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Chapter

Two Faces of Nrf2 in Cancer

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Abstract

Nuclear factor erythroid 2–related factor 2 (Nrf2) serves as a “main regulator” in response to internal or external cell stressors through coordinated induction of a wide range of cytoprotective genes. In cancer cells, Nrf2 increases expression of cytoprotective genes and, as a result, promotes proliferation through inhibition of apoptosis and metabolic reprogramming. Therefore, the activation of Nrf2 is an important regulator for prevention of cancer triggered by stresses and toxins. Defense system is activated by cellular pathways to ensure that response to stresses and toxins is sufficient for needs of the body. Nrf2 is a regulator of genes mediated by antioxidant response elements. Nrf2 is a pleiotropic gene that represents highly researched strategy in cancers. During recent decades, emerging evidence shows that Nrf2 is generally activated in many types of cancer by many mechanisms. Nrf2 has been showed to contribute to chemoresistance of cancer cells, as well as carcinogenesis due to inflammation, in recent studies. This review provides an overview of current mechanisms of regulation of Nrf2 in normal cells and its dual effects in cancer. This chapter aims to rationalize these double roles by criticizing dependence of Nrf2 functions and methods behind these contradictory data.

Keywords: cancer, Nrf2, Keap1, oxidative stress, ARE

1. Introduction

Nrf2 is a central regulator of antioxidant response element (ARE)-related gene expression and immune response. This gene encodes a transcription factor that is a member of basic leucine zipper (bZIP) protein family. The encoded transcription factor regulates genes containing antioxidant response elements (ARE) that many of these genes involve the generation of free radicals. Nrf2 is expressed in the kidney, liver, and intestine where detoxification occurs routinely. Nrf2 is located in cytoskeleton attached to Keap1. Nrf2, encoded by the nuclear factor (erythroid derived 2)-like 2 (Nfe2l2) gene, is a leucine zipper protein and a polypeptide. It has a molecular weight of 66 kDa and is widely expressed [1, 2]. Nfe2l2 gene contains a xenobiotic responsive element (XRE) at −712(XREL1) position of promoter region and two additional XRE-like elements found in +755(XREL2) and +850(XREL3) positions, which are directly modulated by aryl hydrocarbon receptor (AHR) activation [3]. Nrf2, which is found in the cytoplasm in normal or stress-free conditions, migrates to the nucleus in case of oxidative stress and attaches to DNA. Mutations and changes in Nrf2 expression have been described in many cancer types [4–9]. Upregulation of Nrf2 is linked with many types of cancer, including the lung, skin, prostate, breast, and head–neck [6, 8, 10, 11]. Many mechanisms have been reported for the increased activity of Nrf2 in cancer cells. Some of them, (1) somatic mutations in Kelch-like ECH-related protein 1 (Keap1), Cullin 3 (CUL3) or
Nrf2 [12]; (2) epigenetic silencing of Keap1 [13]; (3) abnormal protein accumulation that disrupts the interaction between Nrf2 and Keap1 [14]; (4) transcriptional upregulation of Nrf2 through oncogene-dependent signaling [15]; and modification of Keap1 by metabolic programming [16]. Increasing studies show that Nrf2 activation may not be beneficial in all types and stages of cancer over the past few years. In fact, Nrf2 can ensure survival of not only normal cells, but also cancer cells, and supports the process by which Nrf2 activation in malignant cells can sustain development of the disease. The roles of the bad or good side of Nrf2 [7, 8] have caused debates because it is still not clear whether Nrf2 acts as a tumor suppressor or oncogene [7, 9]. Nrf2 hyperactivity in tumors creates a protective environment that promotes survival by protecting cancer cells from radiotherapy, oxidative stress, and chemotherapeutic agents. Therefore, there is a growing range of research aimed at identifying the boundaries between Nrf2 positive and negative responses in cancer and targeting Nrf2 therapeutically [17–19]. It is clear that Nrf2 exactly plays its protective role without distinguishing for cancer and normal cells. Current studies acknowledge the double roles of Nrf2 in carcinogenesis: protective in the early stages and harmful in the later stages.

