REVIEW

TFL, a hidden post-transcriptional modulator behind inflammation

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Post-transcriptional modulation of inflammatory molecules is recently recognized for fine-tuning of inflammatory initiation and maintenance. In these molecules, some families with three cytosines and a histidine type of zinc finger domain are gaining attention. Among them, MCP-1 induced protein (MCPIP), also known as regulatory RNase 1 (Regnase-1), encoded by the *Zc3h12a* gene is recently recognized as a novel player for the inflammatory response. Meanwhile, the Transformed follicular lymphoma (TFL) gene is identified as a putative tumor suppressor gene for lung carcinoma, as well as malignant lymphoma. *TFL* is a member of the *Zc3h12* gene family; hence, it is named as *Zc3h12d*. It has Nedd4-binding protein 1 and bacterial YacP-like protein domains, which resemble the N-terminus of PilT protein, acts as a ribonuclease, and degrades several cytokines similar to Regnase-1. *TFL* encodes mainly the 58Kda protein, p58[TFL], which is expressed dominantly in lymphoid organs and is upregulated in activated T and B cells according to the inflammatory response. In contrast, MCPIP/Regnase-1 is expressed mainly in macrophages and for a short term in activated lymphocytes. TFL inhibits cell growth via upstream inhibition of the Rb signaling pathway like a tumor suppressor. Moreover, in contrast to other Zc3h12 family members, expression of TFL is increased slowly in activated lymphocytes, and inflammatory resolution is modulated, which is vital for tissue regeneration. Inflammatory dysregulation by TFL deficiencies brings about prolonged inflammation and may give rise to tumor susceptibility in lymphomagenesis. Therefore, TFL can be considered a novel regulatory marker of inflammation, as well as an indicator for tumor progression.

Keywords: *TFL*; *Zc3h12* family*;* EAE, IL-17; Post-transcriptional regulation; Negative feedback

Abbreviations: MCPIP, MCP-1 induced protein; Regnase-1, regulatory RNase 1; TFL, Transformed follicular lymphoma; 3'UTR, 3' untranslated region; miRNAs, microRNAs; RBP, RNA-binding protein; TTP, Tristetraproline; ARE, AU-rich element; PIN, PilT N-terminus; SNP, single nucleotide polymorphism; SG, stress granule; EAE, experimental autoimmune encephalitis; DUB, deubiquitination; RISC, RNA-induced silencing complex.

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Introduction

Post-transcriptional regulation is recently recognized as one of the crucial factors of inflammatory regulation [1].

Among them, mRNA regulation via 3' untranslated region (3'UTR) is widely recognized. Recently, microRNAs (miRNAs) are thought to play crucial roles in the patho-
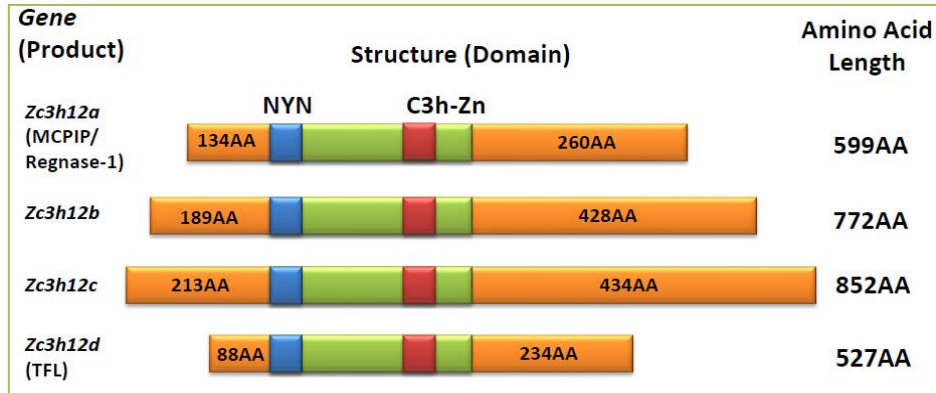
Figure 1. TFL and its family members. The *Zc3h12* family consists of four genes, namely *Zc3h12a* that encodes MCPIP/Regnase-1, *Zc3h12b*, *Zc3h12c*, and *Zc3h12d* that encodes TFL. The putative amino acid sequences have a common NYN (Nedd4-binding protein 1 and YacP-like nucleases) domain, which acts as RNase and regulates several cytokines or receptors in post-transcription. They also have the zinc finger motif, which consists of three cytosines and a histidine (C3h-Zn) and is considered as one of the RNA binding sites. They have different C-terminus motif, including a proline-rich motif, which is speculated to control the functional expression.

