Endothelial Signaling by Ig-Like Cell Adhesion Molecules

Jaap D. van Buul, Edwin Kanters, Peter L. Hordijk

Abstract—The migration of leukocytes across the endothelial lining of the vascular wall requires a complicated series of adhesion and signaling events. Endothelial Ig-like cell adhesion molecules (IgCAMs) such as intercellular adhesion molecule-1 play an important role, not only as ligands for leukocyte integrins, but also as signaling initiators. Clustering these IgCAMs triggers a wide range of events in the endothelial cells’ interior, of which activation of Rho-like GTPases, induction of cytoskeletal changes, and the transient modulation of cell-cell contact are key events. This review discusses recent insights into this IgCAM-driven endothelial signaling and its consequences for leukocyte transendothelial migration. (Arterioscler Thromb Vasc Biol. 2007;27:1870-1876.)

Key Words: ICAM-1, VCAM-1, transendothelial migration, signaling, Rho GTPases

Leukocytes migrate to and from the blood stream both in a constitutive and an induced fashion, both of which are subject to tight regulation. Constitutive trafficking of leukocytes across the vascular endothelium comprises migration of newly formed differentiated cells from the bone marrow into the blood, as well as migration of cells from the blood back into the tissues and through the lymphatic system. On the other hand, stimulus-induced leukocyte transendothelial migration (TEM) mainly occurs in response to inflammatory stimuli or chemokines and occurs in postcapillary venules as well as in arteries, initiating inflammation-driven diseases such as atherosclerosis.

There is a broad range of regulatory molecules involved in leukocyte trafficking. These include cytokines, chemokines, adhesion molecules and their receptors, cell signaling molecules and adapters, and structural proteins such as actin and tubulin. Most of these proteins have specific functions in both the migrating leukocyte as well as in the endothelial cells and are regulated in a spatiotemporally coordinated fashion to ensure efficient TEM at the correct location. The paradigm of multistep leukocyte transendothelial migration has been extensively reviewed previously.1-4 This model has been extended in recent years by accumulating evidence for the active role of the endothelial cells in TEM. It is now clear that the endothelium not only serves as the key adhesive surface for activated leukocytes but also controls the efficiency of TEM, either through differential expression of IgCAMs, through transient or local modulation of endothelial permeability, or through its contribution to transcellular migration.5-4 Irrespective of whether leukocytes cross the endothelium via the para- or transcellular pathway, integrin ligands on the endothelium and the intracellular signaling that follows their engagement appear to play a central role. This review will focus on endothelial signaling induced by the integrin ligands Ig (Immunoglobulin)-like cellular adhesion molecule (ICAM)-1, ICAM-2, and vascular cell adhesion molecule (VCAM)-1 and the role of these signals in leukocyte TEM.
ICAM-1

ICAM-1 binds to the leukocyte integrins $\alpha_4\beta_2$ (Mac-1) and $\alpha_4\beta_1$ (LFA-1),5–7 mediating strong adhesion to and spreading on the endothelial cell surface. ICAM-1 expression is highly upregulated on macrovascular endothelial cells in inflammatory areas in vivo,8 and also on cultured micro- and macrovascular endothelial cells after stimulation with inflammatory mediators such as tumor necrosis factor (TNF)$\alpha$ and interleukin (IL)-1$.9 –11 Overexpression of ICAM-1 in cell-lines that lack endogenous ICAM-1, such as CHO (Chinese Hamster Ovary) cells, promotes transmigration of neutrophils, indicating that ICAM-1 is sufficient to drive leukocyte TEM.12 Moreover, in areas of atherosclerotic plaque formation in mice, the expression of ICAM-1 is elevated as well, which correlates with the local inflammation and the increased infiltration of leukocytes.13–15 Conversely, blocking ICAM-1 function with antibodies prevents leukocytes to firmly adhere to the endothelium, resulting in a significant reduction in leukocyte TEM in various animal models.3,16 In line with these experimental findings, ICAM-1 knock-out mice show an impaired inflammatory response, exemplified by reduced tissue infiltration of neutrophils.17,18 Finally, even under conditions of increased matrix exposure after inhibition of VE cadherin–mediated cell-cell contact in vitro, blocking antibodies to ICAM-1 induced a significant inhibition of TEM of CD34$^+$-cells from peripheral blood across cytokine-activated HUVECs.19

