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Review

Mitochondrial dynamics and cancer

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ABSTRACT

Mitochondrial morphology is regulated by continuous fusion and fission events that are essential for maintaining a normal mitochondrial function. If the last years have witnessed major discoveries in the characterization of the fission and fusion machineries, little is known about the physiological role of mitochondrial dynamics. In this review we report the results showing evidences of relationships between mitochondrial dynamics and cellular metabolism, autophagy or apoptosis. We discuss how different mitochondrial alterations observed in cancer cells could be linked to unbalanced mitochondrial fission or fusion events and how this could impinge on key essential cellular processes, thereby contributing to tumorigenesis.

Mitochondria are dynamic, semi-autonomous organelles surrounded by a double membrane that have their own genome and protein synthesis machinery. They are motile and undergo frequent changes in number and morphology through fusion and fission events. In addition to being the major source of ATP in eukaryotes, they are the site of many important metabolic reactions such as the urea cycle, lipid metabolism, steroid hormone and porphyrin synthesis and interconversion of amino acids. Moreover, mitochondria play a central role in complex physiological processes including cellular proliferation, differentiation, apoptosis [1,2] and in cellular processes like glucose sensing/insulin regulation [3], cellular $Ca^{2+}$and ROS (reactive oxygen species) homeostasis [4–7]. It is therefore not surprising that mitochondrial dysfunctions have been found to be associated with several diseases such as degenerative diseases, aging and cancer [8,9]. Many cancer cells are characterized by a decrease in oxidative phosphorylation and by a high glycolytic activity, as first described 80 years ago by Warburg [10]. Therefore, many cancer cells mainly use glucose, even in the presence of oxygen, a phenomenon called "aerobic glycolysis". Moreover, mitochondria are at the core of the so-called intrinsic apoptotic pathway and appear to be protected in cancer cells explaining, at least in part, cell tumorigenesis. Proteins involved in the fusion/fission machinery were recently found to regulate the intrinsic apoptotic pathway and therefore could participate in the resistance of cancer cells to apoptotic stimuli. Moreover, shaping of mitochondria could have impacts on mitochondrial function and cell metabolism. In this review we report data from the literature addressing the role of mitochondrial dynamics in mitochondrial function, cell metabolism and apoptosis and we will discuss the possibility that a defect in the mitochondrial fusion or fission machinery may have an impact on tumorigenesis.

1. Proteins involved in mitochondrial dynamics

This review will be focused on the proteins involved in the fusion and fission of mitochondria (Fig. 1). We will not describe the mechanisms that allow mitochondria to move in the cell.

1.1. Mitochondrial fusion

The mitochondrial fusion apparatus involves two proteins conserved from yeast to human: the large outer membrane GTPase, Fuzzy onion/Mitofusin, and the inner membrane dynamin-like Mgm1p/Opa1 [2]. In mammals, two mitofusins, Mfn1 and Mfn2, have been described, that hydrolyse GTP with a different efficacy [11], suggesting a different function. These proteins dimerize via their coiled domain, allowing mitochondrial tethering and fusion (Fig. 1). On the other hand, Mgm1p/OPA1 is required for fusion of the inner membrane, mtDNA maintenance and cristae morphology [12,13]. The role of this protein in cristae organization could be mediated by the ATP synthase whose oligomerization appears to have an impact on inner membrane curvature and cristae biogenesis [14–17]. In mammals, there are at least eight isoforms of OPA1, produced by alternative splicing and proteolytic processing by mitochondrial proteases, yet the role of these isoforms is unclear. Other proteins have been reported to play a role in mitochondrial fusion such as Mitofilin which is involved in cristae morphology [18], MitoPLD a mitochondrial phospholipase D [19] and recently mitochondrial morphology and cristae structure (MICS1) an inner

Abbreviations: OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; MFN, mitofusin; CMT, Charcot–Marie tooth; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

