Changes in skeletal muscle mitochondria in response to the development of type 2 diabetes or prevention by daily wheel running in hyperphagic OLETF rats

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Muscle Mitochondria and Transition to Diabetes

FAOX) and mitochondrial gene and protein expression that occur in a transition from insulin resistance to overt type 2 diabetes in the sedentary OLETF rat to measurements made in two groups that maintain whole body insulin sensitivity by either daily exercise or by being nonobese controls. We have measured MitoFAOX, indices of mitochondrial and oxidative enzymes [citrate synthase and β-hydroxacyl-CoA dehydrogenase (β-HAD) activity], and expression of genes controlling mitochondrial fatty acid oxidation [PGC-1α, PPARδ, silent mating type information regulation 2 homolog 1 (SIRT1), mitochondrial transcription factor A (mtTFA), and AMP-activated protein kinase (AMPK)] protein content in skeletal muscle also were examined. Our overall hypothesis was that skeletal muscle MitoFAOX and mitochondrial function and protein expression would be significantly suppressed in sedentary OLETF rats compared with exercising OLETF rats and sedentary Long-Evans Tokushima Otsuka (LETO) controls. We also hypothesized that the transition from insulin resistance to type 2 diabetes in the sedentary OLETF rat would reveal reductions in skeletal muscle mitochondrial function, protein content, and gene expression, effects that would not occur in exercising OLETF rats.

Methods

Animal protocol. The animal protocol was approved by the Institutional Animal Care and Use Committee at the University of Missouri-Columbia. OLETF and LETO male rats at 4 wk of age were kindly supplied by the Tokushima Research Institute, Otsuka Pharmaceutical (Tokushima, Japan). OLETF animals were randomly separated into those with (OLETF-EX) or without (OLETF-SED) access to running wheels. All LETO animals remained sedentary (LETO-SED). The OLETF-EX group was immediately housed (at the age of 28 days) in cages equipped with voluntary running wheels outfitted with a Sigma Sport BC 800 bicycle computer (Cherry Creek Cyclery, Foster Falls, VA) for measuring daily running activity. Voluntary running was selected to approximate the more natural activity state of OLETF rats with access to running wheels; LETO-SED, sedentary Long-Evans Tokushima Otsuka rats. #Significantly different from 20-wk values within respective animal group (P = 0.001). †Significantly different from LETO-SED at respective age (P = 0.001). ‡Significantly different from OLETF-SED at respective age. Fat pad mass was the combination of omental and retroperitoneal fat pads.

Table 1. Animal characteristics

<table>
<thead>
<tr>
<th>Age, wk</th>
<th>Body Weight, g</th>
<th>%Body Fat, g</th>
<th>g/wk</th>
<th>g/wk⁻¹g body wt⁻¹</th>
<th>Fat Pad Mass, g</th>
<th>HW/BW, mg/g</th>
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<td></td>
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<tr>
<td>20</td>
<td>614.6 ± 8.3</td>
<td>30.6 ± 0.9</td>
<td>227.2 ± 7.0</td>
<td>0.37 ± 0.01</td>
<td>26.3 ± 1.0</td>
<td>2.62 ± 0.05</td>
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<td>40</td>
<td>693.7 ± 38.8#</td>
<td>30.9 ± 4.5</td>
<td>302.6 ± 20.4#</td>
<td>0.45 ± 0.05*</td>
<td>57.1 ± 8.5#</td>
<td>2.67 ± 0.15</td>
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<td>OLETF-EX</td>
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</tr>
<tr>
<td>20</td>
<td>425.6 ± 11.7†</td>
<td>9.4 ± 1.2†</td>
<td>244.3 ± 9.3*</td>
<td>0.58 ± 0.02†*</td>
<td>6.8 ± 1.4†</td>
<td>3.67 ± 0.11†</td>
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<tr>
<td>40</td>
<td>538.5 ± 16.8#†</td>
<td>17.9 ± 2.0#†</td>
<td>228.7 ± 7.4#†</td>
<td>0.43 ± 0.01#†*</td>
<td>15.1 ± 1.8#†</td>
<td>3.07 ± 0.06#†*</td>
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<tr>
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<tr>
<td>20</td>
<td>479.3 ± 7.5†</td>
<td>15.4 ± 1.2†</td>
<td>159.1 ± 1.5†</td>
<td>0.33 ± 0.01</td>
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<td>2.92 ± 0.07</td>
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<td>167.5 ± 5.9#†</td>
<td>0.30 ± 0.01</td>
<td>14.3 ± 1.5#†</td>
<td>2.70 ± 0.04</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 6–8). HW/BW, heart weight/body weight ratio; OLETF-SED, sedentary Otsuka Long-Evans Tokushima fatty rats; OLETF-EX, OLETF rats with access to running wheels; LETO-SED, sedentary Long-Evans Tokushima Otsuka rats. #Significantly different from 20-wk values within respective animal group (P < 0.01). †Significantly different from LETO-SED at respective age (P < 0.01). ‡Significantly different from OLETF-SED at respective age. Fat pad mass was the combination of omental and retroperitoneal fat pads.
weighed. Serum glucose (Sigma, St. Louis, MO), triglycerides (TG; Sigma), free fatty acids (FFA; Wako Chemicals, Richmond, VA), and insulin (Linco Research, St. Charles, MO) were measured using commercially available kits according to the manufacturer’s instructions. Hb A1c concentrations were determined in EDTA-whole blood by the Diabetes Diagnostics Laboratory at the University of Missouri using a boronate-affinity HPLC method (Primus Diagnostics, Kansas City, MO).

