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Original Article

CD38 expression on paraffin sections distinguishes follicular lymphoma from reactive follicular hyperplasia

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Abstract: This study explored the utility of CD38 immunodetection in paraffin-embedded tissue sections for differentiating follicular lymphoma (FL) from reactive follicular hyperplasia (RFH) by examining RFH (n = 47) and FL (n = 178). In RFH specimens, uniform weak-to-moderate CD38 immunostaining was observed in centrocytes and centroblasts across germinal centers (GCs). Moreover, these specimens contained a subset of strongly CD38-positive cells predominantly located in the light zone, which may represent antigen-selected surviving centrocytes that are committed to differentiate into plasma cells, i.e., centrocytoid plasma cells (CPCs). In FL specimens, CD38 staining yielded two patterns. In pattern I (146 specimens), weak-to-moderate CD38 staining was observed in tumor cells within neoplastic follicles. Neoplastic follicles in 126 of the 146 specimens did not contain strongly CD38-positive CPCs. Furthermore, individual neoplastic follicles in the remaining 20 FL specimens contained very few strongly CD38-positive cells (which may represent normal residual CPCs). In pattern II (32 cases), neoplastic follicles exhibited loss of CD38 expression accompanied by disappearance of CPCs. In conclusion, compared with RFH, the decrease of strongly CD38-positive CPCs in neoplastic follicles was a striking alteration, reflecting blocks in the lymphoid differentiation pathway. Moreover, loss of CD38 expression in neoplastic GC B-cells in some FL specimens can serve as an immunophenotypic characteristic of FL.

Keywords: Follicular lymphoma, reactive follicular hyperplasia, immunohistochemistry, CD38

Introduction

In pathology practice, follicular lymphoma (FL) and reactive follicular hyperplasia (RFH) are common biopsy findings with extremely different characteristics and prognoses but which sometimes may be confused with each other. Several studies have described histologic and immunophenotypic features in detail for the differential diagnosis of FL and RFH [1-3], but each has its own limitations. The determination of Bcl-2 expression in paraffin sections is the single most useful ancillary analysis, being consistently negative in RFH [4-6]. However, approximately 10%-15% of FL cases are negative, especially in high-grade cases [7-9]. Sometimes, Bcl-2-negative, high-grade FL cases are difficult to distinguish from florid RFH, and repeated biopsies may be required to establish a definitive diagnosis.

Germinal centers (GCs) are the sites of humoral immune responses and where B-cells interact with follicular dendritic cells (FDCs) and T cells differentiate into memory B cells or plasma cells [10-12]. Some studies have used plasma cell markers such as CD138, CD38, MUM-1, and BLIMP-1 to show that some positive GC B-cells possess a phenotype different from that of other GC B-cells [13-15]. These cells are mainly located in the light zone, and their morphology ranges from that of centrocytes to that of plasmablasts/plasma cells. Analysis of these cells by performing polymerase chain reaction (PCR) indicates that they contain rearranged Ig heavy chain genes with a varying number of VH somatic mutations, suggesting they may represent antigen-selected surviving centrocytes that are committed to exit GCs and differentiate into plasma cells [14], i.e., they represent centrocytoid plasma cells (CPCs).

In addition to being a plasma cell marker, CD38 also serves as a hallmark of GC B-cells [16-19]. Several studies have detected CD38 expression in frozen or paraffin-embedded FL sections

Table 1. Panel of antibodies tested

Antibody	Clone	Source	Dilution
CD20	L26	Labvision, Fremont, USA	1:100
CD3	SP7	Labvision, Fremont, USA	1:100
CD21	2G9	Labvision, Fremont, USA	1:100
CD10	56c6	Novocastra, Newcastle, UK	1:100
Bcl-6	LN22	Novocastra, Newcastle, UK	1:100
Ki-67	MIB-1	DAKO, Carpinteria, USA	1:100
CD38	38C03	Labvision, Fremont, USA	1:30
CD138	MI15	Labvision, Fremont, USA	1:80
Kappa	CH15	Novocastra, Newcastle, UK	1:3000
Lambda	SHL53	Novocastra, Newcastle, UK	1:10000
MUM-1	MUM1p	Novocastra, Newcastle, UK	1:200
BCL-2	Sp66	Novocastra, Newcastle, UK	1:100

by immunohistochemical analysis [20, 21]. However, a comparative study examining CD38 expression in FL and RFH has not been performed to date. The present study thus provides the first comprehensive comparative report of CD38 expression in FL and RFH specimens, and indicates that CD38 can serve as an immunophenotypic marker to differentiate between FL and RFH.

