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Role of SREBP and related molecules in the development of endometrial cancer

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Oncogenic growth signal regulates glucose, glutamine and lipid metabolism to provide the bioenergy and biosynthetic requirements of rapidly dividing tumor cells. A class of membrane-bound transcription factors known as sterol regulatory element-binding proteins (SREBPs) activate the genes encoding the enzymes required to produce cholesterol and unsaturated fatty acids. In this study, we discussed the anticancer role of SREBP and its target genes, lipid and cholesterol metabolism enzymes in the development of endometrial cancer. This study comprised 45 patients with endometrial adenocarcinoma, who were further categorized into Grade 1 (n = 15), Grade 2 (n = 15), and Grade 3 (n = 15). The control group consisted of 29 endometrial tissues without an endometrial cancer diagnosis. SREBP, ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), acetyl CoA acetyltransferase (ACAT) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) gene expressions were examined using the real-time polymerase chain reaction (RT-PCR) method. The gene expressions of the patient group were higher than the control group (P <0.05), and there were differences between the grades of the patient group (P <0.05). In general comparison, it was observed that SREBP expression increased in the patient group compared to the control group. While the SREBF1 increased in grade 2 (p=0.0001), the SREBF2 increased in grade 1(p=0.0001). The findings imply that whereas lipogenesis might exhibit various tissue-specific behaviours linked to a few pathways, it might also have a direct connection to endometrial cancer.

Keywords: Cholesterol, Endometrial adenocarcinoma, Gene expressions, Lipogenesis, Sterol regulatory element-binding proteins (SREBP)

Endometrial carcinoma (EC) is the most prevalent gynaecological malignancy and its shows increasing incidence in the developed nations[1,2]. The important risk factors for the disease are increased estrogen, obesity, tamoxifen, age, early menarche and late menopause[3]. Based on the histological characteristics, hormone receptor expression and grade, the EC has been categorized into two types[4]. To supply energy, lipid signaling and the synthesis of membranes, proliferative cancer cells frequently develop high lipid content[5]. While cancer cells are advanced in synthesizing lipids, they also show high performance in lipid uptake[6]. Studies have reported that an increase in enzymes related to fatty acid and cholesterol synthesis is necessary for tumor development[7]. According to research on cancer cell metabolism, metabolic reprogramming can be considered a characteristic of cancer[8].

Lipid synthesis, degradation, and storage are all parts of lipid metabolism. The essential lipid for cell proliferation, differentiation, and membrane biosynthesis is cholesterol. It also acts as a precursor for steroid hormones and sterols, which activate biological processes. More intracellular cholesterol was shown to be produced by tumor cells than by healthy cells[9]. Sterol regulatory element-binding proteins (SREBPs), which are active in cholesterol de novo synthesis along with lipogenesis, are also one of the most studied transcription factors[10]. The SREBF1 and SREBF2 genes encode three SREBP isoforms (SREBP-1a, SREBP-1c, and SREBP-2) that have been found in mammalian cells. According to studies, SREBP1s control fatty acid metabolism while SREBP2 primarily controls cholesterol metabolism (Fig. 1) [11].

Reprogramming of lipid metabolism is a crucial indicator of tumor development[11]. Cholesterol and fatty acids work together to create phosphoglycerides, which are then used to construct cell membranes. Lipid droplets are used to store cholesterylethers and triacylglycerides. These functions can also be served by lipids derived from external sources. When energy is required, fatty acids released from lipid reserves can be oxidized in the mitochondria. SREBPs control a large number of enzymes involved in the manufacture of fatty acids and cholesterol[12].

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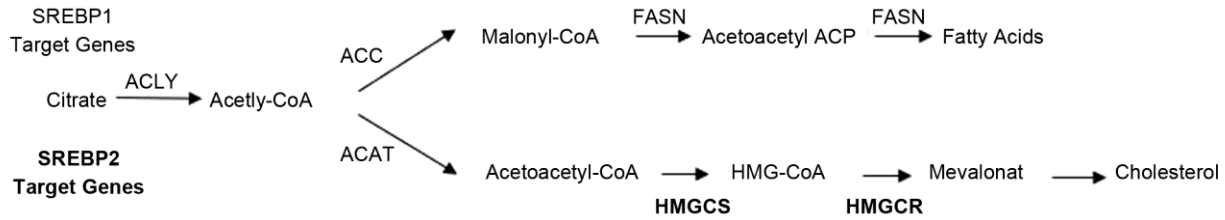

