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Modulation of mitochondrial functions by xenobiotic-induced microRNA: from environmental sentinel organisms to mammals.

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Abstract

Mitochondria play a crucial role in energetic metabolism, signaling pathways, and overall cell viability. They are in the first line in facing cellular energy requirements in stress conditions, such as in response to xenobiotic exposure. Recently, a novel regulatory key role of microRNAs (miRNAs) in important signaling pathways in mitochondria has been proposed. Consequently, alteration in miRNAs expression by xenobiotics could outcome into mitochondrial dysfunction, reactive oxygen species overexpression, and liberation of apoptosis or necrosis activating proteins. The aim of this review is to show the highlights about mitochondria-associated miRNAs in cellular processes exposed to xenobiotic stress in different cell types involved in

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detoxification processes or sensitive to environmental hazards in marine sentinel organisms and mammals.

Keywords: mitochondrial dysfunction; pollutants; microRNA; ROS; hepatocytes; haemocytes

1. Introduction

In eukaryotic cells, mitochondria are the main source of adenosine triphosphate (ATP) production as well as reactive oxygen (ROS) and nitrogen species (RNS) (Heise et al., 2003; Donaghy et al., 2012; Putti et al., 2015; Rivera-Ingraham et al., 2016). Reviews by Donaghy et al. (2015) and Zeeshan et al. (2016) point to the endoplasmic reticulum (ER) as another source of ROS. The synthesis of mitochondrial ROS as well as other essential biological processes seems to be regulated by microRNAs (miRNAs, miRs), both in mammals and non-mammalian organisms (Kren et al., 2009; Christian and Su, 2014; Duarte et al., 2014; Burgos-Aceves et al., 2018a). The miRNAs are a group of small endogenous noncoding segments of RNA, ~18-25 nucleotide (nt) long that play a critical role in modulating gene expression (Filipowicz et al., 2008). To date, there is growing evidence that miRNAs are also present in or associated with other organelles (Fig. 1) such as mitochondria (Sripada et al., 2012; Tomasetti et al., 2014), ER (Li et al., 2013; Montgomery and Ruvkun, 2013; Axtell, 2017), processing bodies (P-bodies), stress granules, multivesicular bodies, and exosomes (Nguyen et al., 2014). Further, it has been suggested that cytosolic miRNAs can be transferred within the mitochondria (Li et al., 2012) or generated within it (Latronico and Condorelli, 2012; Sripada et al., 2012; Bandiera et al., 2013), and modulate genes expression and regulate important

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signaling pathways (Li et al., 2012). Thus, deregulation of miRNAs biosynthesis can be associated with mitochondrial dysfunction (Wang et al., 2017).

The aim of this review is to summarize the current knowledge on the role played by miRNA in regulation of mitochondrial function in condition of xenobiotic exposure. In the first part of the review, we introduced the role played by miRNA in regulating mitochondria and the effect of xenobiotic on mitochondrial function. In the second part, we summarized current knowledge on xenobiotic effect on mitochondrial associated-miRNA in cells from both hazards sentinel organisms and humans. In particular, we focused on bivalve mollusks and fish, as marine sentinel organisms in environmental health programs due to their ability to accumulate toxins inside tissue (Burgos-Aceves et al. 2018b). Then, we focused on mammalian liver cells, since it is well known that liver is the main organ involved in the processes of detoxification from xenobiotics in mammals including humans. Understanding the genetic and non-genetic mechanisms and miRNA involvement in mitochondrial response to toxic xenobiotics in sentinel animals cells facing detoxification processes, could be useful to shed light on etiopathogenesis of mitochondrial related-diseases and their possible therapies in humans.