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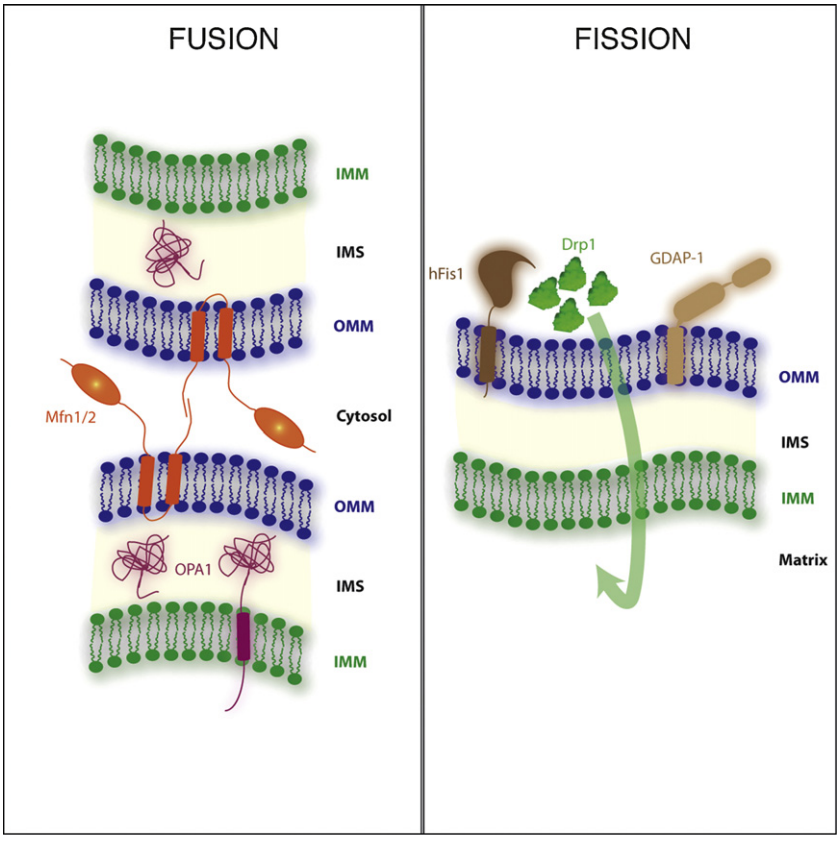

Fig. 1. Proteins involved in the fission and fusion of mitochondria. Left panel: Mfn1 and 2 are responsible for tethering and fusion of the outer mitochondrial membranes whereas OPA1 is responsible for the fusion of the inner membrane. How the fusion of the outer and inner membranes is coordinated is still unclear. Right panel: Drp1 can be recruited at the surface of mitochondria through binding to Fis1. Then the protein forms a ring around mitochondria leading to its fission.

membrane protein necessary for maintenance of mitochondrial morphology in specific cristae structures [20]. Finally, the β-subunit of the protein phosphatase 2A (PPA2) has also been involved in mitochondrial dynamics [21]. The mechanisms that coordinate fusion of the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM) are still unclear.

1.2. Mitochondrial fission

Mitochondrial division is orchestrated by multi-component protein machineries that were first described in yeast [22]. In mammals, the key molecules of the mitochondrial fission process are hFis1 and Drp1 (Dynamin related protein 1). The hFis1 protein is integrated in the OMM and serves as a receptor for Drp1 which translocates from the cytosol to the OMM where it forms a ring that drives fission of the organelle by a still unclear mechanism (Fig. 1). However, in many cases Drp1 does not seem to require Fis1 to bind mitochondria [23]. In yeast, two adaptors Caf4p and Mdv1p cooperate with Fis1 to recruit Drp1 [24–26]. No homolog of these proteins has been identified in mammals. Besides Drp1 and Fis1, the mitochondrial membrane proteins MTP18 [27,28], ganglioside-induced differentiation associated protein 1 (GDAP1) [29] as well as Miro-1 and Miro-2 (Mitochondrial Rho-GTPase) [30,31] are also involved in mitochondrial fission.

2. Regulation of the fission and fusion of mitochondria

2.1. Post-translational modifications of proteins involved in mitochondrial fission and fusion

Components of the fission and fusion machinery have been shown to be regulated at the post-translational level through phosphorylation, ubiquitination and sumoylation.