genesis of some inflammatory diseases [2,3]. In cooperation with miRNA, RNA-binding protein (RBP) is an important player for the regulation of post-transcriptional pathway. Tristetraproline (TTP) is one of the well described molecules which recognizes AU-rich element of 3'UTR (ARE) and regulates several molecules, including cytokines and cyclooxygenase [4,5]. TTP deficiencies lead to inflammatory instability and cause some inflammatory diseases, such as rheumatoid arthritis, in *TTP*-deficient model mice[5]. TTP has tandem zinc finger motifs, which consist of three cytosines and a histidine (C3h). This motif is thought to be a RNA-binding motif, so molecules that possess this motif are predicted to bind some RNA and are related to post-transcriptional regulation. Among these molecules, the Zc3h12 family proteins have recently gathered great attention. MCP1-induced protein (MCPIP), which is *encoded by Zc3h12a*, is first reported as a "transcription factor-like" protein in macrophages being stimulated by MCP1[6]. Thereafter, the putative amino acid sequences of mouse and human Zc3h12a are shown for the conserved N-terminal domain to share a remote homology to the PilT N-terminus (PIN) domain for the degradation of several cytokine mRNAs, such as IL-6 and IL-12[7]. Since the RNase activity is strictly regulated in certain situations, such as inflammation, the *Zc3h12a* gene product is also designated as regulatory RNase-1 (Regnase-1) [8]. The role of MCPIP/Regnase-1 in immunology has been studied extensively. According to human genome analysis, there are four family genes, including *Zc3h12a, 12b, 12c, and 12d* (Fig.1). In contrast to *Zc3h12a*, *Zc3h12d* is first reported as a putative tumor suppressor gene, namely as *p34* for lung cancer [9] and as *TFL* for malignant lymphoma[10]. Thereafter, the gene product, p58[TFL], has been expressed dominantly in several immune cells. Unfortunately, there is less information about the

functional roles of *Zc3h12b and 12c*. In this review, we focus on TFL and the functional roles of p58[TFL] in the immune system.

Identification of p58[TFL] in immune cells

The *TFL* gene is mapped in human chromosome 6q25. The *TFL* is first reported as *p34* by the study on loss of heterozygosity for familial lung cancer gene[9]. This gene has an A/G non-synonymous single nucleotide polymorphism (SNP) at codon 106, which alters the amino acid from lysine to arginine. Although this mutated *p34* has some growth inhibition potency for xenograft mouse model, it has no significant association with familial lung cancer. In contrast, *TFL* is discovered by identification of a break point of the translocation site in "transformed follicular lymphoma" [11]. During transformation to diffuse large B cell lymphoma, the lymphoma cells have acquired an additional cytogenetic abnormality, t(2;6)(p12;q25), which suggests the translocation of the *Immunoglobulin light chain kappa* gene (*Igκ*) to chromosome 6 long arm (6q). Chromosome 6q is widely known to include several tumor suppressor genes, such as *A20* and *EPHA7* [12, 13]. The translocation of *TFL* to *Igκ* (head to head) leads to deletion of its translation initiation codon, ATG, and probably causes the loss of TFL function [10]. Interestingly, other family genes are also located frequently in the chromosomal deletion sites of cancer patients. Therefore, it is of interest whether these also act as putative tumor suppressors or not.