2. miRNAs and mitochondrial function

Canonically, the miRNAs are transcribed from the non-coding regions of DNA by a RNA polymerase II to produce the primary long transcripts (pri-miRNA), which is cut into 70-nt stems and loop precursors (pre-miRNAs) by Drosha/DGCR8 complex (figure 1), (Zeng and Cullen, 2005). In turn, the pre-miRNAs are transporter from the nucleus to the cytoplasm by Exportin 5 (XPO5) along with RanGTP. There, the endonuclease Dicer splicing the pre-miRNAs to produce the mature double-stranded

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miRNA. One of these strands is linked to the argonaute protein (Ago) and forms the RNA-induced Silencing Complex (RISC), becoming active and capable to bind to a 3' untranslated region (3'UTR) of its target mRNA (Bartel, 2004). Some of these mature miRNAs can be translocated to the mitochondria (Fig. 1), and modulate mitochondrial gene expression in normal and disease conditions (Das et al., 2012, 2017). Noteworthy, a very recent review (Macgregor-Das and Das, 2018) focused on the role of a functionally important subset of miRNAs located in mitochondria, known as MitomiRs. It has recently been postulated that the transcription of mitomiRs could also occur from the mitochondrial genome. Bandiera et al. (2011) reported the transcription of at least three miRs with the participation of the protein Ago-2 into the mitochondria; hsa-miR-1974, hsa-miR-1977 and hsa-miR-1978 in HeLa cells. This work confirms the previous finding by Kren et al. (2009) for miR-494 in rat liver mitochondria, as well as the localization of two pre-miRNAs (pre-mir-302a, pre-let-7b) in human mitochondria isolated from muscular cells (Barrey et al., 2011). The presence of the proteins Ago in the mitochondria suggests that mitochondrial outer membrane (Fig. 1) may probably provide novel platform to assemble the miRNA/RISC complexes (Bandiera et al., 2011). These emerging data suggest that mitochondria have a unique population of miRNAs and that the enrichment of miRNAs in mitochondria is independent of the total cellular abundance of miRNAs (Bian et al., 2010). However, miRNAs translocation mechanisms, biological targets, and function at the mitochondrial level are not well understood (Borralho et al., 2014)

Up to date, there is an emerging interest in the identification and putative role of miRNAs in mitochondrial homeostasis (Borralho et al., 2014). In different cell types, miRNAs were found to be involved in regulation of mitochondrial function and may play a role in mitochondrial-associated disease (Bandiera et al., 2013; Duarte et al.,

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2014). In neuron cells, an over expression of miR-338 decreases the cytochrome c oxidase IV (CoxIV) gene and protein expression, which translates into a significant reduction of mitochondrial oxygen consumption, metabolic activity and ATP production, which could be implicated in a subset of neurodegenerative diseases, such as Alzheimer's or Parkinson's disease (Aschrafi et al., 2008). Whereas, up-regulation of miR-15b, miR-16, miR-195 and miR-424 can suppress ATP levels in cardiac myocytes, affecting the integrity of mitochondria, which may contribute to cardiac dysfunction (Nishi et al., 2010). Shen et al. (2016) reported an alteration in mitochondria biogenesis during myocyte differentiation by down-regulation of forkhead box j3 gene (*Foxj3*) upon overexpression of miRNA-27. Jeong et al. (2017) exhibited a correlation between miR-24 and mitochondrial outer membrane protein isoform H2AX. miR-24-mediated knockdown of H2AX impaired both mitochondria and the insulin signaling pathway. An overexpression of miR-24 decreased mitochondrial H2AX level resulting in a mitochondrial malfunction. In addition, hepatic miR-24 levels were significantly increased in diabetic and obese mice, suggesting that H2AX-targeting miR-24 may be a novel negative regulator of mitochondrial function in the pathogenesis of insulin resistance. Burchard et al. (2010) made evident that miR-122 can regulate the mitochondrial metabolism in human hepatic cells, and its under-expression can lead to the development of hepatocellular carcinoma (HCC). On the other hand, it has been reported that miRNAs can indirectly modulate the mitochondrial apoptosis pathway (Fig. 2). The tumorigenic cyclooxygenase-2 (COX-2) overexpression, which is induced under pathologic conditions, is frequently associated with resistance to apoptosis in human cancer cells (Fosslien, 2000; Leng et al., 2003; Liou et al., 2005), and its inhibition has been associated with induction to apoptosis activating the effector caspases in

