Lymphocyte immunophenotyping in inflammatory myositis: a review

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Purpose of review
This is a comprehensive review of the current knowledge on predominant immune cell phenotypes involved in idiopathic inflammatory myopathies (IIM).

Recent findings
Major circulating immune cell subpopulations described in IIM encompass the lymphocyte compartment. An unbalance in T cell subsets seems to consistently affect the peripheral and muscle compartment, with a predominance of CD4+ T and B cells in dermatomyositis, CD8+ T cells in polymyositis/inclusion body myositis (IBM) and novel findings highlighting novel proinflammatory T subsets, that is, CD8+Tbet+ and CD28− T cells across different IIM subsets. On the other hand, an impairment in Treg cells number and function has been described especially across polymyositis/dermatomyositis and IBM. Total T follicular helper (Tfh) cells, increased in immune-mediated necrotizing myopathy, skewed toward Tfh2 and Tfh17 in dermatomyositis, polymyositis, and juvenile dermatomyositis. B cell compartment is more rarely described in IIM, yet an unbalance in this pool is as well likely. Evidence of plasma cells increased in polymyositis, dermatomyositis, IBM, and Bregs decreased in dermatomyositis have been reported. Perturbations in the memory and naïve subsets are common in dermatomyositis/polymyositis and antisynthetase syndrome.

Summary
Protean immune cell abnormalities characterize different IIM subsets, reflecting the complexity of these autoimmune conditions. A deeper understanding of B-cell and T-cell immunophenotyping may promote early diagnosis and identification of new potential therapeutic targets.

Keywords
idiopathic inflammatory myopathies, immune system, peripheral and tissue lymphocytes

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of rare and heterogeneous muscle inflammatory diseases, which differ from each other in muscle involvement and extra-muscular manifestations [1]. Myositis are autoimmune diseases characterized by both inflammatory and non-inflammatory mechanisms, immune abnormalities [2] and nonimmune mechanisms [3], sustained by genetic and environmental predisposing factors [2]. Disease subsets encompass dermatomyositis [2,4], polymyositis, immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome, with a distinctive feature of lung involvement [5], overlap syndrome with myositis, inclusion body myositis (IBM), and cancer-associated myositis (CAM) [2]. Growing evidence demonstrates an interaction between the immune system and skeletal muscle injury in IIM, following different pathogenetic mechanisms [6▪]. Indeed, the histopathological features of IIM share the presence of mononuclear cell infiltrates and muscle fiber necrosis [7]. Although both the innate and adaptive immune systems appear to be involved in the pathogenesis of IIM [8], lymphocytes seem to play a central role [9], where adaptive immunity to self-antigens is induced [10,11]. T and B cells are major components, recognizing specific antigens and generating specific cell-mediated or antibody-mediated responses [12▪▪]. T cells are predominant in muscle inflammatory infiltrates, with differences

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KEY POINTS

- Lymphocytes play a central role in myositis pathogenesis, where adaptive immunity to self-antigens is induced.
- An unbalance in T-cell and B-cell subsets seems to affect the peripheral and muscle compartment of myositis patients.
- The understanding of immune cells abnormalities in the different subsets of IIM may promote early diagnosis and identification of new potential therapeutic targets.

in T cell subpopulations according to myositis subset, while B cells are rare [10]. T-cell subsets include CD4+ T helper (Th) cells, which recognize major histocom-patibility complex (MHC) class II-presenting peptides, and CD8+ cytotoxic T-cells, recognizing MHC class I-restricted peptides [10]. Consequently, CD4+ T cells generate a repertoire of effector T cells, including Th and T follicular helper (Tfh) cells, that activate target cells, besides regulatory T (Tregs) cells with immunosuppressive function [12▪▪]. Significantly, it has been reported an association between HLA alleles and autoantibody specificities in IIM patients [13]. Despite their predominance in biopsy [8], the precise role of T cells in the pathogenesis of IIM has not been clarified; nevertheless, the presence of T lymphocytes expressing restricted T cell receptor (TCR) families suggests that clones capable of recognizing autoantigens effectively participate in the pathophysiology of the disease [6▪]. Consistently, myositis-specific (MSAs) and myositis-associated autoantibodies profile represents a diagnostic tool for adult and juvenile polymyositis/dermatomyositis [14–17]. MSAs are associated with CAM, peculiar skin lesions or pulmonary involvement [14] in IIM, and they are useful in the definition of disease subsets [16]. This review aims to overviewthe major lymphocyte subsets in IIM.