Fig. 1 — Important enzymes involved in fatty acid and cholesterol biosynthesis targeted by SREBPs [Enzymes involved in the cholesterol pathway are in bold]

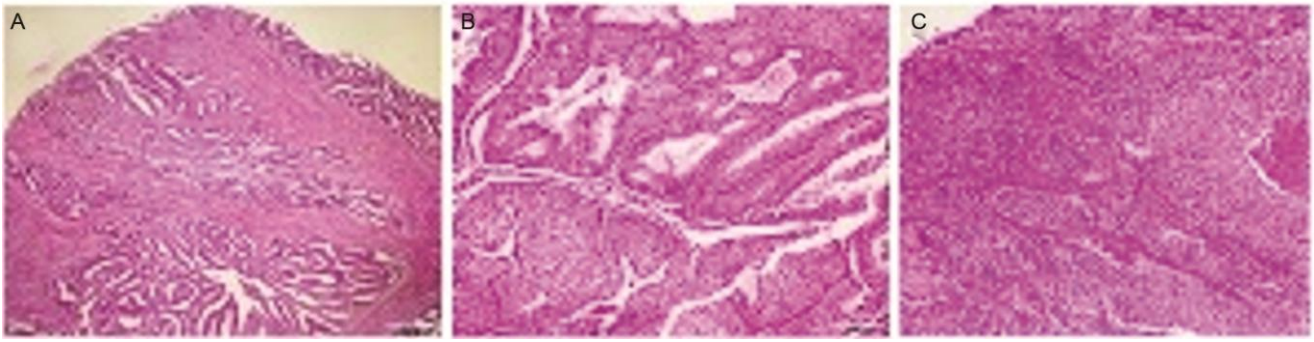

Fig. 2 — Determination of target tissues by marking in archive tissue preparations. (A-C) Endometrial adenocarcinom Grade 1-3, respectively

Linking two important pathways, glycolysis and lipid metabolism, ATP-citrate lyase (ACLY) synthesizes an essential cellular building block, cytosolic acetyl coenzyme A (acetyl-CoA). Abnormal ACLY activity is observed in many diseases[13,14]. Acetyl-CoA is the necessary precursor molecule of cholesterol and de novo lipid synthesis. The most important step in fatty acid biosynthesis is the activation of acetyl-CoA to malonyl-CoA, and energy is needed in this step catalyzed by acetyl-CoA carboxylase (ACC)[15]. There are two forms of ACC encoded by different genes, ACC-alpha (ACCa) and ACC-beta (ACCβ). Alpha is encoded by the ACACA gene and beta by the ACACB gene[16]. Later in the pathway, acetyl and malonyl groups bind to the acyl carrier protein domain of the multifunctional enzyme fatty acid synthase (FASN)[17]. Acetyl CoA acetyltransferase (ACAT), which is an active enzyme in lipogenesis, has two isoforms, ACAT1 and ACAT2[18]. 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is the rate-limiting enzyme of the cholesterol synthesis pathway. Inhibition of these enzymes can affect cancer cell growth if cholesterol availability is reduced. Also, some inhibitors of the mentioned enzymes have effects on cancer treatment[19].

De novo lipogenesis and cholesterol metabolism are crucial in endometrial cancer. In this study, we examined the gene expressions of the transcription factor SREBPs and the related enzymes ACLY, ACC, FASN, HMGCR and ACAT, which are involved in the lipogenesis pathway.

Materials and Methods

A total of 74 formalin-fixed, paraffin-embedded (FFPE) archival tissues were included in the study in four groups viz Gr. I-III, endometrioid adenocarcinoma grade 1 (n=15),grade 2 (n=15) andgrade 3 (n=15); and Control Group with endometrial tissues without endometrial cancer diagnosis (n=29). These FFPE tissue samples were prospectively obtained from the Departments of Obstetrics and Gynecology and Pathology, Faculty of Medicine, Mersin University between 2010-2020.