The interaction between ICAM-1 and LFA-1 on adherent leukocytes depends on the state of activation of LFA-120 and on the dimerization of ICAM-1.21,22 The latter studies showed that monomeric ICAM-1 does not bind to LFA-1 but that ICAM-1 dimers do. The integrin-mediated clustering of ICAM-1 on the endothelial cell surface is mimicked by the crosslinking of antibodies to ICAM-1. When added in solution, these antibodies will lead to ICAM-1 activation and subsequently to changes in the endothelial cells; when induced by adherent leukocytes or antibody-coated beads, crosslinking of ICAM-1 (or VCAM-1) will induce the formation of endothelial docking structures or transmigratory cups,23–25 which is also accompanied by the induction of endothelial cell signaling. These cup structures are formed by apical membrane extensions of the endothelium, which can protrude significantly (see Figure 1), especially when taken into account that endothelial cells are very thin. The formation of these cups depends on actin polymerization, microtubules, and intracellular calcium24 and was found to be required for efficient TEM.25 Carman and coworkers found that inhibiting RhoA by C3 or its downstream effector Rho-kinase did not affect the formation of ICAM-1-projections around adherent activated monocytes.23,24 In contrast, Barreiro et al23 showed that inhibition of Rho-kinase decreased the formation of docking structures in HUVECs by $\alpha_4$ integrin–expressing K562 cells or peripheral blood lymphocytes. Moreover, fewer cells adhered to the endothelial surface following the inhibition of Rho-kinase,23 in line with earlier data on the requirement for RhoA in the clustering of ICAM-1 on HUVECs and the consequent binding of human monocytes.26

The clustering of ICAM-1 induces a wide range of intracellular signaling events into the endothelium, leading to a rise in cytosolic free calcium, activation of the tyrosine kinase p60Src, the small GTPase RhoA, and the induction of cytoskeletal rearrangements, ie, formation of actin stress fibers (Figure 2).27–31 RhoA seems to play a key role in the ICAM-1–induced signaling; its inhibition prevents adhesion-induced clustering of ICAM-1 and the initiation of intracellular signaling toward the actin cytoskeleton.26,32 Also in microvascular endothelial cells isolated from rat brain, crosslinking of ICAM-1 induces the activation of RhoA,29 although the response is faster when compared with RhoA activation in HUVECs.31 ICAM-1 crosslinking also results in the production of inositol phosphate and the phosphorylation of PLC$\gamma$ in rat brain microvascular endothelial cells.33 These authors also showed that a calcium-regulated isoform of PKC is involved in the phosphorylation of the Src tyrosine kinase and cortactin, as also shown by the group of Luscinskas.

Figure 1. Protrusive capacity of the endothelial apical membrane. A human umbilical vein endothelial cell forms a large protrusive structure around an adherent bead, coated with serum proteins. The actin cytoskeleton shows a concentration of F-actin around the bead (X/Y images, top panels). The X/Z images (lower panels) clearly reveal the size of the protrusion, surrounding the 5-$\mu$m bead. F-Actin in red and the bead is shown in green. Scale bar, 1 $\mu$m.
Previous work from the Couraud laboratory identified the phosphorylation of the focal adhesion proteins paxillin, FAK (Focal Adhesion Kinase) and p130Cas downstream from ICAM-1 clustering.29,33 Interestingly, the phosphorylation of these proteins appears to be downstream from RhoA activity, because phosphorylation was inhibited by C3-toxin.29 Other cytoskeletal proteins such as α-actinin, VASP, and focal adhesion proteins such as vinculin, talin, or paxillin have also been implicated in ICAM-1/VCAM-1–mediated signaling and were even found to relocate to the docking structures.23 Thus, the clustering of ICAM-1 (and VCAM-1 as well) triggers the formation of cup structures on the apical surface of the endothelium, which is accompanied by, and partly dependent on, the induction of intracellular signaling. The formation of these structures, as well as the consequent signaling, is strongly correlated with efficient TEM.