T LYMPHOCYTES

Tissue T lymphocytes

The classical infiltrating lymphocyte pattern highlights CD4+ T cells and B cells to be prevalent in the perimysium in dermatomyositis [8], with CD4+ Th cells and B cells infiltrating endomysial capillaries [9] too, while CD8+ T cells predominantly populate the endomysium in polymyositis [8]. CD8+ T cells in polymyositis directly attack muscle fibers expressing MHC class I-presenting antigens [9,6▪], with consequent release of cytotoxic molecules, tissue destruction, and release of autoantigens [6▪]. It has been observed that CD8+ T cells infiltrating IIM muscle express perforin-1, granzyme B [10], and IFN-g [18], indicating their muscle cytotoxicity [10]. The subset CD8+CD57+ T cells exhibit enhanced cytotoxic potency and impaired prolifer-ative capability [18]. Significantly, it has been observed an expansion of these cells in IIM patients compared with healthy controls, particularly in IBM. On the contrary, this population is not increased in antisynthetase syndrome anti-Jo-1+ patients [19▪]. Specifically, it has been observed an increased frequency of CD8+ T cells expressing high levels of T-bet (T-box expressed in T cells) and senescent marker CD57 (CD8+T-bet+CD57+ $CD28^{null}CD27^{null}CD127^{null}$) in both the muscle and blood of sIBM. The presence of also nonsenescent cells (CD8+T-bet+ CD57- $CD28^{low}CD27^{low}$C-$D127^{low}$CD38+HLA-DR+) in the patients suggests continuous proliferative capacity and effector functions of these cells, explaining the progressive and destructive nature of IBM [20▪]. Finally, CD8+T-bet+ cells have been suggested as IBM biomarker [20▪], thus partially justifying the resistance of IBM to glucocorticoid treatment, since terminally differentiated effector T cells seem to be resistant to glucocorticoids [6▪]. Another peculiar infiltrating pattern has been identified in the IBM muscle, that encompasses a signature of highly differentiated cytotoxic CD8+ T cells (effector memory cells, TEMs, and terminally differentiated effector memory cells, TEMRAs) [12▪▪], responsible for myofibers destruction [20▪,21]. The interaction of various inflammatory cytokines and chemokines can lead to an imbalance between regulatory [e.g., regulatory T (Tregs)] and inflammatory (e.g., Th17) cells [11,22], as well as abnormal autoantigen clearance mechanisms and antigen presentation [11]. Tregs reduction is observed within the muscle of IBM patients [23], while in juvenile dermatomyositis (JDM) patients muscle Tregs seem to be increased, despite their loss of function in regulation of the immune system [23,24]. In accordance, many studies report functional deficiency of Tregs in all IIM clinical subsets [25].

A novel highly differentiated CD28− T-cell subset has been found in peripheral blood and inflammatory infiltrates of IIM patients [8], as predominant muscle-infiltrating T-cell phenotype [8,12▪▪]. This long-lived pro-inflammatory T cell [10] is proposed to arise from prolonged T cells stimulation [8], as a result of a chronic inflammatory stimulus [10]. CD28− T cells might display strong myotoxicity [8] because of their high-IFN-g secretion and degranulation potential [12▪▪]. In

comparison with CD28+ T cells, CD28− T cells are hypersensitive and able to release large amounts of cytokines as well as cytolytic granules [12▪▪]. Specifically, CD28− T cells are increased in the muscle of dermatomyositis, polymyositis, and IBM patients [12▪▪]. In polymyositis, CD28−, CD4+, CD8+ T cells can induce a greater degree of muscle cell death. Furthermore, myotubes are more sensitive to CD28− T cell lethality than myoblasts, possibly owing to muscle-specific antigens during differentiation [12▪▪]. In addition, these cells are less responsive and resistant to apoptosis and to immunosuppressive therapies [8]. Indeed, CD28− T cells proliferation and function are only partly suppressed by glucocorticoids and Tregs in dermatomyositis/polymyositis patients [12▪▪].