2. Basal state induction and cellular positions

Nrf2 is inactivated transcriptionally by binding to its regulator Keap1, which targets Nrf2 for proteasomal degradation in basal conditions. CUL3 ubiquitin ligase, which governs the degradation, is a third protein. Under stable conditions, ubiquitous Nrf2 is rapidly disrupted by 26S proteasome (Figure 1). Nrf2 has a very short half-life of less than 30 minutes. Therefore, Nrf2 is not abundant under basal conditions and, in light of current studies, supports the claim that Nrf2 is found at a relatively low level in most organs or tissues [20–22]. Nrf2-Keap1 is of first importance in balancing homeostatic environment since cells need to respond by adapting to different stresses. Cells can use highly toxic molecules to be used in the physiological signal. These molecules contain reactive oxygen species (ROS) and reactive nitrogen types (RNSs) such as hydrogen peroxide ($H_2O_2$) and nitric oxide (NO). Low concentrations of these molecules are used for adaptive intracellular signaling, and high concentrations are used for defense mechanisms against microorganisms [23, 24]. But, physiological concentrations of these molecules need to be precisely regulated, and Nrf2-Keap1 play important role in this signaling.

Nrf2 is a transcription factor that regulates cellular stress signals and reacts by directing different transcriptional programs. Limited number of researchers were working only on inhibiting its protective role and carcinogenesis in suppressing oxidative or electrophilic stress till a little more than a decade ago [25, 26], but recently, Nrf2 has become a topic of widespread interest and research area. Kelch-like ECH-related protein 1 (Keap1) is a negative regulator, has encouraged many publications, and has become an important topic of discussion. The debate focuses on whether Nrf2 is tumor suppressor or reverse oncogenic, leading to the question of whether Nrf2 should be targeted for anticancer therapeutic agents [27].

Genetic analysis has shown mutations in Nrf2 and Keap1 in some cancers. These mutations increase Nrf2 expression and are related with resistance to chemotherapy and poor survival rate from cancer [18, 28]. Sequence analyses of Nrf2 and Keap1 have identified many mutations within Kelch domain and in the Neh2 domain of Keap1-Nrf2; this causes Nrf2 to unstable due to Keap1’s inability to target Nrf2 for degradation and ubiquitination (Figure 1a). Whether activation or inhibition of Nrf2 is a good strategy for treatment or prevention of cancer is still unclear. In vivo studies have shown that basal Nrf2 protein levels decrease with age and associate
with lower expression target genes of Nrf2 \[29, 30\]. Therefore, it is more probable that Nrf2 acts as a defense against the aging process caused by free radicals, which gradually decreases over time, leading to accumulation of free radicals that can cause cancer progression \[31, 32\].

3. Keap1-Nrf2-ARE signaling

Keap1 has more than 20 groups of free sulfhydryl (-SH) in the cysteine residues. These highly reactive molecules for stress act as sensitive sensors. Reactive cysteine thiols are present as (S-) under physiological pH and are more reactive to ROS/RNS than sulfhydryl groups \[33\]. Keap1 alters cysteine residues, giving a response to oxidative or electrophilic stresses \[34, 35\]. Tert-butylhydroquinone (tBHQ), an electrophile, reacts with reactive cysteine residues in Keap1 to activate Nrf2 \[36\]. Binding of tBHQ to Keap1 does not impair binding of Nrf2 to Keap1; this indicates that sequestration of Nrf2 from Keap1 homodimer cannot explain electrophilic mediated induction of Nrf2 accumulation within cells \[37\]. These modifications result in conformational changes of Keap1 and reverse degradation of Nrf2, which is then transcriptionally activated.

Different types of stressors react differently with the cysteine residues in Keap1, suggesting that the residues of cysteine in some way contribute to activity of Keap1.
individually or in combination (23,24). This indicates that Nrf2-Keap1 mechanism is not a simple “on” or “off” button mechanism but can instead respond with different mechanisms by various stress factors [23, 35].