According to their differentiation, the study samples which were from endometrioid adenocarcinoma patients without any mention of prognosis were divided into Grades 1, 2 and 3. The International Federation of Gynecology and Obstetrics (FIGO) grading system for uterine corpus carcinomas, which is based on the following components of structure, only technically classifies endometrioid carcinomas[20]: Nonsquamous solid growth pattern ≤5% as grade 1; 6-50% grade 2; and >50% as grade 3. Samples with little or no necrosis and no detection-tracking artifact were examined using a microscope, the appropriate areas were marked on the preparations (Fig. 2). The marked regions were then used to extract the correct regions

from microtome sections from FFPE tissue blocks. Microtome sections of 4 mm diameter and 10 µm thickness were taken from the paraffin block and transferred to clean slides. Afterward, 8-10 leaf tissue samples were taken from the slides.

The innuPREP FFPE Total RNA Kit from Analytikjena (PN: 845-KS-2050050 / Jena, Germany) was used to separate the sample from the paraffin block by its instructions. After the necessary procedures were done, total RNA was filtered into the tube for cDNA extraction. High-Capacity cDNA Reverse Transcription Kits from Appliedbiosystems (PN: 4375222 Carlsbad, CA, USA), was used to convert the RNAs we obtain into complementary DNA.

The cDNA was amplified in TaqMan Universal PCR master mix from Appliedbiosystems (PN: 4371135 / Carlsbad, CA, USA) with previously developed TaqMan test primers and probes, Hs01088691_m1 (SREBF1*)*, Hs01081784_m1 (SREBF2), Hs01005622_m1 (FASN), Hs01046047_m1 (ACACA), Hs01565914_m1 (ACACB), Hs00982738_m1 (ACLY), Hs00608002_m1 (ACAT1), Hs01125541_m1 (ACAT2), Hs00168352_m1 (HMGCR) and ACTB Hs99999903_m1 as the housekeeping gene (Thermo Fisher Scientific). In the incubation phase of the Real-Time PCR protocol; It is kept at 50ºC for 2 min to activate the UDG enzyme. AmpliTaq Gold is kept at 95ºC for 10 min to activate the UP enzyme.

Amplification was carried out in two stages: step 1, the transition of DNA from double-stranded to single-stranded structure (denaturation) for 15 s at 95^{o}C; and step 2, beta-actin was used as an endogenous control in the quantitative analysis of RT-PCR to normalize the distinguishing expression of tissues. Delta Ct (ΔCt) and $2^{-\Delta\Delta Ct}$ values were calculated and used in statistical analysis[21].

Statistical analysis

The results were analysed using the IBM SPSS Statistics software program. Since the variables did not show the normal distribution in the comparisons between the groups, the Mann-Whitney U test was used for the comparisons of two groups, and the Kruskal-Wallis H test was used for the comparisons of more than two groups. Shapiro-Wilk test was used for the normality test. Spearman analysis was used for correlation analysis. *P* values less than 0.05 were considered significant.

Results

This study included 45 patients with endometrioid adenocarcinoma as well as 29 healthy subjects. The mean age of the patient group was 52.47 ± 5.082, while the mean age of the control group was 42.60 ± 4.063. The SREBF1, SREBF2, ACLY, ACACA, ACACB, FASN, ACAT1, ACAT2, and HMGCR gene expressions were determined. When the differences between the means of gene expressions were examined, it was found that the mean of the patient group was higher than the mean of the control group and was statistically significant (*P* <0.05) (Table 1).

When the patients were compared according to their grades, significant differences were found between the groups (*P* <0.05) (Table 2). According to the Post Hoc test results, a significant difference was found between the control and grade 1 (p:0.0001), grade 2 (p:0.0001) and grade 3 (p:0.0001), respectively. However, there was no difference between the grades (*P* >0.05).

