Interaction of Exosomal MicroRNA and Oxidative Stress in the Pathogenesis of Colitis-Associated Cancer

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1. Introduction

Colorectal cancer (CRC) ranks as the third most common cancer among both men and women in the United States, and is the third leading cause of cancer-related mortality. In 2023, about 153,020 people were diagnosed with CRC, and 52,550 people are expected to die from the disease [1]. Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn’s disease, is an chronic inflammatory condition of the gastrointestinal tract [2]. IBD-associated CRC is worse than non-IBD-associated CRC [3]. Unlike sporadic CRC, which develops from normal colonic mucosa via the progressive accumulation of genetic alterations, colitis-associated cancer (CAC) follows an inflammation–dysplasia–carcinoma progression track. The incidence rate of CRC in IBD patients increases with duration of the illness, as confirmed by a meta-analysis, which showed that the cumulative risk of CRC for patients with UC was 2% at 10 years, 8% at 20 years, and 18% at 30 years [4]. The exact cause of IBD progression to CRC remains unknown; however, the inflammatory reaction of the intestinal mucosa upon exposure to oxidative stress (OS) is considered to be a significant factor in the transition from IBD to CAC [5–7].

OS is caused by an imbalance between free radicals and antioxidants [8]. Under physiological conditions, cells have a certain degree of antioxidant capacity. However, when the increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) is beyond the tolerance level of the cells, OS occurs. This results in DNA, protein, and lipid damage, inducing gene mutation, protein degradation, and lipid peroxidation, respectively, causing physiological and pathological reactions in cells and tissues. Patients with cancer have higher OS levels than the healthy population. Cancer cells have increased levels of nicotinamide-adenine dinucleotide phosphate (NADP), which protects cells from ROS by generating reduced forms of glutathione (GSH) and thioredoxin (Trx) [9,10].

Recently, extracellular vesicles originating from cell membranes have received much attention. Exosomes are small extracellular vesicles that are secreted by cells when multivesicular endosomes fuse with the plasma membrane. They are abundant in bioactive molecules such as proteins, lipids, and nucleic acids, serving as vehicles for cell-to-cell communication [11,12]. During cancer progression, tumor cells secrete exosomes containing cancer-causing proteins and nucleic acids that act on other cells, affecting the function of those cells and reprogramming them. The secretion of microRNA (miRNA) by tumor-associated exosomes not only promotes tumor growth but also changes the tumor microenvironment (TME), providing a favorable environment for further tumor growth [13,14].

MiRNAs are a group of non-coding RNAs composed of 18–22 nucleotides, which play a pivotal role in gene expression regulation by targeting mRNAs. They suppress mRNA translation through specific sequence motifs, typically found in the mRNA 3′ untranslated (UTR) region,
2. Oxidative Stress and Colitis-Associated Cancer

2.1 Oxidative Stress (OS)

OS is triggered by an imbalance between ROS production and antioxidant defense activity. ROS include hydrogen peroxide ($H_2O_2$), superoxide anion, hydroxyl radical, singlet oxygen, and ozone. In addition to ROS, RNS are also important in OS [17]. Because they do not contain paired electrons, they have high chemical reactivity. Mitochondria are the main source of ROS in the cell through the mitochondrial electron transport chain [18]. Endogenous ROS can also arise from catalytic reactions by enzymes such as peroxidase, NADPH oxidase (NOX), nitric oxide (NO) synthase, xanthine oxidoreductase, lipoygenase, cyclooxygenase (COX), and myeloperoxidase [19].

2.2 Role of OS in the Pathogenesis of CAC

CAC correlates with weakened antioxidant defenses and increased oxidative damage to proteins and DNA [20]. During the onset of IBD, inflammatory cell infiltration and crypt abscesses in the small intestine occur. Infiltrating neutrophils produce a large amount of ROS, which in turn cause OS. Because OS damages the intestinal mucosal barrier, harmful bacteria can infiltrate and inflammation will worsen [21]. Under normal circumstances, intestinal ROS play a key role in defenses against invading pathogens. However, when the host produces too much ROS, it can damage proteins, lipids, and nucleic acids, eventually leading to cancer. Prolonged OS can result in the oxidation of biomolecules or the activation of inflammatory signaling pathways [22].