Some of the promising Nrf2 activator or inhibitor agents are currently in different phases of clinical trials [38–40]. Human clinical trials were kept assessing the effects of inducers [41, 42]. These include: (1) approved and other purpose agents such as dimethyl fumarate (DMF) and Oltipraz; (2) compounds purified from natural sources such as broccoli sprouts, curcumin, resveratrol, and sulforaphane; and (3) highly potent triterpenoid derivatives, e.g., RTA 402-408 and CXA-10 [43]. Nrf2 protein, which forms a heterodimer structure with MA or Jun protein in the nucleus (Figure 1b), binds to ARE (Antioxidant Response Element) sequence on DNA and provides regulation of related gene expressions in favor of activation of antioxidant mechanisms [44]. PI3-kinase is responsible for nuclear translocation of Nrf2 and binding of Nrf2 to ARE to induce enzymes such as GST, HO-1, and NQO1. It is essentially a common DNA sequence called an antioxidant response element (ARE) similar to Nrf2-binding motif for induction [45].

Cancer cells have higher ROS levels than normal cells. Nevertheless, they can adapt to high ROS levels with the activating of certain ways that allow them to proliferate and survive. These ways include the activation of antioxidants to reduce ROS, as well as metabolic reprogramming pathways that can produce more ROS and make cancer cells more vulnerable to future stress [46, 47]. Keap1-Nrf2 pathway is one of the most important signaling pathways that play a role in the survival and defense of cell against xenobiotics and oxidative stress.

4. Keap1-dependent regulation of Nrf2

Keap1 contains 27 cysteines, which account for 4.33% of all amino acids, whereas the average cysteines content in human proteins is 2.26% [48]. Proteomic analyses have found that several of the 27 cysteines in Keap1 have been modified to respond to different electrophiles [49]. However, only three of the Keap1 cysteines, Cys151, Cys273, and Cys288, were found to be functionally important for Keap1-Nrf2 regulation [50]. Cys273 and Cys288 target Cys151, which is a subset of Nrf2 activators, although they are essentials for Keap1 to inhibit Nrf2 under basal conditions. During oxidative stress, ROS reacts with cysteine residues of Keap1, including C151, C273, and C288, allowing Nrf2 to escape Keap1-mediated degradation [51].

Human Nrf2 protein has 605 amino acids and seven highly preserved Neh (Nrf2-ECH homology) domains from Neh1 to Neh7 (Figure 2). Neh1 domain contains small musculoaponeurotic fibrosarcoma homologous proteins (MafF, MafG or MafK) and a basic leucine zipper (bZIP) motif that is heterodimerized for DNA binding and transcriptional activation [52]. Neh2 regulatory domain of N-terminal contains DLG and ETGE motifs critical to Keap1 binding and resulting in Nrf2 degradation [53].

Neh3 domain is located in C-terminal of Nrf2 contains VFLVPK motif, which is critical for binding to CHD6 helicase [54]. Nrf2’s N-terminal includes two transactivation domains, Neh4 and Neh5, and both domains were found to be necessary for Nrf2’s maximum transactivation activity [55]. Neh6 domain contains a degron containing a DSG motif embedded in a set of serine-rich residues. This binding region is a docking site for adaptor protein β-TrCP, which mediates ubiquitin ligase of Nrf2 by a Cullin1-Rbx1 complex [56]. Neh7 domain interacts with the retinoic acid receptor α (RARα) and suppresses Nrf2 transcriptional activity in the nucleus [57].

Nrf2 degradation can be stopped when exposed to electrophiles and ROS. Reactive cysteines are a small set of protein cysteines with pKa values relatively low
Around 4 and 5 due to the effect of surrounding amino acid microenvironment, unlike most protein cysteine thiols with pKa values of about 8.5. Reactive thiols are perfectly targets for electrophiles, and indeed, several electrophilic reagents have been shown to directly alter thiols. The modification of Keap1 is thought to impair structural integrity of Keap1–Cul3 E3 ligase complex, causing a decrease in ubiquitination activity, thereby facilitating accumulation of Nrf2 [58, 59]. In recent studies, presence of unrestricted Keap1 has recognized deleterious effects to cellular homeostasis and highlighted Nrf2’s role as Keap1’s suppressor that implies that Nrf2 and Keap1 are mutually blocking each other [60]. Under normal conditions, Keap1 plays an important role in limiting Nrf2 activity by binding to DLG/ETGE motifs in the Neh2 domain and inducing ubiquitination and proteasomal degradation (Figure 1a) [61].