Materials and methods

Case selection

This study included formalin-fixed, paraffin-embedded tissue sections from patients with RFH (n = 47) and FL (n = 178), obtained from the Department of Pathology, Beijing Friendship Hospital, Capital Medical University, Beijing, China.

Immunohistochemical studies

Immunohistochemistry was performed on deparaffinized tissue sections using a polymer-enhanced 2-step immunohistochemical method (EliVision, MAXB, Maixin Bio., Fuzhou, China) according to the manufacturer's instructions. Primary antibodies against the following proteins were used: CD20, CD3, CD21, CD10, BCL-6, CD38, CD138, MUM-1, BCL-2, Ki-67, Kappa, and Lambda. The source, manufacturer, and working dilutions of the primary antibodies are summarized in **Table 1**. Deparaffinized RFH sections were examined for the expression of all the above-mentioned proteins. FL specimens were also examined for the expression of the above-mentioned proteins, except MUM-1, CD138, Kappa, and Lambda.

PCR for clonality analyses

B-cell clonality was examined in 36 FL specimens which were negative for BCL-2. DNA was extracted from the paraffin-embedded specimens using a previously described method [22]. The BIOMED-2 PCR method was performed to test B-cell clonality, including IgK, IgL, and IgH, as described previously [22]. Amplification products were analyzed by performing denaturing gradient gel electrophoresis on 10% polyacrylamide minigels.

Results

Immunophenotypic features of RFH and FL are summarized in **Table 2**.

Clinical and histopathological findings

RFH: The 47 RFH specimens consisted of palatine tonsils (n = 20; 11 male, 9 female; age range, 9-20 years) and lymph nodes (n = 27; 16 male, 11 female; age range, 12-67 years) from patients with lymphadenitis.

Histologically, reactive GCs were divided into four types according to their developmental stage. Developmental stage-1 GCs primarily contained centroblasts, as well as scattered tingible body macrophages, giving them a "dark zone" appearance. These GCs were usually small and distributed sparsely. Developmental stage-2 GCs contained centroblasts and centrocytes, were enlarged, and showed obvious light and dark zones. Developmental stage-3 GCs predominantly contained centrocytes with significantly reduced or no centroblasts, giving them a pure "light zone" appearance. Developmental stage-4 GCs were atrophic and significantly smaller. Although most RFH specimens contained GCs in different developmental stages, two specimens contained GCs predominantly in stage-1, and three specimens contained GCs predominantly in stage-4.

FL: FL specimens from 178 patients (103 male, 75 female; age range, 27–82 years) were ob-

Table 2. Immunophenotypic features of reactive follicular hyperplasia (RFH) and follicular lymphoma (FL)

Diagnosis	Total no. of specimens	CD38 expression in follicular structures			CD10$^+$	BCL-6$^+$	BCL-2$^+$
		GC B cells$^+$	GC B cells$^-$	Presence of strongly positive cells			
RFH	47	47 (100%)	0 (0%)	47 (100%)[I]	47 (100%)	47 (100%)	0 (0%)
FL	178	146 (82%) (Pattern I)	32 (18%) (Pattern II)	20 (11.2%)[II]	151 (84.8%)	178 (100%)	142 (79.8%)

[I]In RHF specimens, the number and distribution of strongly CD38-positive cells were closely associated with the different phases of GC development. In general, most RFH specimens contained GCs in different developmental stages and thus had many strongly CD38-positive cells within GCs. However, two specimens containing GCs predominantly in stage 1 (small GCs that mainly contain centroblasts, were distributed sparsely) and three specimens containing GCs predominantly in stage 4 (atrophic GCs) usually lacked or contained significantly fewer strongly CD38-positive cells within GCs. [II]In all, 20 of 146 FL specimens showed CD38 staining pattern I and these showed strongly CD38-positive cells in neoplastic follicles. The number of these cells in FL specimens decreased significantly compared with those in RFH specimens. Moreover, these cells were only observed in individual or very few follicles and are suggested to represent normal residual GC components.

tained from lymph nodes (n = 168), tonsils (n = 6), and soft tissue (n = 4). Most patients exhibited disseminated disease. Based on the WHO classification [23], 75 cases were classified as grade-I, 53 as grade-II, 31 as grade-IIIa, and 19 as grade-IIIb. All specimens showed an obvious follicular pattern.