2.2.1 Direct Oxidative Damage

ROS have the potential to cause DNA and protein damage, lipid peroxidation, genetic mutations, and cell death. ROS/RNS can react with protein amino acid residues to undergo protein oxidative modification, which is divided into two categories: reversible and irreversible oxidation. The protein adducts modified by oxidation include carboxylation, 3-nitrohydrocarbons, s-sulfidation, s-nitrosylation, s-GSH, and disulfide formation [23]. Cysteine is the residue in protein that most frequently undergoes reversible redox reactions with ROS/reactive halogen species [24].

ROS can disrupt double-stranded DNA; distort purines, pyrimidines, and deoxyribose; and induce transcriptional inhibition or activation, replication, and errors, all of which are linked to carcinogenesis [25]. The DNA damage caused by inflammatory OS is the main reason why patients with IBD are prone to cancer. One of the most researched oxidative metabolites, 8-hydroxy-2-deoxyguanosine, is thought to be a biomarker of DNA oxidative damage [26].

ROS is easily bound to unsaturated fatty acids, triggering free radical chain reactions of fatty acid radicals, peroxyfatty acid radicals, and electrophilic carbonyl groups [27]. Phospholipids are rich in unsaturated fatty acids and mainly participate in the formation of cell and organelle membranes. When OS occurs, excessive ROS leads to mitochondrial damage, oxidative respiratory chain disorders produce more ROS, and membrane damage causes the release of more ROS into the cytoplasm, resulting in a vicious cycle that leads to cell death and tissue damage [28]. Endoplasmic reticulum membrane peroxidation, in which calcium enters the cytoplasm, can promote the generation of nitric oxide, further exacerbating OS [29]. OS leads to lipid peroxidation, and the final product of the free radical chain reaction, malondialdehyde (MDA), reacts with DNA to form an MDA–DNA complex. MDA–DNA complexes can induce mutations in oncogenes and tumor suppressor genes in tumor cells; thus, MDA can serve as a biomarker for OS-mediated lipid peroxidation [30,31].

2.2.2 Nuclear Factor Kappa B and Nuclear Factor Erythroid 2-Related Factor 2

OS is essential for the development of CAC. Tumor growth in the gut is initiated by DNA alterations in intestinal epithelial cells caused by $H_2O_2$ and ROS generated from myeloid cells [32]. The primary NOX expressed in the gut is called NOX1, and NOX organizer 1 has been shown to have protective effects against CRC in mice by reducing superoxide formation in the colon crypt and preventing the apoptosis of colonic epithelial cells [33]. This section mainly...
focuses on NF-κB and Nrf2. ROS can serve as a chemical messenger, activating the inflammatory signaling pathway to affect cell proliferation and differentiation. The ability of free radicals to pass through the transcription factor Nrf2 and NF-κB crosstalk allows cells to respond to cellular stress with more precision [34].

The pathophysiology of colitis involves activation of the NF-κB signaling pathway by macrophages or epithelial cells. This pathway promotes the proliferation, survival, angiogenesis, and invasion of tumor cells, ultimately leading to the development and progression of CRC [15,35]. Tumor necrosis factor α (TNF-α), interleukin 1 beta (IL-1β), and other inflammatory response genes are all transcribed when the NF-κB transcription factor binds to DNA response elements in the enhancers or promoters within target genes. During OS, the IκB kinase (IKK) complex, comprising IKKα and IKKβ, is activated through phosphorylation and ubiquitin-mediated degradation of IκB, which allows NF-κB to translocate to the nucleus and induce transcription [36,37]. In the CAC model, the absence of IKKβ in the intestinal epithelium reduces the incidence of cancer [38]. The presence of IKKβ in intestinal mesenchymal cells correlates with the progression of CAC, and its elimination diminishes colitis and dysplasia in mice during the initial phases of the disease [36]. Loss of IKKβ in bone marrow cells also reduces tumor size [39]. The IκB/NF-κB pair plays an important role in CAC. The NF-κB pathway is activated by TNF-α, which promotes tumor development by inducing the production of ROS and causing DNA damage, leading to an exacerbated inflammatory response [40,41].