Permanent activation of Nrf2 in tumor cells is activation of p62, that is, a multifunctional protein involved in selective autophagy that is often overexpressed in tumors [6]. p62 in phosphoryl form can bind with Keap1 in the same binding domain for Nrf2, thereby competitively inhibiting Keap1/Nrf2 interaction resulting in Nrf2 stabilization and translocated into the nucleus. Nrf2 can consecutively upregulate p62 gene expression, thereby upregulation of a pro-survival circuit that can support tumor formation. The accumulation of proteins and metabolites that disrupt Keap1-Nrf2 can activate Nrf2 in cancer. p62 is the best-known disruptor that competes with Nrf2 for direct attachment to Keap1 through an SQSTM1 motif similar to ETGE motif in Nrf2 [62]. After p62 is bound to Keap1, it causes Keap1 to go into autophagic degradation [63]. Recent studies have shown that p62 gene expression is upregulated in hepatocellular carcinoma and that the activation of Nrf2 induced by p62 is critical for HCC development [64, 65].

Kelch domain of Keap1 interacts with two different sequences of amino acids found in the N-terminal of Nrf2: ETGE and DLG [66]. Based on a series of critical
observations, “Hinge-Latch model” (Figure 3) that is Keap1-Nrf2 interactive two-site binding model was proposed [66]. ETGE motif has a higher affinity for Kelch-repetition domain than DLG motif. Therefore, Keap1 captures Nrf2 through ETGE motif before DLG motif is attached to adjacent unoccupied Kelch-repeat domains; this is called the “hinge and latch” mechanism [67, 68]. The modes of binding DLG and ETGE to Keap1 are quite different [69]. Keap1-DLG binding is

![Figure 3](image)

**Figure 3.**
The regulation of Nrf2 via the Nrf2-Keap1-ARE mechanism under basal and stress conditions, as explained with the “hinge and latch” model. a) under basal condition, two Keap1 molecules and one Nrf2 molecule form a trimer structure and Nrf2 is polyubiquitylated by the Keap1-Cul3 E3 ubiquitin ligases and then disrupted by 26S proteasome (Figure 1a). b) under induced conditions, inducers (ROS/electrophiles) modify Keap1 cysteine thiols and inhibit Nrf2 ubiquitination, causing Nrf2 activation and induction. c) the binding of Nrf2 to Keap1 is disrupted by the modifications of cysteine residues of Keap1, which contains what is known as the “cysteine code.” These modifications lead to conformational changes that enable Nrf2 to escape from degradation and lead to Nrf2 upregulation. It occurred via the loss of binding of the low-affinity interaction with DLG(latch) motif to Keap1 and binding with the ETGE(hinge) motif remains. d) Stress-induced modification of Keap1 cysteines disrupted Keap1 ability to serve as an adapter for the Cul3-Keap1 ubiquitin ligase complex, thereby causing stabilization and transcriptional activation of Nrf2. On both models shown in C and D, Nrf2 translocates to the nucleus, binds to the ARE, and activates gene expression such as NQO1, HO-1, and GSE.
characterized as kinetically a “fast-on-fast-off,” which is thermodynamically guided by both enthalpy and entropy. In contrast, ETGE-Keap1 binding is characterized by completely enthalpy guided and involves a two-state reaction that leads to more stable conformation [70, 71]. These findings support the claim that DLG motif serves as a converter that transmits environmental stress to Nrf2 induction as a latch (Figure 3).