Phosphorylation has been reported to control Drp1's activity. Cdk1/cyclin B protein kinase can phosphorylate and activate Drp1 thereby promoting a transient mitochondrial fission at the onset of mitosis [32]. In contrast, phosphorylation of Drp1 by cAMP-dependent protein kinase (PKA) inactivates the GTPase activity of Drp1, resulting in mitochondrial fusion [33]. This phosphorylation can be reversed by the serine/threonine phosphatase calcineurin leading to mitochondrial fission [34].

The E3 ubiquitin ligases, MARCH-V (membrane-associated ring finger (C3HC4) 5) (also called MITOL), PARKIN and MULAN (Mitochondrial Ubiquitin Ligase Activator of NF-κB), have also been identified as regulators of mitochondrial dynamics [35–38]. MARCH-V is able to bind and to modify Drp1's activity resulting in a change of mitochondrial shape. However, as MARCH-V has been characterized as an inhibitor and an activator of fission [35,36,39], its function needs to be clarified. Recent data have demonstrated that PARKIN promotes mitochondrial fission and is involved in the selective elimination of impaired mitochondria by autophagy [37,40]. MULAN was first identified as an activator of NFκB. This effect, together with its localization at the mitochondria and its impact on mitochondrial morphology [38], provide a link between mitochondrial dynamics and mitochondria-to-nucleus signaling.

In addition to phosphorylation and ubiquitination, sumoylation also influences Drp1 function. SUMO1 and its conjugating enzyme Ubc9 can stabilize Drp1 at the mitochondrial membrane recruitment sites, thereby driving mitochondrial fission [41]. Interestingly during apoptosis, Drp1 is sumoylated in a Bax/Bak-dependent manner [42]. Moreover, the use of SENP5, a SUMO protease reverses this SUMO1-induced fragmentation [43]. If most of these examples concern post-translational modifications of Drp1, several evidences suggest that other proteins involved in the fission and fusion of

mitochondria can also undergo post-translational modifications. During the mating response, the yeast homologue of mitofusin, Fzo1, is ubiquitinated and degraded by the proteasome [44,45]. On the other hand inhibition of the proteasome in mammalian cells leads to increased expression of Mfn1 and 2 [39]. All these post-translational modifications allow mitochondria to adopt rapid and reversible morphological changes and to adapt to continuously changing environmental conditions.

2.2. The role of Bcl-2 family members

Besides post-translational modifications of the proteins involved in the fission and fusion of mitochondria, recent intriguing findings suggest that members of the Bcl-2 family could modulate the morphology of mitochondria. It was shown that Bax and Bak are involved in the regulation of mitochondrial fusion through interactions with Mfn2 in healthy cells [46]. This would explain that mitochondria from Bax and Bak double knock out cells are fragmented and that localization of Mfn2 on mitochondria from those cells is abnormal [46]. Accordingly, it was reported that CED-9, the *C. elegans* Bcl-2 homolog, when ectopically expressed in HeLa cells can interact with Mfn2 and induce mitochondrial fusion [47]. Finally, the anti-apoptotic protein Bcl-xL was found to stimulate Drp1 GTPase activity and to promote mitochondrial fission [48]. The function of Bcl-2 family members as regulators of mitochondrial morphology is interesting but requires further investigations. In addition to Bcl-2 family proteins, a number of potential mitofusin-associated proteins has been identified including SLP-2 (stomatin like protein 2 or Stoml2) and mitofusin-binding protein (MIB) [49,50] that could also regulate mitochondrial dynamics.

3. Mitochondrial dynamics: what for?

Mitochondrial fission and fusion appear to be essential for cell function and tissue development. Knockout of OPA1, or Mfn1 and 2 are embryonically lethal in the mouse [51,52], whereas loss of Drp1 is lethal in *C. elegans* [53]. In addition, in human, mutations in OPA1 are causally linked to dominant optic atrophy, the most common form of hereditary optic nerve degeneration [54] and mutations in Mfn2 result in Charcot–Marie-tooth (CMT) type IIa disease, a neuropathy affecting long motor as well as sensory neurons [55,56]. Another CMT disease (type 4a) is associated with mutations in GDAP1 [29,57]. Finally, a mutation in Drp1 has been reported to be associated with a lethal syndrome in a newborn patient [58]. In order to understand the physiopathology of these diseases, it is essential to understand the physiological roles of mitochondrial fission and fusion.