A key component in the prevention of CAC is Nrf2 [42,43]. Nrf2 is a transcription factor that regulates the redox balance and the expression of antioxidant enzymes, and mediates the induction of phase II detoxification reactions in mammalian cells [44]. Nrf2 is composed of seven functional Neh domains (Neh1–7), of which the Neh2 domain contains two ETGE and DLG motifs that specifically bind to Kelch-like ECH-associated protein 1 (Keap1), an inhibitory protein. Keap1 is responsible for the continuous degradation of Nrf2 by the ubiquitin-proteasome pathway under physiological conditions, maintaining Nrf2 at a low level [45]. The Nrf2/antioxidant response element (ARE) signaling pathway plays a crucial role in protecting cells from carcinogenesis [46]. AREs include NAD(P)H, NAD(P)H dehydrogenase [quinone] 1, superoxide dismutase, glutathione S-transferase, GSH peroxidase (GSH-Px), heme oxygenase-1, glutamate-cysteine ligase, catalase and Trx. When OS occurs, Nrf2 dissociates from Keap1. Then Nrf2 translocates into the nucleus and forms a heterodimer with small Maf proteins, facilitating the binding of Nrf2 to ARE/electrophilic reactive elements, thereby alleviating inflammation-related OS [47–49]. The activation of low-level Nrf2 is believed to inhibit OS and inflammation, which can prevent the development of CAC [50]. However, under the condition of a large amount of ROS, continuous activation of Nrf2 causes it to accumulate in the nucleus and bind to the kinesin family member 9 promoter, leading to ROS elevation and cell death [51].

3. Interaction of Exosomal miRNAs and OS in CAC

Both OS and exosome-derived miRNAs are closely related to the development of CAC. Previous studies have shown that OS can alter the expression level of many miRNAs. Conversely, miRNAs can also regulate signaling pathways involved in OS responses, thereby promoting cancer development [52]. Therefore, OS and miRNAs both play critical roles in the development of CAC. In this section, we discuss the crosstalk between exosomal miRNAs and OS in CAC (Fig. 1; Table 1, Ref. [52–63]).

### Table 1. List of exosomal miRNAs involved in CAC progression.

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Target</th>
<th>Pathway</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-21</td>
<td>PDCD4, TPM1, PTEN</td>
<td>NF-κB</td>
<td>[52]</td>
</tr>
<tr>
<td>miR-19a</td>
<td>TNFAIP3</td>
<td>NF-κB</td>
<td>[53,54]</td>
</tr>
<tr>
<td>miR-6869-5p</td>
<td>TLR4</td>
<td>NF-κB</td>
<td>[56]</td>
</tr>
<tr>
<td>miR-6803-5p</td>
<td>PTPRP</td>
<td>NF-κB</td>
<td>[57]</td>
</tr>
<tr>
<td>miR-183-5p</td>
<td>THEM4</td>
<td>NF-κB</td>
<td>[58]</td>
</tr>
<tr>
<td>miR-361-3p</td>
<td>TRAF3</td>
<td>NF-κB</td>
<td>[55]</td>
</tr>
<tr>
<td>miR-224-5p</td>
<td>CMTM4</td>
<td>NF-κB</td>
<td>[60]</td>
</tr>
<tr>
<td>miR-216a</td>
<td>HMGB1</td>
<td>NF-κB</td>
<td>[62]</td>
</tr>
<tr>
<td>miR-222-3p</td>
<td>BRG1, Nrf2</td>
<td></td>
<td>[59,63]</td>
</tr>
<tr>
<td>miR-200</td>
<td>Keap1</td>
<td>Nrf2</td>
<td>[61]</td>
</tr>
</tbody>
</table>