Expression and cell growth inhibition

The expression of TFL is dominant in the spleen and thymus but less in the bone marrow and brain. It is
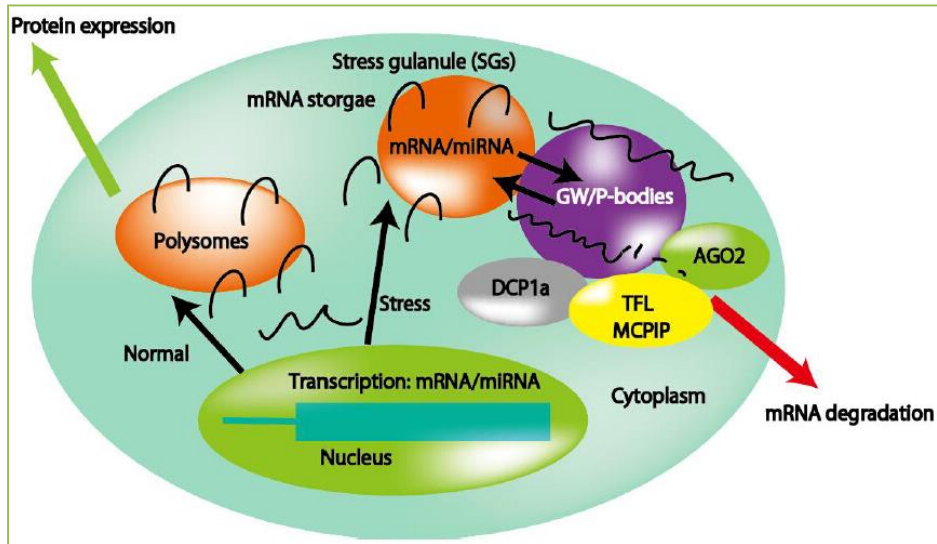
Figure 2. Post-transcriptional regulation. The transcribed mRNA is transported to the subcellular polysomes to produce protein. When cellular stress or missense transcription of mRNA occurs, the transcribed mRNA is transported into the stress granules for tentative storage or into the GW/Processing bodies for degradation. GW/P bodies also play an important role of processing from precursor mRNA to mature RNA. The decapping enzyme, DCP1a, resides in the GW/P-bodies. Argonaute 2 (AGO2; also known as Eukaryotic translation initiation factor 2C, 2) in the GW/P bodies also functions as a processor from precursor microRNA to mature RNA.

particularly prominent in the T and B cells rather than macrophages in the spleen. In human and mouse T and B cells, TFL expression is induced after immune activation *in vivo*, as well as *in vitro*. Introduction of *TFL* cDNA expression vector plasmids into some cell lines, such as Ba/F3 and Jurkat, leads to quick reduction of the cell proliferation[14]. Further analysis shows that TFL inhibits G1 to S entry of the cell cycle and Rb phosphorylation in normal mouse pre-B lymphocyte cell line, Ba/F3, as well as human lymphocytic leukemia cell line, Jurkat. Consistent with these results, T and B cells derived from TFL-deficient mice are facilitated in G1 to S progression of the cell cycle[15]. Therefore, TFL is thought to inhibit cell growth at least by upstream regulation of the Rb signaling pathway.

TFL is first predicted to encode a 34Kda protein according to the putative amino acid sequences of *p34* cDNA. Later, *TFL* has been shown to produce dominantly a 58kda protein, p58^{TFL}. The *p34* mRNA/cDNA can be an alternatively spliced one, because a similar cDNA of which putative amino acid sequences predict the presence of p36^{TFL} is also isolated independently. However, its physiological expression has not been confirmed, so far [14]. Introduction of *p34* cDNA into a lung cancer cell line has been shown to inhibit its growth *in vitro* and tumor progression *in vivo* by using xenograft mouse model.

Of note, the physiological expression of TFL in lymphocytes is upregulated according to cell activation and proliferation. The spatiotemporal expression of *TFL* in

inflammatory tissues raises the possibility that TFL inhibits lymphocytic cell growth via a negative feedback system.