Table 1 — Comparison of baseline characteristics of Patients and the Controls

Genes	Controls (n = 29)	Patients (n = 45)	P value
SREBF1	0,056±0,070	3,388±4,454	0.0001*
SREBF2	0,046±0,050	2,989±3,167	0.0001*
ACLY	0,741±1,101	5,993±3,590	0.0001*
ACACA	0,253±0,325	6,854±4,131	0.0001*
ACACB	0,260±0,335	2,058±1,629	0.0001*
FASN	0,582±0,855	6,968±3,751	0.0001*
ACAT1	0,068±0,085	3,181±4,261	0.0001*
ACAT2	0,010±0,008	4,443±4,511	0.0001*
HMGCR	0,098±0,138	4,898±5,481	0.0001*

[Values are Mean±SD. * *P* <0.05]

Table 2 — Comparison of baseline characteristics of case Grades 1-3 and the Controls

Genes	Controls (n = 29)	Grade1 (n = 15)	Grade2 (n = 15)	Grade3 (n = 15)	P value
SREBF1	0,056±0,070	3,520±3,983	4,293±6,418	2,352±1,797	0.0001*
SREBF2	0,046±0,050	4,015±5,039	3,003±1,745	1,950±0,892	0.0001*
ACLY	0,741±1,101	6,782±4,752	5,856±2,199	5,340±3,455	0.0001*
ACACA	0,253±0,325	8,907±5,785	6,320±3,010	5,336±1,952	0.0001*
ACACB	0,260±0,335	2,378±1,459	2,000±1,954	1,796±1,485	0.0001*
FASN	0,582±0,855	7,327±4,886	6,126±2,994	7,450±3,199	0.0001*
ACAT1	0,068±0,085	3,094±3,753	3,823±6,010	2,627±2,464	0.0001*
ACAT2	0,010±0,008	4,502±3,296	5,100±6,347	3,729±3,433	0.0001*
HMGCR	0,098±0,138	6,471±6,451	5,109±6,708	3,113±1,305	0.0001*

[Values are Mean±SD. * *P* <0.05]

Expression of lipogenesis-related genes

When the FASN gene expression level was compared with the control group, it increased in the patient groups and showed a significant difference (p=0.001). Although not statistically significant, grade 3 is higher than other patient groups (Fig. 3). SREBF1 gene expression was increased in the patient groups compared to the control group, and the grade 2 patient group was found to be higher than the other patient groups, although it was not statistically significant (Fig. 3). Expressions of ACACA, ACLY, and ACACB are higher in the patient groups compared to the control group. When the patient groups were compared with each other, no statistically significant difference was found, but when the averages were considered, it was determined that the highest level was found in the grade 1 group in all three genes (Fig. 3).

Expression of cholesterol-related genes

Similar to lipogenesis, the results obtained in cholesterol-related genes were compared with the control group, an increase in expression was found in the patient groups and a statistically significant difference was found (P <0.05). When the mean values were compared in the patient groups, we observed that *ACAT1* and *ACAT2* gene expression increased by grade 2, while SREBF2 and HMGCR gene expression increased by grade 1, although there was no statistical significance (Fig. 4).

Discussion

In affluent nations, endometrial cancer is the fourth most common gynecological cancer, and its incidence is rising each year[22]. Being able to inhibit genes involved in the lipid metabolism pathway is thought to be an effective method for antitumor therapy in EC[23].Consequently, it may be claimed that lipid metabolism is crucial for understanding tumor biology[24].

As a novel anticancer strategy, targeting the mechanisms controlling lipid metabolism has remained popular[6]. Levels of sterol and intracellular insulin control the expression of SREBP, a gene that regulates lipogenesis. In the study investigating the SREBP1 gene expression in polycystic ovarian syndrome and endometrial cancer, it was discovered that the patient group had much higher levels of SREBP1 gene expression compared to the controls[25]. In a study highlighting the importance of SREBP-2 in cancer cells and oncogenesis, the combination of