PDCD4, programmed cell death 4; TPM1, The shortlisted genes, tropomyosin 1; PTEN, phosphatase and tensin homolog; TNFAIP3, Tumor necrosis factor alpha induced protein 3; TLR4, Toll-like receptor 4; PTPRP, protein tyrosine phosphatase receptor type R; THEM4, thioesterase superfamily member 4; TRAF3, tumor necrosis factor receptor-associated factor 3; CMTM4, CCKF like MARVEL transmembrane domain containing 4; HMGB1, high mobility group box 1 protein; BRG1, brahma-related gene 1.
Fig. 1. Interaction of exosomal miRNA and OS in CAC. Exosomal miR-21, miR-19a, miR-6869-5p, miR-6803-5p, miR-183-5p, miR-361-3p, miR-224-5p, and miR-216a on the left side of the figure act on NF-κB through corresponding targets in intestinal epithelial cells. NF-κB activation produces ROS and results in OS, promoting the proliferation of tumor cells and the development of CAC. Meanwhile, exosomal miR-222-3p and miR-200 on the right side of the figure act on Nrf2 through corresponding targets. Nrf2 is activated, after which it dissociates from Keap1 and binds to ARE/electrophilic reactive elements, thereby alleviating OS and slowing down the development of CAC. miRNA, microRNA; OS, oxidative stress; CAC, colitis-associated cancer; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element.

CRC cells [54]. One significant tumor suppressor gene, PDCD4, is involved in several biological processes, including invasion, metastasis, apoptosis, and cell proliferation. By blocking the nuclear translocation of NF-κB and interfering with the signaling pathways it triggers, PDCD4 modifies NF-κB activity. MiR-21 causes PDCD4 mRNA to be degraded and undergo translational repression by attaching itself to the 3’ UTR of PDCD4 [55,64].

miR-19a is markedly upregulated in the serum of CRC patients [56]. miR-19a directly increases NF-κB signaling and promotes the development of colitis and CAC. Targeting TNF-α-induced protein 3 increases miR-19a levels, which can enhance TNF-α production and activate NF-κB. TNF-α activation, in turn, increases the expression of miR-19a. In addition, inhibition of miR-19a can also alleviate CAC [57].

Decreased levels of miR-6869-5p have been found in serum exosomes from CRC patients. MiR-6869-5p directly targets Toll-like receptor 4 (TLR4) and inhibits cell proliferation and inflammatory cytokine production in CRC cells through the TLR4 NF-κB signaling pathway, which has protective effects on CRC and can be used as an inhibitor in CRC [58].

The exosome miR-6803-5p is increased in CRC and is negatively correlated with protein tyrosine phosphatase receptor type O (PTPRO). PTPRO can exacerbate UC inflammation by activating the TLR4/NF-κB signaling pathway [59]. In CRC, miR-6803-5p promotes cancer cell proliferation and invasion and enhances OS through the PTPRO/NF-κB axis. MiR-6803-5p binds to the 3’ UTR of PTP receptor type 4 (PTPR4), which may promote the degradation and translation repression of PTPR4 mRNA, thereby reducing the expression level of PTPR4 protein [60].
The proliferation and invasion of CAC cells are enhanced by overexpression of the exosome miR-183-5p, which is generated from M2 macrophages. By focusing on thioesterase superfamily member 4 (THEM4), miR-183-5p activates the AKT/NF-κB pathway, accelerating the development of CAC [61]. THEM4 can block downstream signaling by binding AKT and reducing its phosphorylation [9]. Vitamin D can alleviate inflammation by inhibiting the AKT/NF-κB/COX-2 pathway [65].

A crucial regulator of the advancement of cancer is the hypoxic TME. Hypoxia-inducible factor 1 alpha causes CRC metastasis and the substantial upregulation of miR-361-3p in hypoxic exosomes. The NF-κB pathway is activated in CRC through the increased direct targeting of TNF receptor-associated factor 3 (TRAF3), which promotes cell proliferation and inhibits cell death [66]. NF-κB activation can be divided into classical and non-classical pathways. NF-κB-inducing kinase (NIK) is a key member of the non-classical pathway. TRAF3 can degrade and stabilize NIK [66].

It has been discovered that the overexpression of miR-224-5p strongly suppresses OS and increases the migration, invasion, and proliferation of normal human colon epithelial cells. CKLF like MARVEL transmembrane domain containing 4 (CMTM4) is a tumor suppressor gene and in cancer, CMTM4 is a key regulator of NF-κB [67,68]. Exosome miR-224-5p secreted by CRC cells promotes cell proliferation by downregulating the expression of CMTM4, thus promoting the proliferation, migration, invasion, and malignant transformation of normal human colon epithelial cells, and promotes malignant transformation and tumorigenesis [69].