Circulating T lymphocytes

Increased CD4+ T cells are also represented in peripheral blood of dermatomyositis patients, while both dermatomyositis and polymyositis patients exhibit decreased circulating CD8+ central memory T-cells [12▪▪]. On the other hand, Shimojima *etal.* [9] found decreased CD4+, CD8+, and CD3+ T cells within the peripheral blood lymphocytes of poly-myositis/dermatomyositis patients with active disease. Among peripheral blood lymphocytes, the proportion of activated Th cells was significantly increased in both polymyositis and dermatomyositis, when compared with controls, while natural killer and activated B cells were significantly decreased [9]. Immediately after muscle injury, the immune response is dominated by the arrival of Th1 lymphocytes and the stimulation of proin-flammatory cells [6▪]. The increase in the percentages of activated Th1 and Th2 cells, with a decrease of Th17 cells, leads to increased Th2/Th1, Th2/Th17, and Th1/Th17 ratios in patients compared with controls, and reflect disease activity but not severity in polymyositis/dermatomyositis [9]. By contrast, a recent review reported increased Th17 cell subset in the peripheral blood of both adult and JDM [9,12▪▪]. Th2/Th17 in both polymyositis and dermatomyositis, and Th2/Th1 in dermatomyositis, significantly decreased after clinical remission compared with those observed before treatment in patients who received prednisolone with or without immunosup-pressive agents [9].

The increase in CD8+T-bet+ observed in the muscle is confirmed in the blood of sIBM. Moreover, consistently with the decrease in Treg cells in inflamed muscle [6▪], the decrease in peripheral Tregs [8] in polymyositis/dermatomyositis patients would fail to prevent autoimmunity and control inflammation, contributing to the pathogenesis of these diseases. Tregs reduction could be aggravated by conventional therapies, especially immunosuppressive agents, consequently increasing patients' risk of malignancies and infections [26]. The lack of significant differences among peripheral blood lymphocytes subsets in JDM make them poor predictors of disease activity. However, it has been reported a higher Th/T suppressor cell ratio in JDM patients with respect to healthy controls [21], and activated CD3+CD69+ T cells decrease in association with a decreased disease activity [21].

The levels of circulating Tfh cells precursors are found to increase in IIM patients compared with controls, and the dysregulation of Tfh cells and its associated cytokine (IL-21), may cause loss of immune tolerance of B-cells [22]. The circulating Tfh CXCR5+CD4+ T cells are specialized to support B cell maturation in germinal centers. Tfh cells are skewed toward Tfh2 andTfh17, as opposedtoTfh1cells,in dermatomyositis, polymyositis, and JDM patients, and this cell differentiation has been linked to disease activity and the number of blood plasmablasts. In addition, Tfh cells are increasedinIMNMpatient with positive HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase) target [12▪▪,27] autoantibody and subsequently declined after immunosuppressive therapy, with an improved clinical outcome [12▪▪].

The increase of CD28− T cells in the peripheral blood of dermatomyositis, polymyositis, and IBM patients is lower compared with the frequencies detected in inflamed muscle, indicating active recruitment, local proliferation or preferential retention of CD28- T cells in the tissue [8,12▪▪].

B LYMPHOCYTES

Tissue B lymphocytes

B-cell activating factor (BAFF) up-regulation in muscle biopsy, especially in patients with anti-Jo-1 antibodies and dermatomyositis, suggests that a local maturation of B cells to antibody-producing plasma cells may occur in myositis, where B cells may act as antigen-presenting cells [10]. Moreover, BAFF Receptor is expressed in skeletal muscle inflammatory cells, and BAFF expression may be associated with an increased number of CD4+ T cells and CD19+ B cells in dermatomyositis, suggesting that BAFF/BAFF-R pathway contributes to both T and B cell responses [28]. Consistently, both B cells [29] and terminally differentiated plasma cells [21], have been reported in muscle tissue of polymyositis [8,10], dermatomyositis, sIBM [10], and IBM [8] indicating their likely role in muscle inflammation [10]. More recently, it has been shown that plasma cells can be identified in all subtypes of IIMs and may undergo modifications (clonal expansion, class

switch recombination, and somatic hyper mutation) that support an antigen-driven response, while B cells are found in the perivascular infiltrate of dermatomyositis patients [24].