Intraperitoneal glucose tolerance test. Five days prior to euthanization, animals underwent a fasted intraperitoneal glucose tolerance test (IPGTT). Food was removed from the cages 12 h before each animal received an intraperitoneal injection of dextrose (50% solution, 2 g/kg body wt). The running wheels were locked 12 h before the IPGTT procedure began. Venipuncture blood samples were collected from the lateral tail vein immediately before dextrose administration and placed into the ABI 7000 Sequence Detection System for polymerization. RNA isolation from the RNeasy kit and with the optional DNase I step (Qiagen). Purity was ensured and concentration determined with a spectrophotometer. Reverse transcription was performed by combining RNA with the reverse transcription reaction mixture (nuclease-free water, ImProm-II 5× reaction buffer, MgCl2, dNTP mix, and ImProm-II reverse transcriptase), and cDNA was synthesized. The reaction mixture [nuclease-free water, β-actin, PGC-1α, PPAR-β, cytochrome c, SIRT1, and mtTFA mRNA expression] was quantified by real-time PCR (Thermo) and ELISA kit (Primus Diagnostics, Kansas City, MO). Western blotting. Western blot analyses were performed for the cytochrome c, PGC-1α, PPAR-β, cytochrome c, SIRT1, and mtTFA mRNA expression. Comparison of the differences in raw Ct values did not differ (P = 0.4) among groups, indicating that β-actin mRNA was an appropriate normalizer.

Western blotting. Western blot analyses were performed for the determination of the protein content of SIRT1 (Santa Cruz Biotech-
ology, Santa Cruz, CA), PGC-1α (Calbiochem, San Diego, CA), PPARβ (Santa Cruz Biotechnology), total cytochrome c (Cell Signaling, Beverly, MA), COX-IV-subunit I (Molecular Probes, Eugene, OR), and AMPKα (Cell Signaling), as described previously (24, 25). To control for equal protein loading and transfer, the membranes were stained with 0.1% amido black (Sigma), as described previously (25). The total protein staining for each lane was quantified, and these values were used to correct for any differences in protein loading or transfer of all band densities.

Superoxide dismutase, catalase, citrate synthase, and β-HAD activity. Superoxide dismutase (SOD) activity in RG homogenate was determined by commercially available methods (Cayman Chemicals, Ann Arbor, MI). Catalase activity in RG homogenate was determined by commercially available methods (Sigma), as described previously (32). Citrate synthase and β-HAD activities were determined in whole RG homogenate using the methods of Srere (29) and Bass et al. (2), respectively, as described previously (24, 25).