5. Nrf2-regulated cytoprotective genes

Nrf2 plays a major role in the protective mechanism against xenobiotics, which can initiate carcinogenesis by damaging DNA [72]. Nrf2 increases expression of antioxidant enzymes. Gene transcription profiles showed that not all genes around Nrf2 are transcriptionally regulated by Nrf2 binding. These genes require transcription factors, cofactors, and intermediaries for complete activation [73]. Antioxidant molecules such as glutathione (GSH), vitamin C and E, bilirubin, and antioxidant proteins such as thioredoxin (Trx), Superoxide Dismutase (SOD), catalase, peroxiredoxin, glutathione peroxidase (GPx) are major antioxidant molecules that play a role in balancing oxidative stress. Nrf2 and its downregulatory effectors have been shown to be critically important regulators in the regulation of intracellular redox state and in protecting cells from oxidative stress and chemical damage in the lungs and liver [74, 75]. Nrf2 loss has been associated with advanced metastasis. For example, loss of Nrf2 initiates a harmful cascading of decreased GST expression and raises ROS level, ultimately leading to DNA damage and tumor formation [76]. The role of Nrf2 signaling as a tumor suppressor is due to a lot of in vivo studies comparing susceptibility to carcinogenicity chemically induced in Nrf2-knockout mice (Nfe2l2−/−) and wild-type mice. In this context, Nrf2-null mice were found to be more prone to developing bladder, stomach, and skin cancer when exposed to carcinogen substances compared with wild-type mice. This gene has a deficiency and susceptibility to oxidative damage, and chemical carcinogenesis increases in Nrf2-knockout mice [75]. Expression of antioxidant and phase II enzymes was found to be eliminated in mice with Nrf2 deficiency. Heavy quinone-induced made mice with Nrf2 deficiency more prone to skin cancer, while NQO1 and GST expression regulated by Nrf2 decreased compared with wild mice [77]. In addition, expression levels of ARE-mediated genes such as glutathione-S-transferases (GSTs) isozymes, NADP(H): quinone oxidoreductase (NQO1), stress response proteins such as heme oxygenase (HO-1), glutamate cysteine ligase (GCL), and UDP-glucuronosyltransferase (UGT) were found to be significantly repressed in mice with Nrf2 deficiency compared with their wild types [25, 78, 79]. Nrf2 transcriptional targets are not only a well-known antioxidant enzyme such as glutathione peroxidase (GPX) and superoxide dismutase (SOD) to clean ROS, but also two other genes related to detoxification and anabolic reprogramming.

Nrf2 downstream targets are separated into three main groups: phase I and phase II drug metabolizing enzymes (DMEs) and phase III drug carriers. Phase I enzymes oxidize drugs or xenobiotics such as aldo-ketoreductases (AKRs) and cytochrome P450s (CYPs) encoded by genes regulated by Nrf2; Phase II enzymes conjugate products of phase I reactions, while phase III enzymes carry final metabolites out of cells in collaboration to implement a cytoprotective function. Several phase I enzymes also play important roles in removal of xenobiotics through hydrolysis, reduction, and oxidation. Phase I, cytochrome P450 (CYP) family, aldehyde oxidase (ACO) contain modification of xenobiotics by enzymes such as aldehyde dehydrogenases (ALDHs), aldo-ketoreductases (AKRs), alcohol dehydrogenases (ADHs), esterase, flavins-containing monoxygenases (FMOs),
and cyclooxygenases (COXs) [80]; (ii) phase II enzymes such as GST, UGT, Sulfortransferases (SULTs), N-acetyltransferases (NATs), and methyltransferases (MTs) add polar groups to phase I products to prepare them for excretion [81]; and (iii) carriers, ATP-binding cassette (ABC), and dissolved solute-carrier (SLC) export metabolites (modified) out of the cell [82].

Phase II drug metabolism or conjugation reactions involve a different group of enzymes, which often lead to water-soluble products that can be excreted with bile or urine. Conjugation reactions include: glucuronidation, acetylation, sulfation, methylation, amino acid and glutathione conjugation.

The protective effects of upregulation of Nrf2 signaling can be in various forms. Protection can be instantaneous by stimulation of genes that are directly regulated through Nrf2 binding to AREs in the target genes [83, 84]. Protective effects can be secondary through stimulation of macromolecular damage removal/repair mechanisms [84, 85]. Protective effects can be tertial through induction of tissue repair/regeneration pathways [86]. p53, which is a tumor suppressor, reduces Nrf2 activity, stopping cell growth and inducing apoptosis [87].

Regulation of Nrf2 can be unstable against the loss of inducible nature of Nrf2 signaling and acquisition of a structurally active phenotype. The constructive signal for expression of cytoprotective enzymes would give cells surviving chance under stress conditions. This seemingly positive condition would become a serious disadvantage in progression of cancer pathogenesis and treatment. Therefore, structural activation or increased signaling of Nrf2 pathway can be determined for destiny of cell during tumorigenesis and affect response to radiotherapy and chemotherapy. Under these circumstances, Nrf2 can be described as an oncogene [32, 88].