By encouraging macrophage polarization towards the M2 phenotype, exosomes produced from adipose-derived stem cells may be able to reduce colitis inflammation. Exosomes from hypoxia contain more miR-216a-5p than those from normoxia, and the treatment is better. MiR-216a-5p can regulate macrophage balance by regulating the high mobility group box 1 protein (HMGB1)/TLR4/NF-κB signaling pathway [70]. HMGB1 is an inflammatory mediator and activates TLR4 through cluster of differentiation 14 [14]. TLR4 belongs to the TLR receptor family, and TLR signaling can activate NF-κB [15]. TLR4 expression is upregulated in almost all cases of CAC, which enhances ROS production in intestinal epithelial cells (IECs) and induces microbiota [62,71,72].

3.2 Nrf2 Regulates OS and Inhibits Inflammation Resulting in Protective Effects on Colitis

The expression levels of all members of the miR-200 family have been observed in mesenteric vein exosomes at higher levels than in plasma exosomes in Spanish patients with CRC [73]. In dextran sulfate sodium-induced colon injury, miR-200a targets Keap1 and activates Nrf2-regulated antioxidant pathways, alleviating excessive inflammatory activation, intestinal cell apoptosis, and colon dysfunction. OS and inflammatory responses are key factors in the pathogenesis of UC [63].

The integrity of the intestinal barrier and innate immunity depend on IECs. Recent studies have revealed elevated levels of exosomal miR-222-3p in the bloodstream of CRC patients. An essential function of miR-222-3p is to regulate OS. Both in vitro and in vivo studies have assessed the effects of miR-222-3p-mediated OS on UC and CAC in a mouse model of colitis. Targeting Brahma-related gene 1, suppression of miR-222-3p has been found to activate the Nrf2/HO-1 signaling pathway in IECs from CAC, which increases GSH-Px levels while lowering ROS and MDA levels, leading to decreased TNF-α and IL-1β expression. These effects significantly ameliorate OS and inflammation in the injured colon, thereby mitigating colon inflammation and tumorigenesis [74,75].

4. Exosomal miRNA-Based Prevention Approach

There are numerous medications available for treating CAC [76,77]. 5-fluorouracil (5-FU) is commonly used in CRC patients. However, the multidrug resistance caused by long-term use of 5-FU severely weakens the treatment effect, and resistance to 5-FU is one of the main reasons for CRC recurrence. Compared with artificially synthesized drug carriers, exosomes, as natural carriers, are rapidly cleared by the monocyte/macrophage system. Therefore, exosomes have advantages such as stable properties, easy immune escape, long circulation time, no obvious toxic side effects, ability to load multiple drugs to the target, specific delivery, and the ability to utilize different intracellular transport pathways to exert their effects [14,78,79]. There are two ways to prepare exosomes as drug carriers: modify proteins or nucleic acids in exosomes through genetic modification, and place cells that release exosomes into therapeutic agents, so that the therapeutic agent is included in the exosomes [80]. In summary, exosomes have natural advantages over other synthetic carriers and treatment methods, and have great potential for the treatment of tumor diseases.

Exosome miRNAs can regulate the occurrence and persistence of inflammatory responses. Inflammation-related miRNA expression levels can be controlled to prevent the release of inflammatory mediators; lessen inflammation and damage to intestinal mucosa; promote the growth, differentiation, and repair of IECs; preserve the integrity of the intestinal epithelial barrier; and ultimately lower the risk of CRC [81]. The miR-129-5p produced from human umbilical cord mesenchymal stem cell-derived exosomes (HucMSC-Ex) target acyl-CoA synthetase long chain family member 4 (ACSL4) and decreases its expression to lessen intestinal inflammation and repair damage, which helps to relieve IBD. Lipid peroxidation is positively regulated by ACSL4 [82]. According to previous research, husMSC-Ex miRNA is crucial in inhibiting the growth of.
CAC. In a mouse model of colitis caused by dextran sodium sulfate and azoxymethane, hMSC-Ex miR-146a prevented the production of small ubiquitin-related modifier 1 and its attachment to β-catenin, thereby reducing the progression of colitis [83]. Furthermore, in the inflammatory milieu, HuCMSC-Ex expressing miR-203a-3p.2 reduces colitis by inhibiting caspase11/4-induced macrophage pyroptosis [84]. Consequently, exosomal miRNAs are crucial for preventing CAC.