Even though there is a lot of information on ICAM-1– induced signaling, the relevant molecular pathway directly downstream from ICAM-1 remains to be identified. The expression of full-length ICAM-1 completely, and of ICAM-2 partially, restores TEM efficiency of a T-cell line across the murine ICAM-1–/– VCAM-1–/– bEnd (brain-endothelioma) cell line.35 Importantly, expression of an ICAM-1 deletion mutant lacking the C terminus showed that this region is required for efficient TEM.36 Greenwood and colleagues36 showed that this domain is also required for proper adhesion of T-lymphocytes to rat brain microvascular endothelial cells, whereas the group of Engelhardt showed that the tail of murine ICAM-1 is not required for adhesion of T-cells to the murine bEnd cell line.35 Expressing tailless human ICAM-1 in CHO cells also abrogated TEM but not adhesion of human neutrophils.12 Thus, the C-terminal domain of ICAM-1 plays an important role in TEM and, perhaps depending on the cellular context, also in leukocyte adhesion.

The C terminus of ICAM-1 comprises 1 tyrosine residue that can be subject to phosphorylation (Table). However, this residue is not phosphorylated in cross-linked human ICAM-1, expressed in rat brain endothelial cells35 or in murine ICAM-1, expressed in the murine bEnd cells.35 Moreover, peakidomimetics of the ICAM-1 intracellular domain containing a phosphotyrosine at this position are equally effective in blocking lymphocyte transmigration. Finally, phosphodeficient Y-F mutants of ICAM-1 did not affect T-cell adhesion or TEM.35 Thus, tyrosine phosphorylation of ICAM-1 appears not to be relevant for ICAM-1 mediated adhesion and TEM.

The intracellular tail of ICAM-1 comprises only 28 amino acids (Table) and does not encode a clear-cut protein interaction domain. Yet, there are molecular interactions described for the intracellular tail of ICAM-1. The adapter protein α-actinin has been shown to bind a stretch of positively charged amino acids in the ICAM-1 tail.37 The relevance of this binding was further shown by introducing point-mutations into the ICAM-1 tail, which abrogated the binding of α-actinin to ICAM-1 and blocked transmigration of human neutrophils across transfected CHO cells.38 In addition, endothelial ICAM-1 has been proposed to interact with ERN proteins, in particular moesin and ezrin,23 but a parallel study indicated that these interactions are not direct.39 The ERN proteins are of particular interest, given their role as linkers between plasma membrane proteins and the actin cytoskeleton40 and because of the connection between ERM proteins and their phosphorylation/activation through RhoA signaling (Figure 2).41–43 However, direct proof for the requirement for ERM proteins in ICAM-1–mediated endothelial signaling and leukocyte TEM is currently lacking.

Muro and coworkers44 showed that ICAM-1 dimers not only function as adhesion molecules but can also facilitate

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**Primary Sequences of Intracellular Regions of Endothelial Integrin Ligands and E-Selectin**

<table>
<thead>
<tr>
<th>Integrin Ligand</th>
<th>Primary Sequence</th>
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<tbody>
<tr>
<td>ICAM-1</td>
<td>R0/RKIKK/KRL04QKGTPMKPNT0ATPP</td>
</tr>
<tr>
<td>ICAM-2</td>
<td>QGHRL0QRMGTGGR/RKAAWRRLPDAFPR</td>
</tr>
<tr>
<td>ICAM-3</td>
<td>REHGRSSYH/VFEESTYLP7TMS0PMEGEGEPRAE</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>RKANNMKGSYSLEADEQKSKY</td>
</tr>
<tr>
<td>E-SELECTIN</td>
<td>RKCLKR4KKF/PASSCSSLEEDGSYMPSYL</td>
</tr>
</tbody>
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**Figure 2.** Schematic overview of IgCAM-mediated signaling in leukocyte paracellular TEM. Adherent leukocytes cluster, through their integrins, the IgCAMs on the endothelial cell surface (I, ICAM-1/2; V, VCAM-1). This leads to association with adapter proteins and activation of small GTPases of the Rho family. These, in turn, activate a series of effectors including kinases and phosphatases as well as metalloproteases. In parallel, the calcium mobilization has been observed that also modulated regulation of downstream effectors. Either separate or in concert, these effectors regulate the integrity of adherens junctions, through modulating the function of the VE-cadherin-catenin complexes, thereby controlling the efficiency of leukocyte TEM.
endocytosis. Microsphere beads (100 nm), coated with anti-ICAM-1 antibodies, were efficiently internalized by HUVECs. This internalization depends on the activity of PKC, Src, and Rho, suggesting that overlapping signaling pathways control phagocytosis as well as leukocyte TEM.