Within the muscle biopsies of anti-Jo1 antisynthetase syndrome patients, it has been found perifascicular infiltrations of memory B cells. The dysregulated homeostasis of memory B cells between tissue and blood compartments suggests that they target the muscle, where they carry out effector functions [19▪]. Consistently to peripheral blood, IgM+ Jo-1-binding B cells are detected in the muscle biopsy of antisynthetase syndrome [30▪].

Circulating B lymphocytes

It is well known that autoantigens, such as Jo-1 and Mi-2, drive a B-cell antigen-specific immune response in muscles [10], which reflects the presence of MSA as circulating markers of disease entities within the spectrum of myositis [15], including polymyositis/dermatomyositis patients [14,24]. In the peripheral blood of JDM patients with active disease, immature transitional B cells, presenting an inflammatory phenotype, are expanded [30▪]. Conversely, circulating transitional B cells did not differ in dermatomyositis compared with controls, yet their level decreased after treatment [12▪▪]. Circulating naive and memory B cells are abundant in dermatomyositis/polymyositis patients [12▪▪], while a decrease in memory B cells together with an increase in naive B cells have been reported in anti-Jo1 syndrome [12▪▪,19▪].

A recent research highlighted that in antisynthetase syndrome patients, the majority of Jo-1-binding B cells were IgM+ (not class-switched) with a higher percentage of autoimmune-prone $CD21^{lo}$ cells related to disease severity, compared with non-Jo-1-binding B cells. Moreover, $CD21^{lo}$IgM+IgD-CD27+ memory B cells were increased, showing a reduced capacity to differentiate into antibody-secreting cells. Specifically, the detection of IgM+ Jo-1-binding B cells in peripheral blood, consistent with antisynthetase syndrome/IIM patient muscle biopsy findings, suggests that IgG class switch and terminal differentiation of Jo-1-binding B cells occurs at the site of attack. Authors reported that IgG class-switching of Jo-1-binding B cells is not restricted to tissue and that they exit tissues to recirculate after undergoing IgG class switch [30▪]. Consistently, in vitro data showed a reduced frequency of Jo-1-binding B cells differentiated into CD38hiCD24− plasmablasts compared with non-Jo-1-binding B cells [30▪].

To date, the evidence about the role of $CD19+CD24^{high}CD38^{high}$ regulatory B cells (Bregs) with immunosuppressive properties is not fully elucidated and limited to dermatomyositis [31,12▪▪]. It has been observed a significant decrease of Bregs in blood samples of dermatomyositis patients in comparison with healthy controls and patients affected by other autoimmune diseases [31,32], showing a relationship with MSA, pulmonary interstitial fibrosis and global disease scores [12▪▪]. In fact, dermatomyositis patients with positive MSA had lower Bregs levels than negative patients, and lower level of Bregs was also found in dermatomyositis patients with than in those without interstitial lung disease. Indeed, dermatomyositis patients in remission, had Breg levels significantly increased after treatment [31].

NOVEL POTENTIAL CIRCULATING MARKERS IN IMMUNE-MEDIATED INFLAMMATORY MYOSITIS

Recently, it has been compared the number of lymphocytes with that of neutrophils, players of adaptative and innate immunity, respectively. The value of neutrophil-to-lymphocyte ratio (NLR) in adult patients with polymyositis/dermatomyositis was investigated in survived and nonsurvived patients. Polymyositis/dermatomyositis patients in nonsurvivor group exhibited a significantly higher baseline NLR value compared with that in the survivor group. The research revealed that high-NLR value is an independent risk factor for survival in patients with polymyositis/dermatomyositis, especially in association with lung involvement. Furthermore, it has been suggested to be associated with disease activity in many malignant and nonmalignant diseases, including systemic autoimmune diseases [33].