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human hepatocellular carcinoma cells (Kern et al., 2006). An up-regulation of miR-16 can silence COX-2 expression via interaction with its predicted binding sites in the 3'-untranslated region (3'-UTR) (Agra Andrieu et al., 2012), activating mitochondrial apoptosis through a cytochrome c (cyt c)-dependent pathway (Li et al., 2001). Occurs a mitochondrial outer membrane permeabilization (MOMP), and collapse of mitochondrial membrane potential ($\Delta\psi m$) by down-regulation of anti-apoptotic protein Bcl-2. This allows translocation of pro-apoptotic Bax protein to mitochondria to form the complex Bax/Bak (Lalier et al., 2007), and release of cyt c to cytosol activating apoptosis process (Fig. 2) (Sobolewski et al., 2010). However, Guo et al. (2017) reported a down-regulation of miR-142-3p associated with a COX-2 overexpression, an increment in apoptosis process, and inactivation of PI3K/AKT/mTOR signaling pathway in bleomycin-treated mouse lung epithelial type II cells (MLE-12). Therefore, a mitochondrial dysfunction can be assumed because the mechanistic target of rapamycin (mTOR) has been advised as modulator of mitochondrial biogenesis, apoptosis, mitophagy and mitochondrial hormesis (mitohormesis) including the retrograde response and mitochondrial unfolded protein response (mito-UPR) (Morita et al., 2015; Yui et al., 2015; Wei et al., 2015). In any case, regulation of COX-2 expression can be miRNA-mediated, as shown by Yoon et al. (2011), since at least the ectopic expression of another six miRNAs (miR-26a, -143, -145, -199a, -542-3p, and -543) are involved in the regulation of COX-2 expression, suggesting an important role for miRNAs in COX-2 overexpression during inflammation and tumorigenesis.

3. Xenobiotics and xenobiotic-induced miRNAs effect on mitochondrial function

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Overproduction of intra-mitochondrial ROS has been associated to drugs but also to environmental toxicants resulting in serious injuries that may alter the normal mitochondrial functions causing some kind of diseases in mammals and non-mammal organisms, such as anemia, heart disease, hepatic cytolysis and steatosis, inflammation, skeletal muscle disorders, etc. (Pagano, 2002; Begriche et al., 2011; Deavall et al., 2012; Meyer et al., 2013; Brunst et al., 2015; Varga et al., 2015; Vuda and Kamath, 2016; Datta et al., 2016; Eakins et al., 2016; Blajszczak and Bonini, 2017; Dott et al., 2018). To date, very little are known about nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) damage by xenobiotics, and its association to mitochondrial dysfunction (Caito and Aschner, 2015; Roubicek and Souza-Pinto, 2017). Some data indicate that mtDNA seems to be more predisposed to damage because mitochondria are more susceptible to increase ROS and RNS after xenobiotic stimuli and also tend to accumulate them (Kang and Hamasaki, 2002; Venkatraman et al., 2004). Venkatraman et al. (2004) reported a perceived decrement in both nDNA and mtDNA-encoded gene products of oxidative phosphorylation complexes (OXPHOS) in hepatic cells after a chronic ethanol exposition, where mtDNA damage was mostly observed, modifying the mitochondrial protein profile. A similar effect was reported by López-Gallardo et al. (2016) on osteosarcoma and adenocarcinoma cells after environmental exposure to tributyltin chloride (TBTC), a worldwide toxicant ATP synthase inhibitor present in contaminate human food and water. The organotin TBTC seems to trigger mutations on mtDNA, causing an OXPHOS disorder, and inducing striatal necrosis syndromes. Polychlorinated biphenyl (PCB) quinones have been associated to several toxic effects in human, and their exposure increase ROS production, decreasing mitochondrial $\Delta\psi m$, inducing the translocation of cyt c from mitochondria into cytosol, and an increment in caspase-3/9 and p53

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protein and gene expressions in human hepatoma cells (HepG2), resulting in apoptotic cell death (Xu et al., 2015).