The close connection between these 2 events is further supported by the recent studies that have focused on the transcellular migration of leukocytes.\textsuperscript{25,45,46} Millán et al\textsuperscript{45} showed that ICAM-1 is involved in the engulfment of human T-lymphocytes by HUVECs and that ICAM-1 remains bound to the lymphocytes during the passage through the endothelial cell body. Finally, ICAM-1 relocates to the basolateral side of the endothelium. This process required caveolin-1, because knock-down of caveolin-1 prevented lymphocytes to penetrate endothelial cells. As a consequence, instead of migrating via the transcellular route, the lymphocytes were forced to exclusively use the paracellular route, ie, through the cellular junctions. These studies extend earlier work in guinea pigs using electron microscopy that already indicated that transcellular pathway was used in vivo, eg, by fMLP stimulated neutrophils.\textsuperscript{47} Although cell type and endothelial cell shape have been suggested as determinants in the choice between the 2 transmigration pathways,\textsuperscript{46} identifying a molecular mechanism that regulates such a choice remains an key issue for future research in this field.

**ICAM-2**

In contrast to ICAM-1, the contribution of ICAM-2 to leukocyte TEM appears rather limited. ICAM-2 is expressed to significant levels already without cytokine stimulation and localizes to the junctions of resting endothelial cells. Whereas ICAM-1 is upregulated by inflammatory stimuli, ICAM-2 becomes downregulated after treatment of HUVECs with eg, TNFα.\textsuperscript{54} This suggests that ICAM-2 may play a role in the constitutive, rather than the induced leukocyte TEM. This is supported by findings of Lehmann et al,\textsuperscript{49} who showed that ICAM-1 and ICAM-2 in mice are redundant in regulating lymphocyte recirculation through lymph nodes, but that ICAM-1 is specifically required for migration of effector cells into the inflamed skin.

There are, however, some studies that point to a role for ICAM-2 in cytokine-induced transendothelial migration. Eosinophil influx in the lung was found to be significantly delayed in ICAM-2-deficient mice.\textsuperscript{50} In addition, Huang et al\textsuperscript{51} showed, using a peritonitis model in ICAM-2-deficient mice as well as using an ICAM-2 blocking antibody that ICAM-2, in part mediates IL-1β but not TNFα- or thioglycollate-induced neutrophil efflux and that the antibody blocked neutrophil TEM in a tissue specific fashion in PECAM-1-deficient mice.

In addition to binding β2-integrins, ICAM-2 was also shown to bind the dendritic cell (DC)-specific ICAM-3–grabbing nonintegrin DC-SIGN. This interaction has been suggested to mediate TEM of human DCs across resting and TNFα-activated, immortalized HMEC cells.\textsuperscript{52} ICAM-2 also mediates TEM of immature bone marrow–derived mice DC, albeit that under these conditions, neither β2-integrins nor murine DC-SIGN was found to mediate the migration across the immortalized brain endothelioma cells and an unknown counterstructure was proposed.\textsuperscript{53}

The ICAM-2 intracellular tail comprises of only 27 amino acids that lacks any known signaling domains or activity (Table). As eluded to above, Lyck et al\textsuperscript{58} compared the relevance of ICAM-1 and -2 in T-cell TEM across immortalized brain endothelioma cells from ICAM-1−/− and ICAM-2−/− mice. These experiments showed that expression of ICAM-2 had only limited stimulatory effects that also could not further enhance the stimulation of TEM, induced by ICAM-1. Along similar lines, Thompson et al\textsuperscript{51} showed that antibody-mediated crosslinking of ICAM-2 on primary HUVECs does not induce activation of RhoA or rearrangements of the actin cytoskeleton. Similar to ICAM-1, ICAM-2 localizes to microvilli and binds the adapter proteins α-actinin\textsuperscript{37,54} and ezrin.\textsuperscript{55} However, taken these studies together, it appears that ICAM-2 has limited signaling capabilities and that, in line with its downregulation on cytokine stimulation, ICAM-2 plays a limited,\textsuperscript{56} stimulus-specific,\textsuperscript{51} role in regulated TEM.