Significantly, extracellular vesicles has been reported as participating in abnormal activation of the autoimmune system [11]. These heterogeneous lipid bilayer nanoparticles, naturally released from cells [34,35], mediate cell-cell communication. Extracellular vesicles play a role in different immune-related processes: antigen presentation, T-cell stimulation, cell killing, cytokine transport, and Treg cells differentiation (Fig. 1). Moreover, they induce antigen-specific tolerance and establish allograft tolerance [36]. Extracellular vesicles express peptide-MHC [36], thus they can present intracellular self-antigens to activate autoreactive T cells [11], including both CD8+ and CD4+ T lymphocytes [36], which in turn mediate the development of the disease [11]. Furthermore, TCR-enriched extracellular vesicles released by T cells are activation-competent, highlighting a novel form of contact-independent APC-T cell crosstalk [36]. It is noteworthy that extracellular vesicles derived from Treg

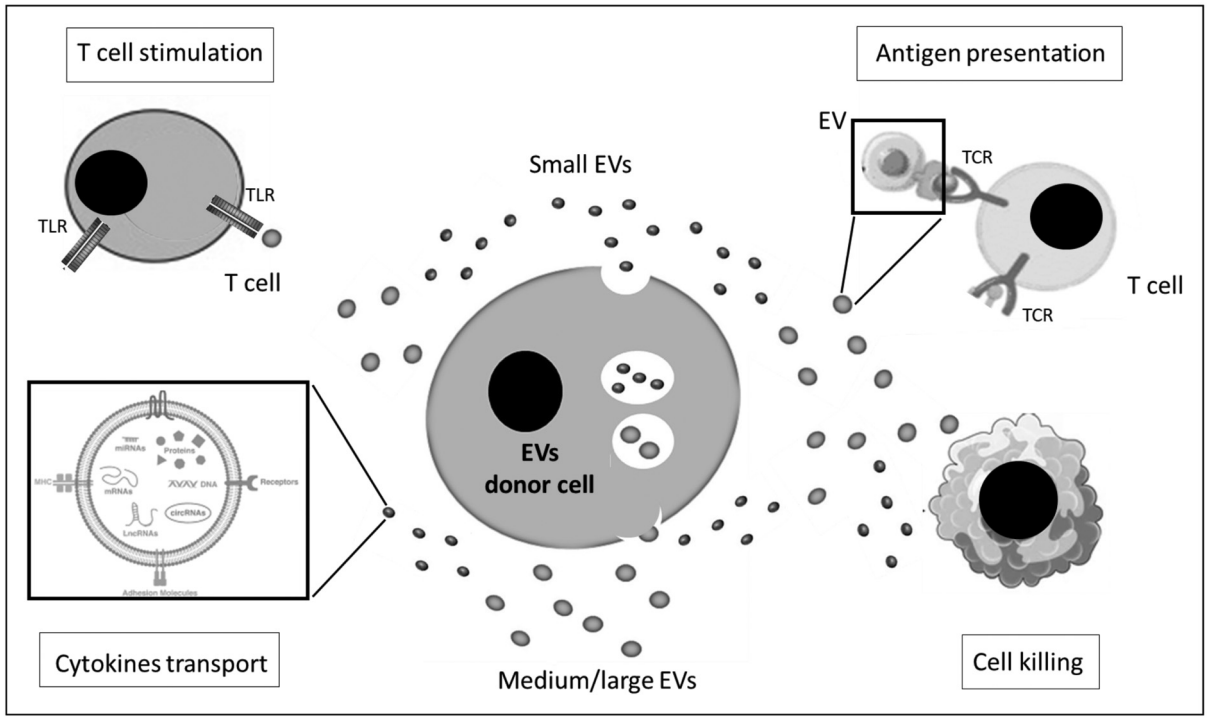

FIGURE 1. Role of extracellular vesicles in immune-related processes. The extracellular vesicles released from cells participate in abnormal activation of the autoimmune system acting at level of T-cell stimulation, antigen presentation, cytokine transport and cell killing. EVs, extracellular vesicles; TCR, T-cell receptor; TLR, Toll-like receptor.

cells could promote other T cells polarized to the Treg phenotype [37]. Indeed, Treg cells inhibit the proliferation and function of Th1/Th17 cells through direct cell-cell contact, producing anti-inflammatory cytokines, and releasing extracellular vesicles with regulatory activity [36]. On the other hand, extracellular vesicles from endothelial cells possess the modulation ability which blocks T cells activation and dampens tissue chronic inflammation [37]. In addition, immune cell-derived extracellular vesicles not only promote immunity but can also reduce immune activity [11], for example modulating the suppressive function of Treg cells [36]. Finally, mesenchymal stem cells release immunosuppressive extracellular vesicles, which are actually used to treat autoimmune diseases [37].