Immunophenotypic findings

RFH: Reactive GCs showed CD10 and BCL-6 expression but were negative for BCL-2. Ki-67 staining indicated a high proliferation index (> 60%). CD21 staining highlighted a sharp FDC meshwork in GCs.

Uniform weak-to-moderate CD38 immunostaining was observed in centrocytes and centroblasts throughout GCs. Strong CD38 immunostaining was also observed in a cell subset within GCs, indicating a typical dual expression pattern. The number and distribution of strongly CD38-positive cells were closely associated with the different phases of GC development. These cells were rare or absent in developmental stage-1 GCs that were small and primarily contained centroblasts (**Figure 1A**, **1B**). Developmental stage-2 GCs contained abundant strongly CD38-positive cells in the light zone and sparse, scattered these cells in the dark zone. (**Figure 1C**, **1D**). Developmental stage-3 GCs usually contained numerous strongly CD38-positive cells whose number was up to 40% of the total number of GC B-cells (**Figure 1E**, **1F**). Developmental stage-4 (atrophic) GCs contained limited numbers of or even no strongly CD38-positive cells (**Figure 1G**, **1H**). Strong CD38 immunoreactivity was observed in plasma cells outside GCs, and weaker CD38 immunoreactivity was observed in some activated lymphoid and mononuclear cells in interfollicular areas.

MUM-1 staining revealed that the distribution and number of MUM-1-positive cells in GCs was similar to that of strongly CD38-positive cells (**Figure 2A-C**). CD138 staining was observed in fewer cells in sub-capsular or sub-mucosal follicles but not in GCs in deeper areas (**Figure 2D**). Kappa and Lambda staining indicated the polyclonal nature of these GC cells (**Figure 2E**, **2F**).

FL: All FL specimens showed BCL-6 expression and moreover, 151 FL specimens exhibited CD10 expression. Interfollicular areas of 26 specimens lacked obvious BCL-6- and/or CD10-positive tumor cells. Ki-67 staining showed variable numbers of proliferating cells within neoplastic follicles. Thirty-six specimens were negative for BCL-2, including twelve grade-II, sixteen grade-IIIa, and eight grade-IIIb cases.

CD38 immunostaining exhibited two patterns. Pattern I (146 specimens) exhibited uniform weak-to-moderate CD38 staining in neoplastic follicles. Neoplastic follicles in 126 of the 146 specimens entirely lacked strongly CD38-positive cells (**Figure 3A**, **3B**). Only rare, scattered strongly CD38-positive cells were observed in a very few neoplastic follicles in the remaining 20 cases. CD38 expression was also observed in tumor cells in the inter-follicular