3.1. Mitochondrial dynamics and mitochondrial function

In 1966, Hackenbrock reported that the ultrastructure of mitochondria varies according to their metabolic activity [59]. Upon treatment of tissue sections with ADP, mitochondria that displayed an expanded matrix and thin cristae ('orthodox conformation') adopted a 'condensed conformation' with a dense matrix and large intercristae spaces. The condensed conformation was associated with sustained OXPHOS, whereas the orthodox conformation was associated with reduced oxygen consumption. In addition to the cristae, the entire morphology of mitochondria appears to be modified depending on the OXPHOS activity. Indeed when cells are cultured in the presence of galactose and with reduced levels of glucose, mitochondrial OXPHOS is highly stimulated. This was found to be accompanied by a change in the morphology of the organelle which became thinner and elongated [60]. Conversely, an exchange of the non-fermentable carbon source glycerol by a fermentable medium containing glucose led to mitochondrial fission events in budding yeast [61]. Together these data tend to suggest that mitochondrial fusion and elongation could be associated with increased OXPHOS. This raises an interesting question. Are these morphological changes required for optimal OXPHOS or are they the consequences of changes in OXPHOS activity? Several experiments point to a role of balanced mitochondrial fusion and fission events in the maintenance of mitochondrial integrity. Enforced mitochondrial fusion by down-regulation of proteins responsible for fission such as Drp1 was found to lead to a drop in mitochondrial ATP production, drop in cell proliferation and increased autophagy [62,63]. Yeast cells with a defect in mitochondrial fusion cannot grow on non-fermentable media because their mitochondria are dysfunctional [64]. The cause seems to be a loss of mtDNA indicating that mitochondrial fusion is required for maintenance of mtDNA [64,65]. Accordingly, mouse embryonic fibroblasts (MEFs) lacking OPA1 or both Mfn1 and Mfn2 show severe defects in mitochondrial fusion as well as cellular dysfunction including poor cell growth and decreased oxygen consumption [66]. In addition, in MEF cells ($MFN1^{-/-}$; $MFN2^{-/-}$; $MFN1\&2^{-/-}$; $OPA1^{-/-}$) with mitochondrial fission due to impaired mitochondrial fusion, a loss of mtDNA also occurs explaining at least in part the bioenergetic defects of these cells [67]. Thus, the link between mitochondrial fusion and mtDNA maintenance provides a molecular mechanism for the dependence of respiratory activity on mitochondrial fusion. However, the molecular basis that link mitochondrial fusion and mtDNA maintenance are still unclear.

If mitochondrial fusion influences mitochondrial OXPHOS, the inverse is also true since fusion of mitochondria is dependent on the mitochondrial inner membrane potential ($\Delta\psi$) [68,69] and the OXPHOS activity [62,70]. On the other hand there are many examples of mitochondrial fission being triggered by OXPHOS dysfunction. Pharmacological inhibition of complex I of the respiratory chain is associated with a decreased mitochondrial membrane potential, an increase in ROS production and mitochondrial fission [62]. Similarly, in high glucose conditions an increased ROS production occurs that is mediated by mitochondrial fragmentation, as inhibition of the fission machinery abrogates mitochondrial fragmentation and ROS production. mtDNA mutations caused by ROS could also lead to OXPHOS alterations and mitochondrial fission [71]. A common link between all types of mitochondrial dysfunctions and mitochondrial fission appears to be OPA1 whose proteolysis of the long isoform is a common event in mitochondrial fission [72–74].

3.2. Mitochondrial dynamics during cell cycle

The shape of mitochondria changes during cell cycle progression, possibly according to the cellular energy demand of the cell. During the G1-phase that is associated with a global enhancement of mitochondrial function [75], mitochondria are mainly filamentous and interconnected. In contrast, during late S and M-phases mitochondria are smaller, a phenomenon required for a good segregation of the organelles between the two daughter cells [76–78]. However, for Arakaki and colleagues mitochondria are filamentous throughout the cell cycle phases except during prophase where they observed their condensation around the nucleus [79]. They conclude that this perinuclear localization not only could provide the cell with more ATP – needed in nuclei from prophase to cytokinesis – but could also be required for a proper distribution of mitochondria during cell division. It is unclear how important are the changes in mitochondrial morphology *per se* to ensure a normal cell cycle progression. This question is difficult to answer because the morphology of mitochondria being intrinsically linked to mitochondrial function, attempts to enforce mitochondrial fission or fusion results in mitochondrial dysfunction [62,63]. It then become impossible to decide whether the impact on cell cycle progression is primarily due

to defects in mitochondrial dynamics or is the direct consequence of an impairment of energy production.