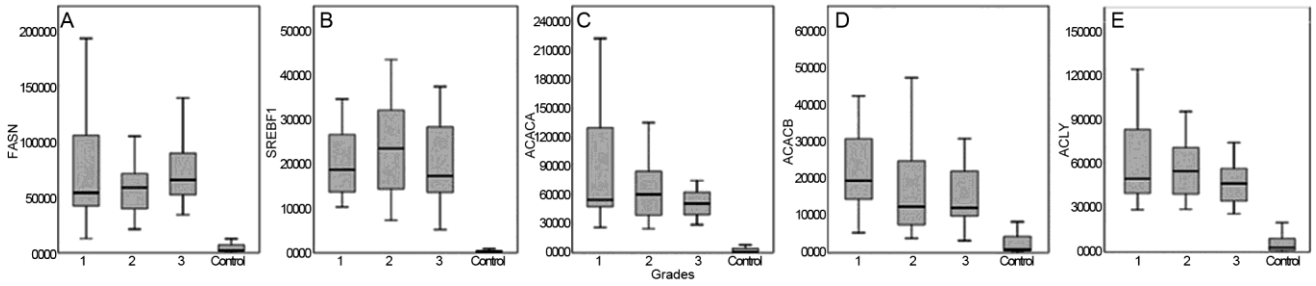

Fig. 3 — Expression of lipogenesis-related genes. Comparison of (A) FASN; (B) SREBF1; (C) ACACA; (D) ACACB; and (E) ACLY delta ct values

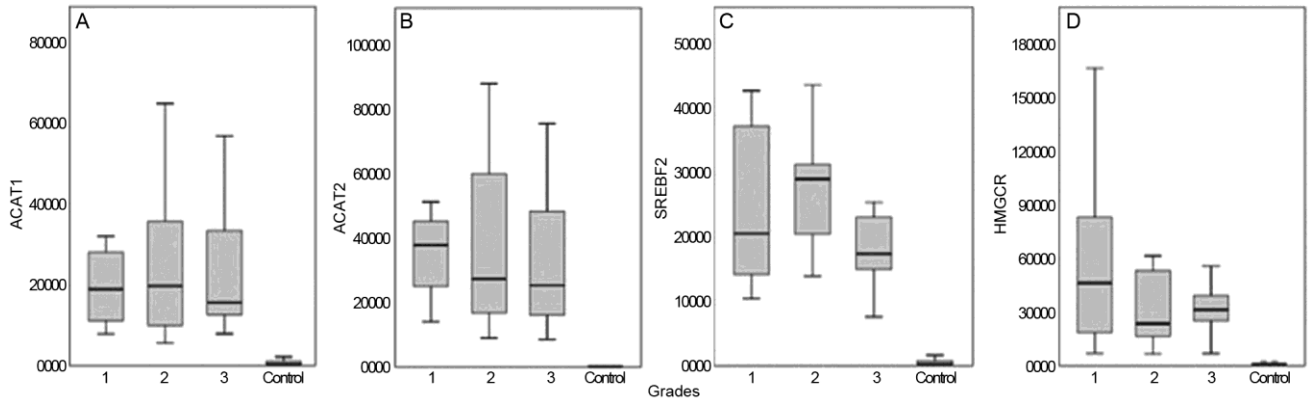

Fig. 4 — Expression of cholesterol-related genes. A. Comparison of (A) ACAT1; (B) ACAT2; (C) SREBF2; and (D) HMGCR delta ct values

SREBP-2 and SREBP-1 in cancer cell lines induces EC stress and induces apoptosis in lipoprotein-depleted conditions[11]. Here, SREBP1 and SREBP2 gene expression increased in the patient group compared to the control group. Our results, which agree with the results of other cancer studies, suggest that inhibiting SREBPs with pharmacological agents or at the molecular level can significantly suppress tumor growth and induce cancer cell death, making SREBPs promising therapeutic targets.

SREBPs are interesting therapeutic targets because they greatly reduce tumor development and trigger cancer cell death when they are genetically or chemically inhibited[26, 27]. Yet, it is difficult to directly inhibit SREBPs since transcription factors are frequently unsuitable candidates for pharmacological targets. Preventing SREBP from moving from the ER to the Golgi is a more effective strategy. Accordingly, fatostatin, botulin and PF-429242 have all been demonstrated in pre-clinical tests to block SREBP activation and exhibit promising antitumor properties[28].

An essential mechanism connecting the glycolytic pathway and lipid metabolism is the transition from coenzyme A to acetyl-CoA and oxaloacetate. This transition's involvement in ACLY inhibition has been shown to reduce cancer cell growth and trigger apoptosis, indicating the therapeutic potential of ACLY inhibitors in cancer therapy[29]. Consistent with the evidence, ACLY expression increased in the EC patient group in the results of our study. Among the grades, expression was highest in the grade 1 group, which is the onset of the disease. Upregulation of ACC in the next step after ACLY supports the orientation towards fatty acid synthesis. In addition, the increase in grade 1 promotes a shift of metabolism to lipogenesis for cell remodeling.

