal of Physiology: Cell Physiology* **299** C477–C487. (<https://doi.org/10.1152/ajpcell.00427.2009>)
- van Esterik JC, Verharen HW, Hodemaekers HM, Gremmer ER, Nagarajah B, Kamstra JH, Dolle ME, Legler J & van der Ven LT 2015 Compound- and sex-specific effects on programming of energy and immune homeostasis in adult C57BL/6JxFVB mice after perinatal TCDD and PCB 153. *Toxicology and Applied Pharmacology* **289** 262–275. (<https://doi.org/10.1016/j.taap.2015.09.017>)
- van Esterik JC, Bastos Sales L, Dolle ME, Hakansson H, Herlin M, Legler J & van der Ven LT 2016 Programming of metabolic effects in C57BL/6JxFVB mice by in utero and lactational exposure to perfluorooctanoic acid. *Archives of Toxicology* **90** 701–715. (<https://doi.org/10.1007/s00204-015-1488-7>)
- Villa E, Proics E, Rubio-Patiño C, Obba S, Zunino B, Bossowski JP, Rozier RM, Chiche J, Mondragón L, Riley JS, et al. 2017 Parkin-independent mitophagy controls chemotherapeutic response in cancer cells. *Cell Reports* **20** 2846–2859. (<https://doi.org/10.1016/j.celrep.2017.08.087>)
- Wahlang B, Falkner KC, Gregory B, Ansert D, Young D, Conklin DJ, Bhatnagar A, McClain CJ & Cave M 2013 Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL6/J mice. *Journal of Nutritional Biochemistry* **24** 1587–1595. (<https://doi.org/10.1016/j.jnutbio.2013.01.009>)
- Wali JA, Rondas D, McKenzie MD, Zhao Y, Elkerbout L, Fynch S, Gurzov EN, Akira S, Mathieu C, Kay TWH, et al. 2014 The proapoptotic BH3-only proteins Bim and Puma are downstream of endoplasmic reticulum and mitochondrial oxidative stress in pancreatic islets in response to glucotoxicity. *Cell Death and Disease* **5** e1124. (<https://doi.org/10.1038/cddis.2014.88>)
- Walters MW, Bjork JA & Wallace KB 2009 Perfluorooctanoic acid stimulated mitochondrial biogenesis and gene transcription in rats. *Toxicology* **264** 10–15. (<https://doi.org/10.1016/j.tox.2009.07.003>)
- Wan HT, Zhao YG, Leung PY & Wong CK 2014 Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring. *PLoS ONE* **9** e87137. (<https://doi.org/10.1371/journal.pone.0087137>)
- Wang SL, Tsai PC, Yang CY & Guo YL 2008 Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. *Diabetes Care* **31** 1574–1579. (<https://doi.org/10.2337/dc07-2449>)
- Wang RH, Kim HS, Xiao C, Xu X, Gavrilova O & Deng CX 2011 Hepatic Sirt1 deficiency in mice impairs mTORC2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. *Journal of Clinical Investigation* **121** 4477–4490. (<https://doi.org/10.1172/JCI46243>)
- Wang T, Li M, Chen B, Xu M, Xu Y, Huang Y, Lu J, Chen Y, Wang W, Li X, et al. 2012 Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *Journal of Clinical Endocrinology and Metabolism* **97** E223–E227. (<https://doi.org/10.1210/jc.2011-1989>)
- Wang L, Ishihara T, Ibayashi Y, Tatsushima K, Setoyama D, Hanada Y, Takeichi Y, Sakamoto S, Yokota S, Mihara K, et al. 2015 Disruption of mitochondrial fission in the liver protects mice from diet-induced obesity and metabolic deterioration. *Diabetologia* **58** 2371–2380. (<https://doi.org/10.1007/s00125-015-3704-7>)
- Wei J, Lin Y, Ying C, Chen J, Song L, Zhou Z, Lv Z, Xia W, Chen X, et al. 2011 Perinatal exposure to bisphenol A at reference dose

- predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology* **152** 3049–3061. (<https://doi.org/10.1210/en.2011-0045>)
- Wei Y, Chiang WC, Sumpter R, Mishra P & Levine B 2017 Prohibitin 2 is an inner mitochondrial membrane mitophagy receptor. *Cell* **168** 224–238.e10. (<https://doi.org/10.1016/j.cell.2016.11.042>)
- Whitehead R, Guan H, Arany E, Cernea M & Yang K 2016 Prenatal exposure to bisphenol A alters mouse fetal pancreatic morphology and islet composition. *Hormone Molecular Biology and Clinical Investigation* **25** 171–179. (<https://doi.org/10.1515/hmbci-2015-0052>)