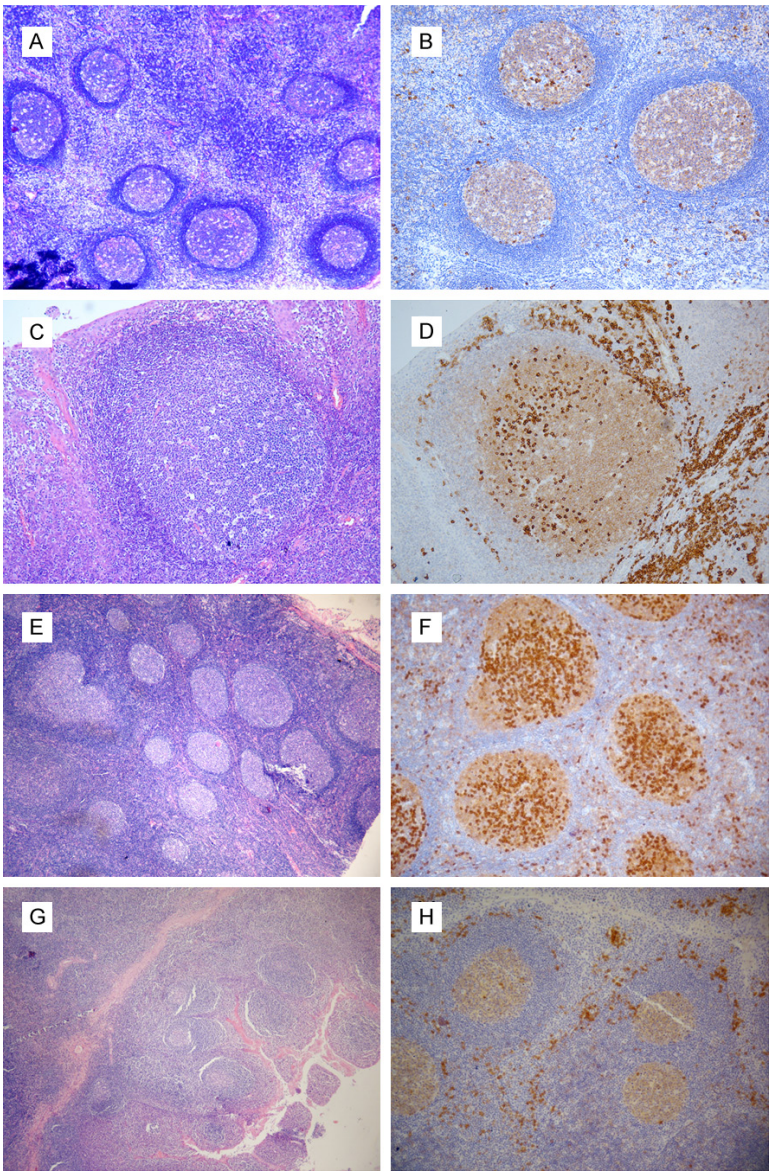

Figure 1. Results of CD38 immunostaining pattern in RFH specimens. CD38 immunoreactivity was observed in centrocytes and centroblasts across GCs with uniform weak-to-moderate staining intensity. In addition, strong CD38 immunoreactivity was observed in a subset of cells in GCs, indicating a typical dual expression pattern. The number and distribution of strongly CD38-positive cells were closely associated with the different phases of GC development. A and B: GCs in developmental stage 1. A: A RFH specimen containing GCs predominantly in developmental stage 1. GCs are small, primarily contain centroblasts and scattered tingible body macrophages, giving them a "dark zone" appearance, and show sparse distribution (H&E stain). B: Cells showing strong CD38 expression are sparse or absent. C and D: GCs in developmental stage 2. C: GCs showing polarization (light and dark zones) (H&E stain). D: Many strongly CD38-positive cells predominantly located in the light zone of GCs, with limited number of these cells scattered in the dark zone. E and F: GCs in developmental stage 3. E: GCs predominantly containing centrocytes (H&E stain). F: The number of strongly CD38-positive cells was high (up to 40% of the total number of GC B-cells). G and H: GCs in developmental stage 4. G: A RFH specimen containing GCs predominantly in developmental stage 4 (atrophic GCs) (H&E stain). H: The number of strongly CD38-positive cells is greatly reduced or no strongly CD38-positive cells can be observed.

areas and was usually down-regulated. Pattern II (32 specimens) showed tumor cells within the follicles had lost CD38 expression, and the strongly CD38-positive cells had also disappeared. (**Figure 3C**, **3D**).

Molecular study

In all, 36 FL specimens which were negative for BCL-2 showed clonal Ig gene rearrangements.

Discussion

Several plasma cell markers, including CD138, CD38, MUM-1, and BLIMP-1, have been reported to highlight the antigen-selected surviving centrocytes in GCs which are committed to differentiate into plasma cells [13-15], i.e., CPCs. Of these markers, we focused on CD38. CD38 is a type-II transmembrane glycoprotein with a complex and distinct enzyme activity and is widely expressed by hematopoietic and non-hematopoietic cells [24-27].