5. Future Perspectives

In recent years, there has been increasing research on exosomes. Extracellular miRNAs from tumors can recode other untransformed cells in the TME. Extracellular miRNAs are more stable than free miRNAs. Extracellular miRNAs protect miRNAs and transport them to target mRNA, playing a key role in cancer progression by acting as tumor inhibitors or oncogenes.

Detecting the changes in exosomal miRNA before and after treatment can improve the efficiency of treatment. However, exosome extraction presents some challenges because of its small size and low density. Extracellular vesicle separation has been achieved through the development of six techniques: precipitation, size exclusion chromatography, ultrafiltration, ultracentrifugation, immunoaffinity-based capture, and microfluidics [85]. Future studies need to further establish more accurate and reliable detection techniques of exosomal miRNAs.

Several studies have shown that certain exosomes miRNAs can prevent the development of CAC by suppressing inflammatory responses, regulating the immune system, and alleviating damage to IECs, among other mechanisms. For example, by binding to the coding region of large tumor suppressor kinase 1 (LATS1), exosomal miR-590-3p generated from M2 macrophages downregulate LATS1 expression. The transcription mechanism mediated by Yes-associated protein/β-catenin is subsequently triggered by this activity, leading to the increased proliferation and wound healing of epithelial cells. In addition, pro-inflammatory cytokine production is reduced by miR-590-3p. These results may lead to new therapies for UC [86]. To slow down the evolution of CAC, relevant gene expression can be targeted and controlled based on the expression of exosomes. Additionally, individualized care can be provided by examining how each patient expresses miRNA.

6. Conclusion

These review summaries the association between exosomal miRNAs and OS in CAC. These exosomal miRNAs act on the NF-κB and Nrf2 signaling pathways through different targets, promoting or inhibiting OS. The existing literature has proved that exosome miRNAs can play a key role in the treatment and prevention of CAC as potential biomarkers and therapies for the disease. However, the research on exosomal miRNAs in the prevention of CAC is still limited, and more experimental and clinical studies are needed to further verify its mechanism of action and clinical application prospects. Future research could further develop clinical studies based on large samples to evaluate the safety and efficacy of exosomal miRNAs in the treatment and prevention of CAC. At the same time, the combined application of exosomal miRNAs with other therapeutic means should also be explored to improve its therapeutic effect.

Abbreviations

IBD, inflammatory bowel disease; ROS, reactive oxygen species; RNS, reactive nitrogen species; PPP, pentose phosphate pathway; AMPK, adenosine 5′-monophosphate-activated protein kinase; EVs, extracellular vesicles; MVB, multivesicular body; TME, tumor microenvironment; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; NOX, NADPH oxidase; NOS, nitric oxide synthase; XOR, xanthine oxidoreductase; LOX, lipoygenase; COX, cyclooxygenase; MPO, myeloperoxidase; 8-OHdG, 8-hydroxy-2-deoxyguanosine; MDA, malondialdehyde; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1 beta; ARE, antioxidant response element; TNFAIP3, Tumor necrosis factor alpha induced protein 3; IEC-6, intestinal epithelium cell-6; MDR, multidrug resistance; Keap1, Kelch-like ECH-associated protein 1; OXPHOS, oxidative phosphorylation; 5-FU, 5-fluourouracil; TRAF3, tumor necrosis factor receptor-associated factor 3; ASCs, adipose-derived stem cells; NAPD, nicotinamide-adenine dinucleotide phosphate; PTPR, protein tyrosine phosphatase receptor type R; DSS, dextran sulfate sodium.

Author Contributions

YFL and HYL reviewed the literature and drafted the manuscript. MLC and YZ: Data curation, Writing-original draft. MXZ and MZZ: Conceptualization, Writing-Review & Edition. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest
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