3.3. Mitochondrial dynamics, apoptosis and autophagy

During the apoptotic process, mitochondria are permeabilized by pro-apoptotic members of the Bcl-2 family such as Bax and Bak [80–82]. This allows the release of many mitochondrial proteins including cytochrome *c* that once in the cytosol contribute to caspase activation. The mechanisms underlying permeabilization of the outer mitochondrial membrane (MOMP) is still elusive. Recently, mitochondrial fission has been proposed to participate in MOMP. This hypothesis was raised following the observation that mitochondria fragment at the same time as MOMP [83,84]. Importantly, Drp1, Mfn2 and Bax co-localize at mitochondrial fission sites during apoptosis [85]. Either silencing of Fis1 or Drp1 or overexpressing fusion proteins reduce cell death to some extent and impairs cytochrome *c* release induced by several stimuli [23,85–87]. In addition, several reports have pointed to the importance of the fusion protein OPA1 in the mobilization of cytochrome *c* via remodeling of cristae [13,88], which is thought to be the consequence of a loss of OPA1 oligomers [13]. Accordingly, it was recently shown that expression of an OPA1 mutant that forms stable oligomers could prevent cytochrome *c* release and cell death downstream of Bax/Bak activation [89]. Thus, proteins of the fission and fusion machinery appear to play a critical role in MOMP and in the release of mitochondrial apoptogenic factors.

In *C. elegans*, rather than being involved in the core apoptotic program, proteins of the fission machinery as Drp1 and Fis1 appear to play a role later by triggering mitochondrial elimination also called mitophagy [90]. More generally, it seems that damaged mitochondria are eliminated by mitophagy [91] and that a fission of the mitochondrial network into individual units seems to be necessary for efficient mitophagy [92]. This could occur via proteolytically processing of the fusion protein OPA1 occurring in energetically compromised mitochondria [72] or by an increased activity of the fission proteins, such as Fis1, as recently reported by Gomes and Scorrano [93]. As reported by Twig and colleagues, mitophagy could constitute a quality checkpoint for the maintenance of mitochondrial bioenergetics and could prevent aging-related disorders and senescence [94]. Indeed, elimination of damaged mitochondria could stimulate mitochondrial biogenesis and thereby maintain cells with efficient organelles. For example, inhibition of autophagy in yeast results in increased ROS production and a decrease of mitochondrial OXPHOS associated with a higher mtDNA mutation rate [95]. Interestingly a decline of both fusion and fission events has been observed in aged HUVEC cells indicating that these processes are sensitive to aging [96]. Mitochondrial dynamics impairment could contribute to the accumulation of damaged organelles resulting in senescence [96], especially if the processes that are responsible for mitochondrial elimination and mitochondrial turnover are also impaired.

4. Alteration of mitochondrial dynamics in cancer?

Six hallmarks have been proposed by Hanahan and Weinberg to define a cancer cell: independence for growth signals, insensitivity to antigrowth signals, apoptotic resistance, acute replicative potential, sustained angiogenesis and invasive potential [97]. Among these, resistance to apoptosis is of course linked to mitochondria and to proteins involved in mitochondrial dynamics. However, it is unclear whether cancer cells can modify mitochondrial dynamics to acquire resistance to apoptosis. A survey of the morphology of mitochondria and of the proteins involved in this process in cancer cells is required. Since mitochondrial dynamics is essential for preserving the integrity and function of the organelle, it is highly