Subcellular localization for post-transcriptional regulation

The GFP-tagged p58^{TFL} is expressed in the cytoplasmic granules where the mRNA processing body marker, DCP1a, co-localizes with one of the components of miRNA processing complex, AGO2[14]. Indeed, TFL co-localizes with a part, but not all of DCP1a-positive granules. In contrast, TFL does not overlap with a stress granule (SG) marker, TIA-1, but it localizes adjacent to p58^{TFL}. For post-transcriptional processing, the stress granules have a crucial role (Fig. 2). Transcribed mRNAs are not always translated into proteins. Some mRNAs are also stored temporarily in SGs under a stressful condition. They are released when needed for acute response; wherein, the time for expression is vital. As another crucial function of GW/P-bodies, nonsense-mediated mRNA decays to promote rapid degradation of aberrant mRNAs, such as transcripts including premature termination codon. These granules are functionally linked; hence, transient contacts are frequently observed[16]. Recently, GW/P-bodies are also highlighted in the field of precursor miRNA processing. Therefore, both transcriptional and post-transcriptional regulations are mutually affecting and controlling protein expression very precisely. Recently, another TFL family member, MCPIP has also been reported to localize with GW182 and partially with DCP1a[17,18]. Endogenous expression analysis of TFL localizes in most GW/P-bodies in THP-1 cells and activates
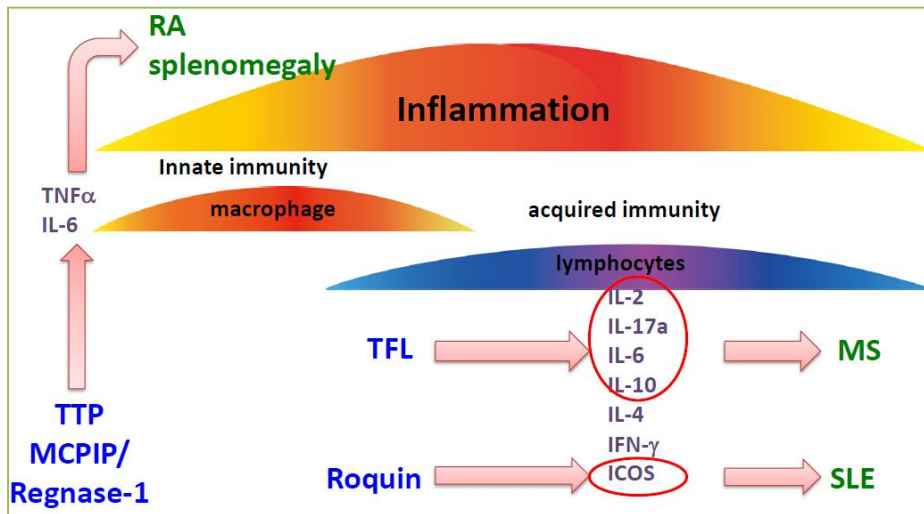
Figure 3. Regulation of inflammatory initiation & resolution via post-transcription pathway. Inflammation can be described into two phases, namely initiation and resolution. In the initiation phase, innate immunity, which is mainly governed by macrophages, plays an important role. Deregulation of this kind of inflammatory response causes severe inflammatory diseases, such as autoimmune and infectious diseases. For example, *Tristetraproline* (*TTP*)- deficient mice, in which TTP controls TNFa on macrophages, demonstrates rheumatoid arthritis-like phenotype. MCPIP/Regnase-1-deficient mice, in which MCPIP/Regnase-1 controls IL-6 on macrophages, demonstrates severe inflammation and cause early death. On the other hand, in the resolution phase, acquired immunity in which lymphocytes engage is overlapped. Therefore, immunity based on deregulatory lymphocytes has impact on inflammatory resolution. These kinds of deregulations provoke prolonged inflammation and may lead to irreversible tissue damage. Roquin regulates inducible costimulator (ICOS) on CD4$^+$ T cell, and *Roquin*-deficient mice demonstrate lupus-like phenotype. TFL regulates IL-2 and IL-17a, which are produced by T cells, and *TFL*-deficient mice demonstrate prolonged inflammation on experimental autoimmune encephalopathy (EAE).

human peripheral T cells. Based on all these observation, it is reasonable to consider that TFL, as well as MCPIP, is a component of GW/P-bodies[14-16]. Importantly, the cytoplasmic granules that express p58^{TFL} are assembled after cell activation. Also, the deletion mutant of the C-terminus domain of TFL, such as p36^{TFL}, loses the subcellular localization at the cytoplasmic granules. It indicates that this domain is indispensable for the localization at GW/P-bodies, where TFL works in a restricted manner.