THERAPEUTIC OPTIONS

Most of therapeutic strategies for IIM are directed to suppressing or modifying immune cells activity [10] as immunotherapy treatment [38]. Current treatment in polymyositis/dermatomyositis is focused on the efficacy of glucocorticoid-sparing immunosuppressive agents. Glucocorticoids are used empirically as first-line treatment despite their various adverse effects. However, the concomitant treatment with glucocorticoid-sparing immunosup-pressive agents, even as combined multitarget treatment, successfully reduces the initial glucocorticoid dose for remission induction, the relapse risk during glucocorticoid tapering, and adverse effects of glu-cocorticoids [39]. Finally, biologics drugs seem promising in some IIM patients [39]. Indeed, a recent study conducted in polymyositis and derma-tomyositis patients highlighted that absolute numbers of Tregs is restored by low-dose IL-2, which also allows a modest increase of other circulating lymphocytes populations. This treatment, coupled with conventional therapy, leads to clinical remission reducing muscle tissue inflammation and chemo-kines secretion by fibroblasts, thus decreasing peripheral lymphocytes infiltration [26]. Finally, a suggested therapy against antisynthetase syndrome (Jo-1+) should target both nonclass-switched Jo-1-binding B cells and IgG class-switching to more effectively block cross-talk with autoreactive T cells [30▪].

CONCLUSION

The growing interest in the characterization of lymphocyte populations involved in the pathogenesis of myositis aims to use them for differential diagnosis of disease subsets (Table 1). Moreover, the

Table 1. Abnormalities in lymphocyte subsets in idiopathic inflammatory myopathies (IIM)

Tissue T lymphocytes	
DM	↑ CD4+ T cells; CD28− T cells
PM	↑ CD8+ T cells; CD28− T cells
IBM	↑ TEMs and TEMRAs cells; CD28- T cells; CD8+T-bet+ cells
	↓ Treg cells
JDM	↑ Treg cells
Tissue B lymphocytes	
DM	↑ B cells; plasma cells
PM	↑ B cells; plasma cells
IBM	↑ B cells; plasma cells
ASS	↑ IgM+ Jo-1 binding B cells; memory B cells
Circulating T lymphocytes	
DM	↑ CD4+ T cells; Th1, Th2 cells; Tfh2, Tfh17 cells; CD28− T cells
	↓ CD8+ T cells; CD8+ memory T cells; CD3+ T cells
PM	↑ Th1, Th2 cells; Tfh2, Tfh17 cells; CD28− T cells
	↓ CD8+ T cells; CD8+ memory T cells; CD3+ T cells; Th17 cells; Treg cells
IBM	↑ CD28− T cells; CD8+T-bet+ cells
JDM	↑ Th17 cells; Tfh2, Tfh17 cells
Circulating B lymphocytes	
DM	↑ Naïve B cells; memory B cells
	↓ Breg cells
PM	↑ Naïve B cells; memory B cells
JDM	↑ Immature transitional B cells
ASS	↑ Naïve B cells; CD21lowIgM+IgD-CD27+ memory B cells
	↓ Memory B cells

Characterization of T and B lymphocytes in tissue and circulating compartments in myositis subsets. Up and down arrows indicate expanded and reduced population, respectively. ASS, antisynthetase syndrome; Breg cells, regulatory B cells; DM, dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathies; JDM, juvenile dermatomyositis; PM, polymyositis; TEMRAs, terminally differentiated effector memory cells; TEMs, effector memory cells; Tfh cells, T follicular helper cells; Th cells, T helper cells; Treg cells, regulatory T cells.

recent correlations between lymphocytes and neutrophils (NLR), as well as the study of extracellular vesicles role in autoimmune diseases indicate the continuous research for new disease-specific biomarkers. Myositis therapeutic strategies are constantly evolving with the aim of affecting the immune response. Further understanding of the lymphocyte populations that dominate myositis will help to manage the differential diagnosis and appropriate therapy for these diseases.

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Conflicts of interest

There are no conflicts of interest.

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