Functional modification in mitochondria is one of the parameters that can be used to detect spatial and temporal alterations in organisms by external effectors like environment pollutants, hypoxia, and temperature or combined effect (Yawetz et al., 2010; Hamanaka and Chandel, 2010; Ivanina et al., 2012). Hence, elucidating the roles of microRNAs in mitochondria will provide the basic framework to investigate their functions in mitochondria and to unravel their potential in designing new therapeutic strategies for mitochondrial diseases (Li et al., 2012).

4. Xenobiotics impact on mitochondrial function and related miRNAs in marine environmental sentinel species

To study the effects of xenobiotics and environmental pollutants on human health, it can be useful to analyze how they impact on organisms that may be considered sentinel species (Neo and Tan, 2017). Animals in many habitats can be used as a surveillance tool for monitoring environmental and human health hazards (Reif, 2011), since they allow detecting risks to humans by providing warning of a danger in advance. Indeed, they share the same environment as humans, but they have a higher exposure risk since they spend more time outdoors than humans. In addition, taking into consideration their compressed lifespans, mechanisms of injury by environmental hazards may develop more rapidly than in humans (Rabinowitz et al., 2010). A variety of marine species are excellent to monitor health hazards in the environment. For example, shellfish and fish are sentinel organisms and the presence of residues of environmental contaminants in their tissues is well documented in the literature (Reif, 2011).

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191 4.1 Xenobiotics effects on mitochondrial function and related miRNAs in bivalves

192 Bivalves, due to their lifestyle, are species with a greater risk of contact with the
193 increasing discharge of municipal and industrial wastewater effluents in their
194 environment, affecting the ROS production involved in cellular and tissue
195 homeostasis (Winston et al., 1996; Donaghy et al., 2012; De Lisi et al., 2013). The
196 digestive gland or hepatopancreas is the organ associated with the processes of
197 detoxification and elimination of xenobiotics, as well as the immune response to
198 pathogens (Moore and Allen, 2002; Torre et al., 2013a,b), and the haemocytes are
199 responsible for carrying out these processes (Faggio et al., 2016; Pagano et al., 2016,
200 2017). The haemocytes contain organelles in cytoplasm, including several
201 mitochondria and considerable amount of endoplasmic reticulum (Cajaraville and Pal,
202 1995; Yanyan et al., 2006), and it has been observed that environmental contaminants
203 like benzo[a]pyrene (B[a]P) can down-regulate the mitochondrial activity in adults
204 mussel of *Mytilus galloprovincialis* (Banni et al., 2017), or structurally distort the
205 mitochondria by bioaccumulation of heavy metals (Torre et al., 2013b; Pagano et al.,
206 2017; Savorelli et al., 2017), as observed in the marine Indian green mussel *Perna*
207 *viridis* (Vasanthi et al., 2013, 2017). Besides, xenobiotics, such as the herbicide
208 fomesafen, can activate the apoptotic program of haemocytes through the collapse of
209 the mitochondrial $\Delta\psi m$, a subsequent membrane asymmetry with phosphatidylserine
210 (PS) release in a dose-dependent way (Russo and Madec, 2007). A mitochondrial
211 ROS production can occur by breaking lysosomes (Moore et al., 2009), resulting in
212 the release of mitochondrial proteins, including cyt c, and promote the apoptotic
213 cascade (Zhao et al. 2003). The presence of PS onto the membrane is required for
214 apoptotic cell recognition and has been proposed in the intrinsic death program,
215 following cell injury (Martin et al. 1995). Therefore, apoptosis pathway might provide

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a sensitive indicator of environmental pollution (Russo and Madec, 2007). Other organs can also be used as biomarkers of ecotoxicity. In the freshwater mussel *Elliptio complanata*, some pharmaceutical products (ibuprofen, cotinine, fluoxetine, coprostanol, trimethoprim) as well as municipal effluents can increase mitochondrial electron transport (MET), lipid peroxidation and respiration rates in isolated mitochondria from gonad. Environmental factors such temperature could enhance the susceptibility of mitochondrial energy production and oxidative stress in environments contaminated by domestic wastewater. So, it is suggested that organisms exposed to polluted environments are more susceptible to temperature fluctuations (Gagné et al., 2006).