Statistics. Each outcome measure was examined in six to eight animals. For each outcome measure, a one-way analysis of variance was performed (SPSS 15.0; SPSS, Chicago, IL) to compare animal groups within a respective age. A significant main effect (P < 0.05) was followed up with Student-Newman-Kuels post hoc comparisons. Unpaired t-tests were utilized to examine differences between 20- and 40-wk values within respective animal groups. Values are reported as means ± SE, and P ≤ 0.05 denotes a statistically significant difference.

RESULTS

Animal characteristics. Similar to what we have reported previously (19, 21), initial running distance at 4 wk of age averaged ~5 km/day (~170 min/day, ~33 m/min), with daily distances peaking between 8 and 11 wk of age (~11–12 km/day, ~275 min/day, ~43 m/min) and declining to ~6–8 km/day (~200 min/day, ~32 m/min) at 20 wk of age, and ~4 km/day (~150 min/day, ~27 m/min) by 40 wk of age in the OLETF-EX rats. It remains unknown why the OLETF animals exhibited decreased voluntary wheel running as they aged, but perhaps the OLETFs appropriately mirror the human condition, in which aging is often associated with reduced physical activity. Consistent with our previous reports (19, 24, 25), body mass, fat pad mass, and body fat percent were significantly greater in the OLETF-SED animals compared with LETO-SED and OLETF-EX at all ages studied (Table 1). A marker of exercise training, higher heart weight/body weight ratio, was found in all OLETF-EX animals compared with OLETF-SED (Table 1).

Absolute weekly food consumption was significantly greater (P < 0.05) in OLETF-SED and OLETF-EX rats at 20 wk, with the OLETF-SED animals consuming more than OLETF-EX and LETO-SED by 40 wk (Table 1). Food consumption relative to body weight was significantly greater in the OLETF-EX animals at 20 wk of age and was significantly greater in both OLETF groups compared with LETO animals at 40 wk of age (Table 1).

Serum characteristics. Serum TG and FFA concentrations were significantly greater in the OLETF-SED animals compared with OLETF-EX and LETO-SED at 20 and 40 wk of age (Table 2). In addition, serum TG levels observed in the OLETF-EX rats were significantly higher than those seen in LETO-SED rats at 20 and 40 wk of age (Table 2). As we have reported previously (19), OLETF-SED animals displayed insulin resistance at 20 wk of age, demonstrated by elevated levels of insulin and glucose compared with OLETF-EX and LETO-SED, and developed overt diabetes mellitus by 40 wk of age with a ~50% drop in serum insulin and a twofold increase in Hb A1C (Table 2), whereas OLETF-EX animals remarkably maintained whole body glycemic control to the level of the LETO-SED animals at all ages studied (Table 2).

IPGTT and glucose transport in skeletal muscle. Differences in peripheral insulin sensitivity estimated by serum glucose, insulin, and Hb A1C levels were confirmed with IPGTT analysis and ex vivo assessment of glucose transport in skeletal muscle. At 20 wk of age, OLETF-SED animals displayed significant peripheral insulin resistance, with both glucose and insulin AUCs being twofold higher than in OLETF-EX and LETO-SED rats (Fig. 1, A and B). In addition, insulin AUC was significantly lower in the OLETF-EX compared with the LETO-SED animals (Fig. 1B). By 40 wk of age, glucose AUC remained significantly higher in the OLETF-SED animals compared with the other groups, but the OLETF-EX had an impaired insulin response (Fig. 1, A and B), suggesting loss of pancreatic insulin secretion in the 40-wk-old OLETF-SED rats. Basal and insulin-stimulated skeletal muscle glucose transport did not differ among groups at 20 wk (Fig. 1, C and D). However, the OLETF-SED rats exhibited a significant 40–50% reduction in basal and insulin-stimulated skeletal muscle glucose transport from 20 to 40 wk. Smaller but statistically significant (P < 0.05) reductions were also observed in the sedentary LETO animals from 20 to 40 wk. On the other hand, skeletal muscle glucose transport was maintained from 20 to 40