6. Tumor suppressor and oncogenic roles of Nrf2

Nrf2 protects cells from oxidative stress, in vivo studies with rats have shown that basal Nrf2 protein levels decrease with age and correlate with lower expression of Nrf2 target genes [89]. Increasing Nrf2 activity, which facilitates tumor formation and proliferation of K-Ras, B-Raf, and Myc in cancer cells, helps reduce intracellular ROS levels. Overexpression of Nrf2 also regulates cell proliferation by directing glucose and glutamine to anabolic pathways, increasing purine synthesis and affecting pentose phosphate pathway to promote cell proliferation [90]. In addition, under hypoxia/reoxygenation, Keap1 reduced expression and increased expression of Prx1, Nrf2, and peroxiredoxin-1 (Prx1) proteins, which reduce ROS levels and ultimately protect cancer cell [91]. In a study of Nrf2+/− mice exposed to diesel exhaust and N-nitroso butyl (4-hydroxybutyl) amine, increased pulmonary DNA adducts and bladder tumors were shown [92, 93].

Mutations that cause Keap1 loss of function and Nrf2 function gain and gene mutations that lead to electrophilic metabolite accumulation can also trigger continuous Nrf2 activity in cancer [94]. Nrf2 and its target gene expression levels can serve as biomarkers for diagnosis of lung cancers. Large-scale multi-tumor sequencing efforts by The Cancer Genome Atlas (TCGA) project found that CUL3 and Keap1 function loss and Nrf2 functional gain mutations were significantly enriched in lung adenocarcinoma, pulmonary squamous cell carcinoma and lung squamous cell carcinoma, and bladder cancer [95–97].

Oncogene activation, including oncogenic mutants of K-Ras, B-Raf, and c-Myc, may cause upregulated expression of Nfe2l2 gene [98]. K-Ras and B-Raf activations induce transcription of Nrf2 through activation of Jun and Myc transcription factors. This activation of Nrf2 has been shown to be critical for increased chemoresistance and tumor growth of Ras mutant cancer cells [15, 99].
mRNA and protein levels of AKRs have been shown to be biomarkers for diagnosis of cancers activated by Nrf2 [100]. AKRs are detected with greater precision than Nrf2. Several studies have shown that cancer cells with high levels of Nrf2 are less susceptible to common chemotherapeutic agents such as etoposide, carboplatin, cisplatin, 5-fluorouracil, and doxorubicin [10, 11, 101, 102].

Nrf2-targeting agents with advanced specificity are needed to increase effectiveness of cancer treatment. In addition, controversial roles of Nrf2 in cancer prevention and progression suggest that more issues need to be addressed to determine optimal use of Nrf2 activators or inhibitors in the clinic [103]. Nrf2 may have both tumor-suppressive and -promoting effects (Figure 4). Nrf2 target genes regulate autophagy, mitochondrial physiology, redox homeostasis, proteasomal degradation, energy metabolism, iron metabolism, amino acid metabolism, survival, reproduction, DNA repair, and drug metabolism and excretion [104–106].

Overexpression of sMaf proteins results in a decrease in transcriptional activity of Nrf2. However, there are no studies that identify different gene expressions or mutations of sMaf family proteins in tumors [107].

Dysregulation of epigenetic mechanism is hallmark of cancer. It is shown that acetylation conditions resulted in promoting nuclear localization of Nrf2, while deacetylation promoting cytoplasmic rather than nuclear localization of Nrf2. Hypermethylation of Keap1 promoter has been detected in the breast, lung, brain, and colorectal [108–110] and causes a decrease in Keap1 mRNA production and therefore Nrf2 activation [111–113].

7. Conclusions

In general, the question of whether Nrf2 activation is bilateral role is explained via several contexts, levels, and mechanisms. The above data strongly suggest that inhibition or activation of Nrf2 alone or in combination can be a promising therapeutic strategy for cancer treatment. In numerous in vitro and in vivo studies, multiple genomic, transcriptional, and proteomic mechanisms related to Nrf2 activation in cancer have been explained in detail. Targeting one of redox signaling
factors, such as Nrf2, seems like a crucial challenge for designing efficient cancer therapeutic strategies. Nrf2 is a well-known regulator that regulates antioxidant system and mediates tumorigenesis and suppression. Nrf2 should be considered an important therapeutic target. Nrf2 is in the focus of worldwide research, and we are expected to continue to see more research outputs in the future.

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Conflict of interest

There is no conflict of interest.
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