To date, studies have been developed concerning the modulating role of miRNAs against the effects of environmental stress in marine invertebrate animals (Biggar et al., 2012; Bao et al., 2014; Burgos-Aceves et al., 2018b). Notwithstanding, there are any published data related to the role of miRNAs in mitochondrial haemocyte function under xenobiotic stress. However, there is evidence indicating that miRNAs can play a key role in the direct regulation of genes coding for mitochondrial proteins and consequently mitochondrial function in other cell types (Duarte et al., 2014; Tomasetti et al., 2014; Macgregor-Das and Das, 2018; Murri and El Azzouzi, 2018), but the mode of action in mitochondria are largely unknown (Srinivasan and Das, 2015). Besides, the role of mitochondria extends beyond energy metabolism to many other cellular processes like metabolism, cell death and inflammation (Sripada et al., 2012), reason why miRNAs can play a key role in mitochondrial haemocyte functions.

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Consequently, alteration of digestive gland functions as other organs or tissues can reflect disturbances at molecular level and identification of these disturbances can aid in the understanding of whole animal impact due to pollutants and other stress factors (Vasanthi et al., 2012; Faggio et al., 2018). Therefore, it is necessary to carry out further investigation to determine which miRNAs might be regulated by xenobiotic. How these miRNAs act, may allow us to increase our understanding of miRNAs roles in regulation of xenobiotic challenge and stress. This finding would have important implications for our understanding of gene regulation under environmental stress and make a significant contribution to the long-term goal of a complete miRNA profile for bivalve haemocytes.

4.2 Xenobiotics effects on mitochondrial function and related miRNAs in fish cells

Fish are known as very sensitive to anthropogenic impacts and are often being used as sentinel species in the aquatic environment (Burgos-Aceves et al., 2018a). One of the main effects of xenobiotics is the direct or indirect ROS production, where lysosomal membrane rupture and mitochondrial metabolism alteration can be associated to ROS overproduction (Pourahmad et al., 2001, 2004), and promote activation of caspase enzymes and apoptotic cell death (Pourahmad et al., 2001; He et al., 2012; Yu et al., 2018). In fish, the production of ROS under normal condition is by the red muscle mitochondria during swimming activity, and also in liver, heart, swimbladder, roe and blood in resting fish. The mechanism of fish mitochondrial function and ROS production seems to be similar to that of mammals with the difference that fish erythrocytes possess nuclei and mitochondrial membrane is highly flexible (Wilhelm Filho, 2007).

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Many xenobiotics tend to accumulate in the liver, making this organ particularly sensitive, triggering structural and distribution of almost any cell organelle system (Grund et al., 2010), in order to carry out a morphological restructuring in adaptation to the need for intensified metabolization/detoxification capacities (Triebskorn et al. 2004). Then, alterations on hepatic mitochondrial function and other subcellular organelles by xenobiotics have been reported in several fish species (Myers et al. 1994; Pedrajas et al. 1995, 1996; Krumschnabel and Nawaz, 2004; Miller et al., 2007; Schnell et al., 2009; Wu et al., 2014; Lin et al., 2017; Du et al., 2018). Recent studies indicate that several chemicals with pharmaceutical or personal care products have toxic effects on liver mitochondria in fish acting as endocrine disruptors (Burgos-Aceves et al., 2016; Plhalova et al., 2017; Sehonova et al., 2017a,b; Fiorino et al., 2018), similar to that reported in mammals (Brown et al., 2014). They can inhibit function such as the mitochondrial electron transport system (Chan et al., 2005). A work done by Yeh et al. (2017) showed that certain chemicals considered as contaminants of emerging concern (CECs), even at low concentration, could affect liver mitochondrial functions in individuals of Chinook salmon, owing to bioaccumulative effect. These chemicals can affect both liver mitochondrial quality and content, reduce the expression of the positive transcriptional regulator of mitochondrial biogenesis peroxisome proliferator-activated receptor (PPAR) Y coactivator-1alpha (pgc-1α) and elevate the respiratory activity per mitochondria. The respiration rate can significantly rise in fish hepatocytes as a response mechanism in the reduction and elimination of intracellular xenobiotic concentration via the use of P-glycoproteins (Bains and Kennedy, 2004, 2005). Perchlorate (ClO_4^-), lanthanum (La^{3+}), and calcium (Ca^{2+}) can have toxic effects in liver of *Carassius auratus*, inducing mitochondrial oxidative stress, and subsequently a gradual opening of