![Fig. 2. Changes in superoxide dismutase (SOD: A) and catalase (B) activity in the red gastrocnemius (RG) muscle. Values are means ± SE (n = 6–8). #Significant difference between 20- and 40-wk values within respective animal group (P < 0.01). †Significantly different from OLETF-EX at respective age (P < 0.05). *Significantly different from LETO-SED at respective age (P < 0.05).](http://ajpendo.physiology.org/10.1152/ajpendo.00173.2009)
wk in the OLETF-EX rats (Fig. 1, C and D). This resulted in significantly higher basal and insulin-stimulated glucose transport in the OLETF-EX rats at 40 wk compared with OLETF-SED (Fig. 1, C and D).

**SOD and catalase activities.** SOD activity in the RG did not differ among groups at 20 wk of age but was significantly elevated by 40 wk in the OLETF-SED animals (Fig. 2A). This same pattern was observed in RG catalase activity, with significant increases observed by 40 wk in the OLETF-SED animals (Fig. 2B). Increases in free radical scavengers in the OLETF-SED animals are likely in response to increases in oxidative stress in the skeletal muscle of these animals.

**RG citrate synthase and β-HAD enzyme activities and RG mitochondrial fatty acid oxidation.** RG β-HAD activity did not differ between OLETF-SED and OLETF-EX at 20 wk, but activity levels were significantly higher compared with LETO-SED (P < 0.05; Fig. 3A). However, β-HAD activity dropped ~50% from 20 to 40 wk in OLETF-SED animals, reductions that were not observed in OLETF-EX and LETO-SED rats, and thus led to significantly lower β-HAD levels in the OLETF-SED compared with OLETF-EX at 40 wk (P < 0.01; Fig. 3A). RG citrate synthase activity tended to be higher in OLETF-EX compared with OLETF-SED rats at 20 wk of age (P = 0.06; Fig. 3B) and was significantly higher than in OLETF-SED at 40 wk (P < 0.01). RG citrate synthase activity in LETO-SED animals did not differ from either group at any age examined (Fig. 3B). Both complete (to CO₂) and total (CO₂ and ASMs) MitoFAOX were significantly higher in both OLETF groups compared with LETO animals at 20 wk (Fig. 3, B and D). By 40 wk, complete MitoFAOX was maintained and significantly higher in the OLETF-EX animals compared with other groups (Fig. 3B); however, incomplete and total MitoFAOX were reduced in all groups and did not differ statistically (Fig. 3, C and D).

**Markers of mitochondrial protein content and genes controlling MitoFAOX.** We measured potential regulating factors of MitoFAOX as well as indices of mitochondrial protein content. SIRT1 mRNA did not differ among groups regardless of age but was significantly reduced from 20 to 40 wk in the OLETF-SED animals (Fig. 4A). PGC-1α mRNA was significantly higher at 20 and 40 wk in the OLETF-EX rats compared with OLETF-SED (Fig. 4B). PPARα mRNA expression did not differ among groups at 20 wk but was significantly elevated at 40 wk in the OLETF-EX compared with OLETF-SED and LETO-SED animals (Fig. 4C). Both cytochrome c and mtTFA mRNA were significantly elevated in the exercising OLETFs.
compared with sedentary OLETFs and LETOs at 20 and 40 wk of age (Fig. 4, D and E).

Despite elevated gene expression of several of the mitochondrial markers in the OLETF-EX group, only cytochrome c protein content was significantly elevated in the OLETF-EX compared with both sedentary groups at 20 wk of age (Fig. 5C). In addition, at 20 wk, mitochondrial-encoded COX-IV subunit I protein content was significantly elevated in the RG of OLETF-SED and OLETF-EX animals compared with LETO-SED animals (Fig. 5D). However, by 40 wk, COX-IV content was reduced and no longer significantly different among groups. SIRT1 protein content did not differ among groups regardless of age but did drop significantly by 50–60% in the LETO-SED animals from 20 to 40 wk. In 20-wk-old animals, PGC-1α protein content did not differ among groups. By 40 wk, PGC-1α protein content was reduced in the OLETF-EX rats (P = 0.06) to a level significantly lower than that of LETO-SED (P < 0.05). AMPKα and PPARδ protein content did not differ among groups regardless of age (data not shown).