Most studies have identified the upregulation of ACACA and the downregulation of ACACB[30]. In some studies, like our study, up-regulation of ACACA and ACACB was determined, and the reason has not been fully understood yet. According to our results, the upregulation of ACCs in the endometrial cancer group suggested that fatty acid synthesis was stimulated, and beta-oxidation was inhibited for cell remodeling. In this case, significant suppression of tumor cell growth can be achieved by inhibiting ACCs. In addition, when the patient group averages are compared, the grade 1 increase in both ACC indicates that fatty acid synthesis is active in the first stage of the disease.

The primary enzyme that catalyzes the last step in the *de novo* synthesis of fatty acids, FASN, has been thoroughly studied in several cancers[31,32]. It has been reported that this situation was also correlated with poor prognosis in cancer types where increased fatty acid synthesis is observed due to the increase in FASN[33]. As a result of our study, it has been determined that FASN expression increased in endometrial cancer patients, like many studies.

Cholesterol is essential for the functions of malignant cells, including membrane integrity, cell signaling, and protein synthesis[34]. Recent research has demonstrated that the control of cholesterol levels in relation to the tumor environment is crucial for the growth of tumor cells. Additionally, cholesterol metabolism regulates ferroptosis, autophagy, tumor and immune cell stemness, as well as the cellular response to DNA damage[35]. The rate-limiting enzyme in endogenous cholesterol biosynthesis is HMGCR, which has been associated with tumor cell growth and proliferation[36]. In the current study, HMGCR expression increased in the EC group and when we evaluated it according to the averages, it was found to increase in Grade 1. Also, HMGCR is upregulated by SREBP-2, which is one of the main regulatory transcription factors of cholesterol metabolism[37,38]. Consistency between SREBP-2 and HMGCR in our results has been promising for the development of a new antitumor therapeutic strategy.

Statins anticancer properties have been investigated for several cancer types in both pre-clinical and in patients. The anticancer benefits of statins may be diminished if cholesterol synthesis is inhibited since this can result in the feedback activation of SREBPs. Consequently, combination treatments that block both cholesterol production and SREBP activation are being created[39].

ACAT1 and ACAT2 have been revealed in studies to be possible therapeutic targets and indicators in neoplastic tissues that may affect cancer prognosis[40]. In the ketogenesis pathway, the tetrameric enzyme ACAT1 transforms two acetyl-CoA molecules into acetyl-CoA and CoA. According to studies, ACAT1 may be an effective anticancer target[41]. ACAT2, which is crucial for lipid metabolism, has been downregulated, and studies have linked this to a worse prognosis for cancer-specific survival[42]. ACAT

protein expression in ovarian cancer cells increased significantly in both isoforms of Western blot analysis as compared to control cells, and this finding was also correlated with qRT-PCR and ELISA data[43].

On the little known function of ACAT1 and ACAT2 in endometrial cancer, we showed that ACAT1 and ACAT2 are upregulated in EC tissues. In addition, increased expression of both genes was higher in the grade 2 group, suggesting that it may be associated with malignant progression. This result indicates that ACATs may be a new therapeutic target for EC.

As a result, additional thorough research is still required to fully comprehend SREPB1 and its potential clinical application, including studies of its regulation of expression, roles in different cell processes, signal pathways, and interrelated key regulators. Studies on the SREBPS and enzymes in the lipid and cholesterol pathways to maintain women's fertility with less or non-invasive interventions will shed light on the development of diagnosis and treatment strategies for the disease due to the increasing incidence of endometrial cancer in women.

Conclusion

The above findings show the functional significance of lipid production mediated by SREBP in endometrial carcinoma (EC). However, unresolved problems in the processes governing lipid synthesis, storage, and metabolic pathway flow in cancer cells pose an obstacle to the development of cancer treatments. The effectiveness of lipid and cholesterol metabolism in the treatment and prevention of EC requires further recommendations and procedures that can be determined by experimental, clinical, *in vivo* and *in vitro* research.

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Conflict of Interest

Authors declare no competing interests.

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