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permeability transition pore leading to mitochondrial swelling and lipid peroxidative membrane damage (Zhao et al., 2014; Wu et al., 2015). Similar effects have been observed in liver mitochondria of rainbow trout *Oncorhynchus mykiss* and yellow croaker *Pseudosciaena crocea* at highly elevated zinc (Zn) concentration (Sharaf et al., 2017; Zheng et al., 2017). The insecticide Rotenone has the faculty of inhibit the mitochondrial respiratory complex I function in both mammals and fishes (Caito and Aschner, 2015). Then, hepatic mitochondria seem to be the commonly acting site of most toxicants, suggesting that oxidative stress played a significant role in the mechanisms of the hepatotoxicity of xenobiotics (Lin et al., 2017).

Lately, studies indicate that molecular regulation of mitochondrial metabolism, structure, and function are genetically modulated by miRNAs (Huntzinger and Izaurralde, 2011; Li et al., 2012), and the expression of these can be extensively modified by different stress factors in fish (Burgos-Aceves et al., 2016, 2018a; Tong et al., 2017). Nevertheless, despite the emerging interest of mitochondria as target for environmental toxicants, little has been discussed about the effect of xenobiotics on hepatic mitochondria of fish and even less about the modulating action of miRNAs on mitochondrial functions under pollutants presence. Cohen et al. (2008) have previously shown differential miRNA expression patterns in the zebrafish tissues after exposure to estradiol (E2), where a comprehensive miRNA downregulation was predominantly observed in the liver (Cohen and Smith, 2014). Instead, there are reports indicating that E2 can have deleterious effects on mitochondria through the accumulation of Ca^{2+} by delaying the opening of the permeability transition pore (Moreira et al., 2007; Thiede et al., 2012), while other reports indicate an upgrade hepatic mitochondrial function (Kozlov et al., 2010). Meanwhile, Renaud et al. (2017) showed that in liver of zebrafish 15 miRNAs where differently expressed after

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bisphenol A (BPA) exposure, affecting the oxidative phosphorylation and cell cycle pathways, perturbation on mitochondrial respiratory electron transport chain, and development of liver disease like the non-alcoholic fatty liver disease (NAFLD) and genetic disease. Additionally, some other reports indicate the possible role of miRNAs in the adaptation mechanisms in fish from extreme environments, denoting that several conserved miRNAs play a key role in the regulation of gene expression associated to signal transduction, cell differentiation and biosynthetic process. While other miRNAs seem to be species-specific and involved in ion binding, transport and oxidoreductase activity (Tong et al., 2017).

5 Xenobiotics impact on mitochondrial function and related miRNAs in mammals: focus on hepatic cells.

Liver is the main organ involved in detoxification processes in humans and therefore, modulation of hepatic cell metabolism and mitochondrial function by miRNA may play a key role in the response to xenobiotics in both liver tissue and whole organism. There is a growing evidence that drug overdose-induced mitochondrial malfunction is associated to several human diseases (Begriche et al., 2011; Zhou and Guilarte, 2013), although mitochondrial dysfunction has been reported in many *in vitro* studies (Roubicek and Souza-Pinto, 2017). Analyses have been carried out to identify reliable and sensitive early markers for liver injury using state-of-the-art technologies, so an early diagnosis of drug-induced liver injury (DILI) is important, especially in the case of idiopathic DILI where the underlying cause is difficult to determine (Hayes and Chayama, 2016). Recently, studies have shown the involvement of miRNAs in liver diseases caused by drug abuse and other external factors (Bala et al., 2009; Wang et al., 2009; Lewis et al., 2011). Acetaminophen (APAP) is one of the most commonly