RNase activity for several cytokine mRNAs

The N-terminus of TFL has homology with those of other Zc3h12 family members. The PIN domain of Regnase-1 encoded by *Zc3h12a* acts as RNase, which results in mRNA degradation of cytokines, such as IL-2, IL-6, and IL-12[7]. Similarly, TFL is involved in the decay of several cytokine mRNAs, including IL-2, IL-6, IL-10, TNFα, and IL-17a. Especially in IL-17a, TFL in CNS-infiltrating CD4$^+$ T cells acts as a cytokine regulator during the resolution phase of experimental autoimmune encephalitis (EAE) [15]. Of note, the expression of TFL is persistently elevated in CNS-infiltrating CD4$^+$ T cells induced by MOG stimulation even during the resolution

phase. Therefore, this negative feedback regulation by TFL seems to be indispensable for the resolution of cytokine storm induced by inflammation. The C3h type of zinc finger motif has an important role for binding at a specific site of 3'UTR of target transcripts, such as ARE.

Deubiquitination activity

A family member, MCPIP, is first reported to have a deubiquitination (DUB) activity which modulates NFκB cellular signaling[19]. TFL also seems to have the same activity that affects NFκB signaling in the macrophage cell line, Raw 264.7[20]. In this study, a SNP variant of p36^{TFL} with lysine at codon 106 instead of arginine has been shown to lose the DUB activity. However, in our recent study, there is no difference in the DUB activity between wild type and TFL-deficient lymphocytes harvested from the CNS, spleen, and lymph nodes during the resolution phase of EAE. Moreover, IL-17a-induced NFκB signaling is not altered significantly in *TFL*-transfected HeLa cells[15]. Therefore, it is not yet determined how the DUB activity of TFL associates with its physiological function *in vivo*.

miRNA processing

Another possible mechanism for inhibition of

proliferation of inflammatory conditions is miRNA regulation via TFL. MCPIP has been reported to associate with miRNA biogenesis[18]. TTP interacts with miR-16 in the regulation of TNFα[21]. TFL also recognizes the stem loop-like hairpin structure but not the ARE in 3'UTR of IL-6 mRNA[15]. Moreover, some miRNAs, such as miR-195 and let-7g, are downregulated in activated T cells derived from *TFL⁻/⁻* mice in comparison with those from wild-type mice (unpublished data). Since TFL, as well as MCPIP, localize in the GW/P bodies that exist in the RNA-induced silencing complex (RISC), miRNA maturation can be regulated by TFL also. It is interesting to examine if TFL is associated with miRNA processing. Inhibition of miRNAs by TFL may also contribute to the inhibition of some signaling of cell proliferation.

Novel feedback mechanism in inflammation

In the discussion of inflammation, we consider at least two distinctive phases; initiation and resolution phases (Fig. 3). Both phases are tightly controlled by transcriptional and post-transcriptional factors[1]. In the initiation phase, innate immunity is more focused on the macrophage, which is the key player. For example, TTP controls TNFα and IL-10 expressions in the macrophage. The TTP-deficient mice demonstrate a rheumatoid arthritis-like phenotype. MCPIP/Regnase-1 also controls IL-6 mRNA expression and provokes plasma cell accumulation and early death. As regards the resolution phase, lymphocytes play vital roles in association with acquired immunity. Moreover, the focus is on post-transcriptional factors, which play a role on fine-tuning of inflammatory control, since the resolution phase is important for the regeneration of damaged tissues. More damaged tissues require a smoother resolution. If the resolution phase is not efficient, tissue recovery will be impaired. Therefore, in some chronic inflammatory diseases, delayed or prolonged recovery may be inevitable. A RING-type ubiquitin ligase family member, Roquin, is discovered through the search for lupus-like severe autoimmune disease mouse model (san roque mice). It regulates an inducible costimulatory molecule, ICOS, via post-transcriptional pathway[22]. Previous study revealed that TFL-deficient mice showed prolonged inflammation when EAE was induced by MOG in spite of marginal difference at the initiation phase of encephalitis[15]. It means that TFL is one of the possible important post-transcriptional regulators for inflammatory resolution. Thus, it is of interest whether TFL dysfunction may or may not be associated with human neuro-inflammatory diseases, such as multiple sclerosis.

Interestingly, TNF-induced early response genes frequently possess ARE[23]. Therefore, the post-transcriptional regulation of such early inducible genes is thought to be important for the regulation of inflammation. On the other hand, the functional role of mRNA regulation in T cells for the resolution of chronic inflammation is also thought to be important. However, the latter regulation seems to be overlooked, so far. If induced TFL in activated T cells has a functional role only for the resolution of chronic inflammation, it is reasonable to describe that the post-transcriptional machinery via TFL has little effect from induction to peak of disease not to dampen down the necessary inflammation. This function will in turn limit the expression of toxic inflammatory cytokines, such as IL-17a, during the resolution phase in order to inhibit excessive inflammation.