Analysis of B cells in human tonsils indicates that CD38 serves as a hallmark of GC B-cells [16-19]. Although the precise role of CD38 in GC B-cell development is unclear, an *in vitro* study suggested that CD38 signaling prevented the apoptosis of tonsilar GC B-cells [28]. Normal tonsils and lymph nodes were examined in the present study. In all of these biopsies, uniform, weak-to-moderate CD38-positive cells were observed throughout GCs, as well as in a subset of strongly positive CPCs (usually 3%-15%, occasionally up to 40%), demonstrating a typical dual

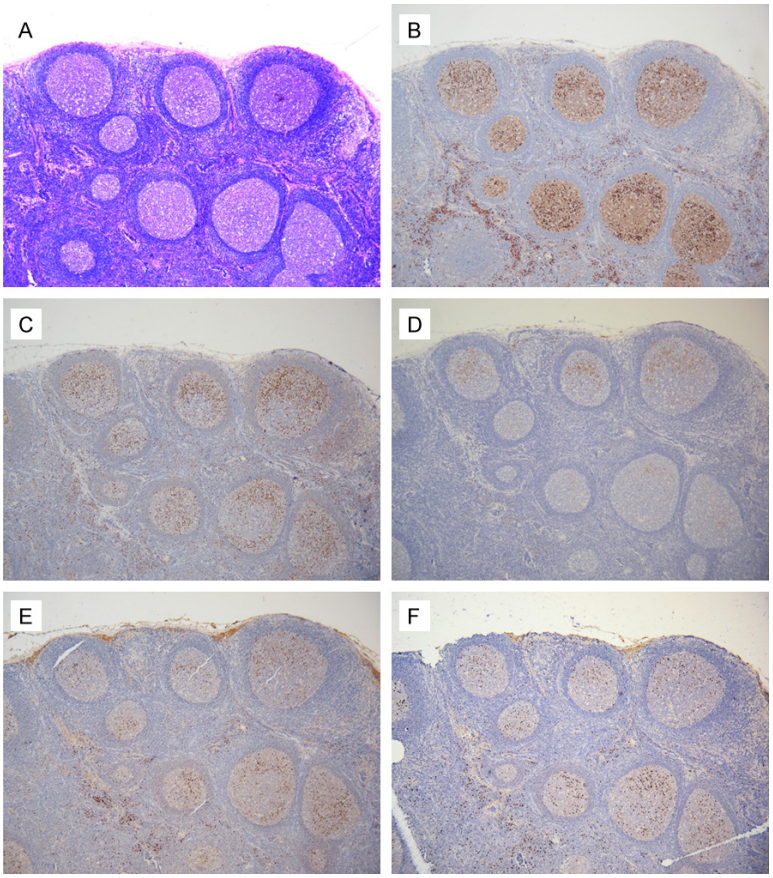

Figure 2. Results of a comparative study of CD38, MUM-1, CD138, Kappa and Lambda staining in RFH. (A) A lymph node specimen containing reactive follicles ((H&E stain)). (B) CD38 and (C) MUM-1 staining revealed that the number and distribution of strongly CD38-positive cells were similar to those of MUM-1-positive cells in GCs. (D) CD138 staining indicated that the positive cells were located predominantly in GCs near the capsule and were usually absent in GCs in deeper areas. (E) Kappa and (F) lambda staining indicate the polyclonal nature of cells in GCs.

expression pattern. Notably, the number and distribution of CPCs was associated with the different phases of GC development.

Several studies detected CD38 expression in frozen or paraffin-embedded tissue sections obtained from a small number of FL cases by performing immunohistochemistry [20, 21]. However, a comparative study of CD38 expression in FL and RFH has not been performed to date. The present study showed that CD38 expression in FL was extremely different from that in RFH. In all, 146 FL specimens with CD38 staining pattern I showed weak-to-moderate staining in neoplastic follicles. Of these 146 specimens, 126 entirely lacked strongly CD38-positive CPCs in neoplastic follicles, whereas the remaining 20 specimens exhibited only rare, scattered strongly CD38-positive cells in very few neoplastic follicles. Using immunohistochemistry, microdissection, and PCR analysis, Su et al. observed the infiltration of benign GCs by tumor cells in FL. Even in cases where the entire follicle appeared Bcl-2 positive, residual normal GC cells were still present [29]. Although we did not characterize these individual strongly CD38-positive cells in neoplastic follicles, we speculate that they most likely represent normal residual GC components.

Thirty-two cases of FL with pattern II exhibited loss of CD38 expression accompanied with the disappearance of strongly CD38-positive cells. This was consistent with another study showing decreased CD38 expression in FL compared with that in RFH by performing flow cytometry analysis [30].