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used drugs for pain and fever in adults and children, and an APAP-overdose is the most common cause of DILI (Williams et al., 2010). Fukushima et al. (2007) denote that an overdose of APAP or carbon tetrachloride (CCl_4), added to the histological damages in rat liver, triggered a decrease in the expression of miR-298 and miR-370, which is speculated to be bind to thioredoxin reductase 3 messenger RNA and regulate the oxidative stress-related genes. Therefore, their down-regulation would be associated with an increase in the production of ROS. A study in mouse liver showed an up-regulation of liver-specific miR-122 was observed correlated with an increment in alanine aminotransferase (ALT) resulting in APAP-induced liver injury (Bala et al., 2012). Yang et al. (2015) also reported an overexpression of miR-122 and miR-375 associated with mitochondrial DNA damage, collapse of mitochondria, and necrotic cell death. This may be due to excessive ROS or the opening of the mitochondrial membrane permeability transition pores (Jaeschke, 2005). The miR-122 is considered as a mitochondrial function regulator (Burchard et al. 2010), and both miR-122 and -375 are cholesterol and lipid metabolism regulators (Esau et al., 2006; Christian and Su, 2014). Moreover, APAP also can induce liver inflammation and the miR-155 is known to mediate inflammatory responses via mediating NF-κB signaling pathway, through regulation of p65 and IKKε expression. Inhibition of miR-155 entails an increment in the inflammatory mediators tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) in liver (Yuan et al., 2016). Streptozotocin (STZ), a drug used for treating metastatic cancer of the pancreatic islet cells, can induce type 1 diabetes and mitochondrial dysfunction (Ghosh et al., 2004). According to studies conducted by Bian et al., (2010) a mitochondrial dysfunction in mouse liver can be associated with significantly altered expression pattern of mitochondria-associated miRNAs after

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STZ treatment, where the principal miRNAs up-regulated were miR-494, miR-202–5p, miR-134, and miR-155 and the miR-122 was down-regulated.

Unhealthy diets can imbalance the supply and utilization of fatty acids (FA), contributing to intrahepatic lipid (IHL) accumulation in obesity (Ciapaite et al., 2011). The cause of obesity can be associated also with mitochondrial biogenesis and dynamic dysfunction (Ji et al., 2015), since there is an unbalance between energy intake and energy expenditure, resulting in an excessive energy accumulation in adipocytes (Ciapaite et al., 2011). Recently, mitochondria-related miRNAs have emerged as key regulators in metabolic disorder (Iacomino and Siani, 2017; Murri and El Azzouzi, 2018), where the epigenetic modifications can have effects on cellular lipid metabolism and energy expenditure. Epigenetic modifications are now closely involved in non-alcoholic fatty liver disease (NAFLD) associated with excess transfer of fat to the adipose tissue and the induction of obesity (Martins, 2015). It has been reported that a diet containing elevated components (sugar, fats, xenobiotics, drugs) may alter the expression of miRNAs associated to adipocyte differentiation, insulin action and fat metabolism (Xie et al., 2009; McGregor and Choi, 2011). According to Ji et al. (2015) in a high-fat-diet (HFD) an up-regulation of mitochondrial-related miR-141-3p with a marked hepatic mitochondrial dysfunction was observed. Their results indicate that the overexpression of miR-141-3p contributed to an up-regulation of ATP and ROS production, through the promotion of oxidative phosphorylation (OXPHOS) by increasing the expression of the mitochondria-encoded subunits of cytochrome c oxidase (COX or complex IV) Cox2 and Cox3, and a reduction of antioxidant enzymes capacity by silencing phosphatase and tensin homolog (PTEN) gene. These changes lead to an energy imbalance can be

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associated with obesity development due to induced alterations in hepatic and adipose lipid metabolism by miRNAs (Martins, 2015; Giroud et al., 2016).