**DISCUSSION**

Our design allowed a direct comparison of skeletal muscle mitochondrial changes in OLETF-SED rats to two different groups of rats that maintained insulin sensitivity: nonobese sedentary controls (LETO-SED) and OLETF rats that performed daily physical activity (OLETF-EX). During the transition from insulin resistance to type 2 diabetes, OLETF-SED animals did not display significant alterations in skeletal muscle mitochondrial measurements when compared with LETO-SED animals, except for a loss of β-HAD activity. These findings suggest that skeletal muscle mitochondrial dysfunction may not play a role in the transition from insulin resistance to type 2 diabetes, but rather, a constant caloric overload and expanding adiposity may be the primary driver in this hyperphagic animal model. In contrast, significant differences in mitochondrial measurements between the OLETF-SED and OLETF-EX rats were revealed most prominently at 40 wk. Maintenance of insulin sensitivity in the OLETF-EX rats was paired with elevated complete MitoFAOX, elevated β-HAD and citrate synthase activity, and increased markers of mitochondrial gene expression compared with OLETF-SED animals. Whether these exercise-associated changes in mitochondrial measurements are an obligatory feature or merely associated with the maintenance of insulin sensitivity remains unknown. Regardless, daily physical activity and higher energy expenditure completely protected against insulin resistance in the hyperphagic OLETF rat.
The role of skeletal muscle mitochondrial dysfunction in the development of insulin resistance and type 2 diabetes is highly debated (11). High-fat diets are commonly used to induce insulin resistance but can also trigger increased mitochondrial content and fatty acid oxidation (8), contradicting the hypothesis that impaired mitochondrial lipid metabolism is a cause of insulin resistance. In the OLETF-SED rats, excessive consumption of normal chow (16% of energy from fat) led to elevated circulating FFAs, which putatively increased mitochondrial enzyme activities and MitoFAOX in muscle to levels witnessed in OLETF-EX rats at 20 wk, both of which were higher than in LETO-SED. Thus, sedentary-hypercaloric conditions paired with insulin resistance evoked similar changes in mitochondrial measurements, as did daily physical activity and prevention of insulin resistance at 20 wk. It was only at 40 wk that the OLETF-EX rats displayed higher measurements of mitochondrial function, with the most prominent differences being revealed for complete vs. incomplete MitoFAOX.

High-fat feeding has been shown to induce glucose intolerance in association with high rates of incomplete fatty acid oxidation (flux through β-oxidation is higher than flux through the TCA cycle), resulting in the intramuscular accumulation of lipid metabolites (15). In the same study, exercise training enabled a coordinated regulation of β-oxidative flux, TCA cycle activity, and enhanced skeletal muscle mitochondrial capacity to completely oxidize fatty acids, which coincided with lower metabolite accumulation and improved glucose tolerance (15). In addition, prevention of mitochondrial fatty acid entry during high-lipid conditions protects against insulin resistance in part through reduced accumulation of lipid metabolites (17). In support of these findings, complete (to CO2) MitoFAOX was ~25% higher in the exercising OLETF rats compared with LETO and OLETF sedentary animals at 40 wk of age. The maintenance of complete MitoFAOX occurred in conjunction with the conservation of glycemic control. Whether complete degradation of fatty acids in the isolated mitochondria in the OLETF-EX rats plays a primary role in maintaining insulin sensitivity or is merely an associated factor remains unanswered, but one could speculate a metabolic benefit by decreasing fat storage and less production of incomplete metabolites.