Compared with reactive GCs, the disappearance of or greatly decreased numbers of strongly CD38-positive CPCs in neoplastic follicles was a striking alteration, reflecting blocks in the lymphoid differentiation pathway of the neoplastic GC B-cells. Moreover, loss of CD38 expression in neoplastic GC B-cells observed in some specimens can serve as an immunophenotypic characteristic of FL.

We also observed that the distribution and number of MUM-1-positive cells in GCs were similar to those of strongly CD38-positive CPCs, whereas fewer CD138-positive cells were observed within the sub-capsular and the submucosal follicles. GCs in deeper areas were usually CD138 negative, which may reflect a higher requirement of tissue fixation for reliable CD138 staining. Falini et al. reported that many MUM-1-positive cells in GCs did not show CD138 expression, suggesting that MUM-1 expression most likely preceded CD138 ex-

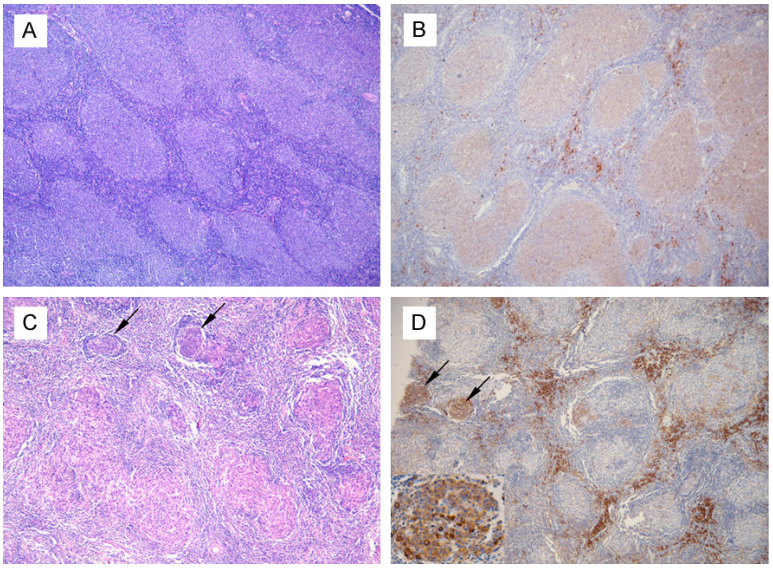

Figure 3. Result of CD38 staining pattern in FL specimens. A and B: pattern I. A: Low-power magnification of a grade-I FL specimen showing back-to-back arrangement of neoplastic follicles ((H&E stain)). B: Uniform moderate CD38 staining can be observed across neoplastic follicles; strongly CD38-positive cells, as observed in normal GCs, are absent. C and D: pattern II. C: Low-power magnification of a grade-IIIb FL specimen showing neoplastic follicles and several residual reactive follicles (arrows; H&E stain). D: The neoplastic follicles did not show CD38 staining, and the residual reactive follicles exhibited a reactive pattern for CD38 staining (arrows). (High-magnification image of a residual follicle with a reactive pattern of CD38 staining in the lower left corner).

pression [14]. CD138 and MUM-1 were not used to compare FL and RFH in the present study, because in our experience and that of others [14], CD138 stained fewer CPCs in GCs compared with MUM-1 and CD38. However, MUM-1 may be expressed by tumor cells in some FL cases, especially in high-grade cases [31-33].

When using CD38 immunostaining as a tool to distinguish between FL and RFH, it should be noted that analysis of CD38 expression patterns is only suitable for groups of follicles and not for individual follicles. Moreover, comprehensive judgment should be made based on morphological features because reactive GCs in developmental stages 1 (small GCs that predominantly contain centroblasts, and were distributed sparsely) and 4 (atrophic GCs) usually lacked or contained significan-tly less number of CPCs. Moreover, some FL specimens may contain sparse strongly CD38-positive cells in individual neoplastic follicles.

Conclusion

Our results indicate that immunohistochemical staining of paraffin-embedded sections for CD38 is a simple and easy method for differentiating between FL and RFH. Moreover, our results indicate that CD38 staining has differentiating value even for Bcl-2-negative cases.

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Disclosure of conflict of interest

None.

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