Recently, miRNAs have been postulated a key modulators in mitochondrial apoptosis (Cai et al., 2009; Duarte et al., 2014; Su et al., 2015). At least, a potential interaction between miR-130a and mitochondrial encoded cytochrome c oxidase III (Cox3) has been established in liver of rat (Kren et al., 2009). Apparently a xenobiotic-induced miR-130a suppression can be associated with an inhibition of Cox3, while, an over-expression of miR-181c causes a decrement in cytochrome c oxidase subunit I (Cox1), and an increased rate of O2 consumption by complex IV, caused probably by increased generation of ROS (Latronico and Condorelli, 2012). This alteration on mitochondrial complex IV function in turn may cause the synthesis of C16:0 ceramide by a transcriptional up-regulation of (dihydro)ceramide synthases-6 (CerS6) gene in the ER membrane, a key cellular stress response to Cox inhibition. Increment in cellular ceramide levels specially promotes permeability of mitochondrial outer membrane and consequently release of cyt c and activation of caspase pathway (Fig. 3) (Aflaki et al., 2012; Schüll et al., 2015).

6. Conclusions and Perspectives

Carry out evaluations of mitochondrial function and related miRNA can help us to determine the degree of disturbance of cell metabolism in marine sentinel organisms, such as shellfish and fish, according to the level of contamination of environment. Additionally, pollution can genetically affect a population splitting sub-genotypes (Yawetz et al., 2010). With regard to genetics, the importance of these pathways is underscored by the fact that inherited mitochondrial diseases are caused by mutations in genes encoding proteins involved in each of these processes that can be inherited

maternally (Nunnari and Suomalainen, 2012). Thus, it will be important to determine whether toxicity of a specific xenobiotic is directly due to toxicity to the mitochondria or whether the mitochondria is damaged as a secondary event after exposure. This may give insight into the role of miRNAs, mitochondria and environmental exposures in disease, so that, modulation of miRNA levels may provide a new therapeutic approach for the treatment of mitochondria-related diseases in humans.

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902 **Figure caption**

903 **Figure 1.** Schematic microRNAs (miRNAs, miRs) translocation to mitochondrion.
904 Once the biogenesis process (canonical) of miRNAs has been carried out, both pre-
905 miRNAs and mature miRNAs can be translocated to various subcellular locations as
906 nucleus, mitochondria, Endoplasmic Reticulum, P-bodies, etc. Mitochondrial outer
907 membrane may itself serve as a novel platform for the miRNA transport or assembly,
908 and the presence of pre-miRNAs also in mitochondria, suggesting that mitochondria
909 may provide a miRNAs assembly platform. miRNAs have been suggested to augment
910 translocation under specific circumstances through a separate importation of miRNAs
911 and argonaute (Ago) protein by a yet unidentified protein import complexes located in
912 the mitochondrial intermembrane space (channels in red and green). Abbreviations:
913 RISC, RNA-induced silencing complex; Exportin, 5 XPO5; DGCR8, Di-George
914 syndrome critical region gene 8.

915 **Figure 2.** Indirect modulation of apoptosis by microRNAs through the inhibition of
916 cyclooxygenase-2 (COX-2). The inhibition of COX-2 by miR-16 (black cross)
917 depletes the activity of the anti-apoptosis proteins Bcl-2 favoring the activation and
918 translocation (blue arrow) of the pro-apoptotic protein Bax to mitochondria, and
919 activation of mitochondrial surface Bak to form the Bax/Bak complex thus leading to
920 mitochondrial outer membrane permeabilization (MOMP), collapse of mitochondrial
921 membrane potential ($\Delta\psi m$), and release of cytochrome c (cyt c; purple arrow) through
922 Bax/Bak complex into cytosol to form the apoptosome initiating the apoptosis
923 program.

924 **Figure 3.** Schematic proposal of miR-130a (orange) and miR-181c (green) role in
925 mitochondrial function. Cox1, 2, and 3, are transcribed from the heavy and light

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926 stands of the circular mtDNA. The miR-181c binds to the cognate site on the 3'
927 untranslated region of the mRNA of Cox1 inhibiting its translation, whereas miR-
928 130a induce the translation of Cox3, which is blocked by xenobiotic action. Alteration
929 on COX Complex IV, in yellow) leads by an as yet unknown mechanism to enhanced
930 expression of CerS6 (mainly associated with ER membranes) and accumulation of
931 intracellular C16:0 ceramide. The increased intracellular C16:0 ceramide promotes
932 permeability of mitochondrial outer membrane allowing the release of cytochrome c
933 inducing the activation of apoptosis pathway.