Functional expression in spatiotemporal manner

As shown above, TFL regulates several cytokine expressions in T cells, as well as B cells. In our EAE model, however, cytokine regulation via TFL is limited only within CNS-infiltrating lymphocytes even though TFL is activated in most peripheral immune organs, such as the spleen and lymph nodes. This is probably because post-transcriptional regulation is subtle compared with the transcriptional effect. For example, TFL-deficient T cells secrete more IL-2 under anti-CD3 stimulation without a costimulatory signal compared with the wild type. However, the wild type T cells can secrete sufficient IL-2 under anti-CD3 in the presence of co-stimulation with anti-CD28. Alternatively, post-transcriptional regulation of the immune system can be restricted only to the inflammatory site. The EAE model using TFL-deficient mice has an impaired recovery from neuroinflammation due to the accumulation of Th17 cells in the spinal tissues. On the contrary, there is no accumulation of peripheral Th17 even though TFL in lymphocytes is fully upregulated but not activated. Moreover, this cannot be recapitulated *in vitro* merely under the Th17 skew condition, such as the addition of TGF-β and IL-6 in the lymphocyte culture. Interestingly, there is no demonstration of more severe neuroinflammation in TFL-deficient than wild type mice during the initiation phase. Although there is enhanced paralysis in TFL-deficient mice at the peak of the disease, there is no increased accumulation of Th17 cells compared with the resolution phase. These results indicate that the role of TFL as a post-transcrptional regulator is more crucial for the resolution rather than initiation of inflammation. The regulatory mechanism of TFL has not been elucidated, so far. However, Regnase-1 is reported to be regulated via phosphorylation by IκB kinase activity[8,24]. TTP is also reported to have similar regulation by mitogen-activated protein kinase p38[25]. TFL can be regulated by such kinds of mechanisms, as well. In addition, since TFL has the same Malt-1/paracaspase cleavage site for Regnase-1[24], it can also be regulated by the same enzymatic cleavage.

Similarity and specificity of family members

The *Zc3h12* family consists of four independent genes (Fig.1). The putative gene products have one conserved region in the middle, which includes a NYN domain and a C3h zinc finger motif. The N and C terminus of these molecules are divergent, and they probably define the specific function of each member. Moreover, each family member shows a specific pattern in its tissue expression. For example, the human brain expresses only *Zc3h12b* and *Zc3h12c*. On the contrary, the fetal liver expresses only *Zc3h12a* and *Zc3h12d* mRNAs. They are all inducible proteins, but the induction pattern is also different. In the macrophage cell line, Raw264.7, *Zc3h12a* and *Zc3h12c* mRNAs are quickly induced (about 2-4 hours after stimulation) and then return to basal level by 24 hours[26]. On the other hand, *Zc3h12d* mRNA is slowly induced after 18 hours of stimulation in the macrophage. Even in T and B cells, induced p58[TFL] is expressed persistently at least until 72 hours after activation. Therefore, TFL is thought to be involved in the negative feedback loop to suppress excess inflammation.

However, the spatiotemporal regulation of each family member in inflammation seems to be different. In the light of inflammatory initiation and resolution, TFL has a critical role for controlling inflammatory resolution rather than initiation. The ZC3h12 family seems to utilize its function to orchestrate the whole immune reaction.

Future directions

TFL is a novel post-transcriptional regulator for cytokine expression in immune reaction. Its deficiency induces some dysfunction in the resolution of inflammation. Post-transcriptional regulation has not been fully elucidated; however, more understanding of this type of regulator can lead to a discovery of a new molecular target that can be useful for clinical diagnosis, as well as treatment for inflammatory diseases. Moreover, since TFL is first reported as a tumor suppressor gene, it may be associated with lymphomagenesis via the dysregulation of NFκB pathway in the lymphoma itself or lymphoma microenvironment where post-transcriptional regulation can also occur. The TFL study has just been started, but further studies can unveil the hidden pathway of immune regulation that governs not only autoimmune diseases but also many other inflammatory diseases.

Acknowledgement

Conflict of Interest

The authors declare that there is no conflict of interest.

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