The overall importance of MitoFAOX in the development of insulin resistance is complicated by the drawbacks of assessing lipid metabolism with in vitro maximal capacity methods. As stated previously (11), it is unlikely that the mitochondrial capacity is ever reached in skeletal muscle of sedentary rats during fasting or fed conditions. It also is unlikely that voluntary wheel running evoked a maximal capacity response in the mitochondria of the OLETF-EX, especially at later time points, because daily running distances began to fall off. Therefore, future studies that measure lipid metabolism with indirect calorimetry or with tracers at the whole body level, rather than just in vitro capacity means, are needed to elucidate the true role of MitoFAOX in the development of insulin resistance. Furthermore, the importance of whole body measurements of fatty acid oxidation has recently been reinforced by Hoehn et al. (10), showing that raising fatty acid oxidation through pharmacological or genomic methods without raising total energy expenditure does not positively affect adiposity or insulin sensitivity.

PGC-1α is known to coactivate multiple mitochondrial transcription factors, including PPARδ (35), leading to the upregulation in fatty acid oxidation, in part through increased PGC-1α protein stability by the protein deacetylase SIRT1 and through mtTFA activation, a key component in transcription of multiple

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**Fig. 5. Changes in silent SIRT1 (A), PGC-1α (B), cytochrome c (C), and cytochrome c oxidase IV (COX-IV)-subunit I protein content (D) in the RG muscle. Values are means ± SE (n = 5–8). #Significant difference between 20- and 40-wk values within respective animal group (P < 0.05). †Significantly different from OLETF-SED at respective age (P < 0.05). *Significantly different from LETO-SED at respective age (P < 0.05). AU, arbitrary units.**
oxidative genes, including cytochrome c (6). In the sedentary OLETF and LETO animals, the gene expression and protein content of many of these factors did not differ between groups and remained largely unchanged from 20 to 40 wk despite a large reduction in total MitoFAOX, suggesting the lack of a primary role in skeletal muscle MitoFAOX. However, the one exception was mitochondrial-encoded COX IV-subunit I protein content, which was significantly higher in OLETF-SED and OLETF-EX compared with LETO-SED at 20 wk and dropped to the LETO-SED levels by 40 wk. The elevation and subsequent reduction corresponded with the reductions seen in total MitoFAOX in both the OLETF-EX and OLETF-SED groups from 20 to 40 wk.

Previous exercise training studies have demonstrated increases in skeletal muscle fatty acid oxidation (1, 16), PGC-1α mRNA content (23), mitochondrial size and number (7, 12), and normalization of skeletal muscle mitochondrial content in patients with type 2 diabetes (33). Using daily voluntary wheel running to prevent type 2 diabetes in the current study, OLETF-EX rats had ~50% higher skeletal muscle PGC-1α, mtTFAM, and cytochrome c mRNA levels at 20 and 40 wk in the OLETF-EX compared with OLETF-SED rats. However, despite elevated gene expression, only the protein content of total cytochrome c was higher at 20 wk in the OLETF-EX rat. This suggests that either posttranscriptional modifications are affecting protein translation or stability in the skeletal muscle of the hyperphagic OLETF-EX animals or the decline/reduced intensity in daily running distance may be playing a significant role.

In conclusion, under sedentary conditions, skeletal muscle mitochondrial dysfunction and insulin resistance. We have previously shown that 16 wk of daily voluntary exercise in the OLETF rat was associated with lower levels of lipid peroxidation without significant changes in intramyocellular lipids (21). In the current report, OLETF-SED rats exhibited increases in SOD and catalase activity from 20 to 40 wk when the health of the animal deteriorated, changes not witnessed in OLETF-EX and LETO-SED rats. These are likely responses to increased production of reactive oxygen species in the skeletal muscle of OLETF-SED animals and suggest that increased oxidative stress may be involved in the disease progression but likely do not mediate the changes observed in mitochondrial measurements in this report.

In conclusion, under sedentary conditions, skeletal muscle mitochondrial dysfunction does not appear to be associated with the transition from insulin resistance to type 2 diabetes in the hyperphagic OLETF rat. Rather, expanding adiposity and hyperlipidemia may play a more primary role. However, chronic prevention of type 2 diabetes through increased daily physical activity in hyperphagic conditions is associated with the maintenance or enhancement of skeletal muscle mitochondrial enzyme activity and fatty acid oxidation. Future studies are needed to elucidate whether the mitochondrial changes evoked by daily physical activity are obligatory or merely associated with the maintenance of insulin sensitivity.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


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