- Williams JA & Ding WX 2017 Mechanisms, pathophysiological roles, and methods for analyzing mitophagy – recent insights. *Biological Chemistry* **399** 147–178. (<https://doi.org/10.1515/hsz-2017-0228>)
- Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, Troy A, Cinti S, Lowell B, Scarpulla RC, *et al.* 1999 Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* **98** 115–124. ([https://doi.org/10.1016/S0092-8674\(00\)80611-X](https://doi.org/10.1016/S0092-8674(00)80611-X))
- Wu H, Bertrand KA, Choi AL, Hu FB, Laden F, Grandjean P & Sun Q 2013 Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis. *Environmental Health Perspectives* **121** 153–161. (<https://doi.org/10.1289/ehp.1205248>)
- Xia W, Jiang Y, Li Y, Wan Y, Liu J, Ma Y, Mao Z, Chang H, Li G, Xu B, *et al.* 2014 Early-life exposure to bisphenol a induces liver injury in rats involvement of mitochondria-mediated apoptosis. *PLoS ONE* **9** e90443. (<https://doi.org/10.1371/journal.pone.0090443>)
- Xin F, Jiang L, Liu X, Geng C, Wang W, Zhong L, Yang G & Chen M 2014 Bisphenol A induces oxidative stress-associated DNA damage in INS-1 cells. *Mutation Research: Genetic Toxicology and Environmental Mutagenesis* **769** 29–33. (<https://doi.org/10.1016/j.mrgentox.2014.04.019>)
- Xu S, Pi H, Chen Y, Zhang N, Guo P, Lu Y, He M, Xie J, Zhong M, Zhang Y, *et al.* 2013 Cadmium induced Drp1-dependent mitochondrial fragmentation by disturbing calcium homeostasis in its hepatotoxicity. *Cell Death and Disease* **4** e540. (<https://doi.org/10.1038/cddis.2013.7>)
- Yamada S, Asanagi M, Hirata N, Itagaki H, Sekino Y & Kanda Y 2016 Tributyltin induces mitochondrial fission through Mfn1 degradation in human induced pluripotent stem cells. *Toxicology In Vitro* **34** 257–263. (<https://doi.org/10.1016/j.tiv.2016.04.013>)
- Yamada S, Kubo Y, Yamazaki D, Sekino Y & Kanda Y 2017 Chlorpyrifos inhibits neural induction via Mfn1-mediated mitochondrial dysfunction in human induced pluripotent stem cells. *Scientific Reports* **7** 40925. (<https://doi.org/10.1038/srep40925>)
- Yang G, Zhou X, Wang J, Zhang W, Zheng H, Lu W & Yuan J 2012 MEHP-induced oxidative DNA damage and apoptosis in HepG2 cells correlates with p53-mediated mitochondria-dependent signaling pathway. *Food and Chemical Toxicology* **50** 2424–2431. (<https://doi.org/10.1016/j.fct.2012.04.023>)
- Yoon Y, Galloway CA, Jhun BS & Yu T 2011 Mitochondrial dynamics in diabetes. *Antioxidants and Redox Signaling* **14** 439–457. (<https://doi.org/10.1089/ars.2010.3286>)
- Youle RJ & Strasser A 2008 The BCL-2 protein family: opposing activities that mediate cell death. *Nature Reviews Molecular Cell Biology* **9** 47–59. (<https://doi.org/10.1038/nrm2308>)
- Yu T, Robotham JL & Yoon Y 2006 Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. *PNAS* **103** 2653–2658. (<https://doi.org/10.1073/pnas.0511154103>)
- Zhang J & Choudhury M 2017 The plasticizer BBP selectively inhibits epigenetic regulator sirtuin during differentiation of C3H10T1/2 stem cell line. *Toxicology In Vitro* **39** 75–83. (<https://doi.org/10.1016/j.tiv.2016.11.016>)
- Zhang S, Wu T, Chen M, Guo Z, Yang Z, Zuo Z & Wang C 2015a Chronic exposure to aroclor 1254. Disrupts glucose homeostasis in male mice via inhibition of the insulin receptor signal pathway. *Environmental Science and Technology* **49** 10084–10092. (<https://doi.org/10.1021/acs.est.5b01597>)
- Zhang J, Ali HI, Bedi YS & Choudhury M 2015b The plasticizer BBP selectively inhibits epigenetic regulator sirtuins. *Toxicology* **338** 130–141. (<https://doi.org/10.1016/j.tox.2015.10.004>)
- Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ & Vom Saal FS 2012 Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology* **153** 4097–4110. (<https://doi.org/10.1210/en.2012-1422>)

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