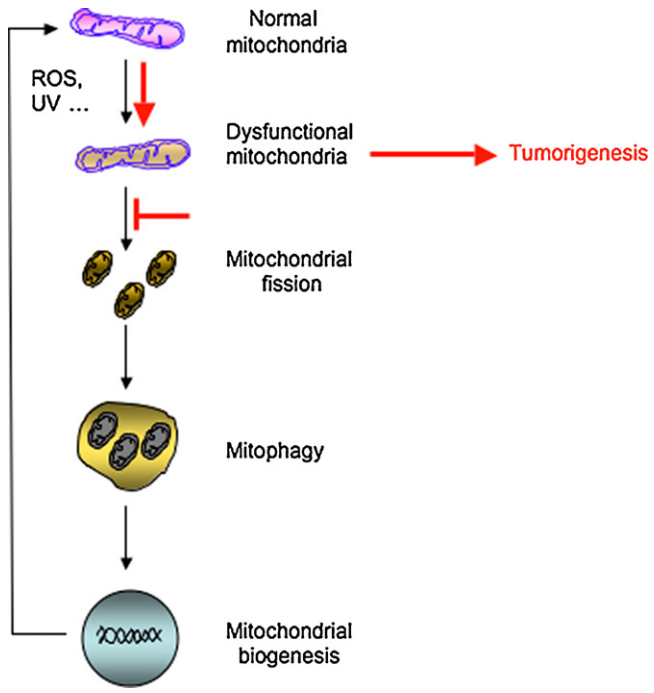

Fig. 2. Model linking a mitochondrial fission defect, accumulation of dysfunctional mitochondria and tumorigenesis. Damaged mitochondria are normally fragmented and eliminated by autophagy (mitophagy). This in turn stimulates mitochondrial biogenesis to ensure a stable pool of functional mitochondria within each cell. In this model, we postulate that mitochondria that are damaged upon production of ROS, mtDNA mutations or deletions, that all lead to respiratory defects, cannot be eliminated because the mitochondrial fission machinery is impaired. Then dysfunctional mitochondria accumulate within cells, causing additional damages that could contribute to tumorigenesis.

possible that mitochondrial dynamics alterations could participate in tumorigenesis by contributing to the accumulation of damaged mitochondria in cells (Fig. 2). In many cancers, mitochondria are known to be dysfunctional, explaining why cancer cells mainly rely on glycolysis to generate ATP (Warburg effect). Even though the Warburg effect could correspond to a cell adaptation to environment pressure (hypoxia for example) and be a way for cells to put mitochondria at rest, it could also be the consequence of mitochondrial damages. Besides a number of mitochondrial protein defects that have been described in the Warburg effect, including alterations of the β subunit of the ATP synthase [98], mutations of the succinate dehydrogenase and fumarate hydratase [99] or of the p53 mitochondrial target SCO_2 (Synthesis of Cytochrome *c* Oxidase 2) [100], mtDNA mutations seem to be frequently encountered in cancer cells [101–103]. These mutations could be the consequence of ROS damages accumulated over time, mtDNA being at risk due to its proximity with the respiratory chain and due to a poor DNA repair machinery. Numerous mitochondrial DNA mutations, deletions and depletions have been identified in cancer cells. Yu and colleagues have demonstrated that reduced mitochondrial DNA copy number could be involved in breast cell transformation or progression [104]. Interestingly, a loss of mtDNA has also been involved in the resistance of anti-oestrogen therapy in breast cancer [105]. In this study, the authors have generated MCF-7 Rho0 cells (totally depleted of mtDNA) and found that they were resistant to tamoxifen. However, upon mtDNA recovery, they again became sensitive to the drug. As discussed above since mitochondrial fusion activity is necessary for mtDNA maintenance, it is possible that an impairment of this process could contribute to the loss of mtDNA observed in some cancers. Moreover, as mitochondrial fission is also important for elimination of damaged mitochondria, it is possible that an impairment of this process may contribute to the accumulation

of damaged mitochondria (Fig. 2). However, it remains to determine whether and how dysfunctional mitochondria could contribute to tumorigenesis.

5. Concluding remarks

In conclusion, our understanding of the mechanisms involved in mitochondrial fusion and fission has considerably progressed over the past few years. However, we still do not know precisely how mitochondrial dynamics can be integrated into cellular physiology. Understanding how various signaling pathways could impinge on mitochondrial dynamics will facilitate our understanding of the physiological role played by this process. It then will be important to test whether these pathways may be altered in cancer cells. It could then become clearer whether targeting proteins of the fission or fusion mitochondrial machinery can be an interesting therapeutic strategy to fight cancer.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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