Recently, Huang et al\textsuperscript{57} defined a role for ICAM-2 in the stimulation of angiogenesis of murine cardiac endothelial cells. From these experiments, it was concluded that ICAM-2 not only could mediate homotypic interactions, but that ICAM-2-crosslinking by antibodies on HUVEC induced a modest activation of Rac1 and that on the murine cardiac endothelial cells, ICAM-1 was required for sustained Rac1 activation. Whether these events are relevant for leukocyte TEM remains to be established. Rac1 activation has been observed on activation of VCAM-1 (see below) and ICAM-1 (J.D.v.B., unpublished results), so this may be a more general feature of Ig-CAM activation on endothelial cells.

**VCAM-1**

VCAM-1 is well established as an important endothelial molecule in inflammatory conditions because of its dramatic upregulation by inflammatory cytokines and its role in β1 integrin–mediated leukocyte TEM. Compared with ICAM-1, however, VCAM-1–mediated signaling in endothelial cells has received relatively little attention. Similar to ICAM-1, VCAM-1 antibody–coated beads induce docking structures after binding to activated endothelial cells and VCAM-1 does become redistributed to these structures.\textsuperscript{23,24}

For VCAM-1, no studies using a C-terminally deleted version have been reported. Importantly, like the ICAMs, VCAM-1 localizes to microvilli and associates to ERM proteins ezrin and moesin,\textsuperscript{23} which seems to be a general feature of this class of integrin ligands (Figure 2). This interaction may well explain the accumulation of cytoskeletal regulatory proteins and, eg, actin in VCAM-1/ICAM-1 cup structures. In contrast to ICAM-1 and E-selectin, VCAM-1 does not have a basic region in its juxtamembrane domain (Table). Such regions have been implicated previously in ERM binding by proteins such as CD43 and CD44.\textsuperscript{59} Although ERM binding to E-selectin has not been reported, E-selectin crosslinking not only induces a rise in intracellular Ca\textsuperscript{2+}, but also leads to actin rearrangements,\textsuperscript{59} indicating that E-selectin activates similar endothelial signaling events as the ICAMs and VCAM-1. ERM linkage may also be mediated by other than just basic residues, as was shown for a series of
serine residues in the C terminus of ICAM-3. Intriguingly, VCAM-1 is unique in that its extreme C terminus encodes a putative PDZ-domain binding motif (Table). However, whether any PDZ domain–containing protein directly associates to VCAM-1 is unknown, but such an interaction would present an additional means of linking an integrin ligand to the endothelial intracellular signaling machinery.

Various labs have shown, using antibody-mediated crosslinking on activated murine and human endothelial cells, that VCAM-1 signaling results in the activation of Rac1, via an unidentified pathway, and that Rac1, in turn, induces generation of reactive oxygen species (ROS) in endothelial cells. Whereas our laboratory has provided evidence that these ROS serve a role in intracellular signaling through the Pyk2 tyrosine kinase, others have shown that these ROS can in fact act in the extracellular milieu, modulating metalloproteases, and regulation of integrin-ligand interactions. The mechanism by which PTP1B regulates endothelial cell activity is currently not known whether VCAM-1 has any specific role in transcellular migration.

The group of Cook-Mills has recently taken this work further by showing that VCAM-1 engagement through anti-VCAM-1-antibody–coated beads leads in human microvascular cells and murine lymph node endothelial cells to activation of the intracellular tyrosine phosphatase PTP1B. The activation of PTP1B through serine phosphorylation is found to be required for efficient TEM, but not for adhesion under flow of mouse spleen cells. This ROS-PKCo–driven activation of PTP1B contrasts with the ROS-mediated oxidation and inhibition of tyrosine phosphatases, which results in increased tyrosine kinase activity. In fact, Deem et al showed that, although VCAM-1 signaling is accompanied by ROS production, this does not lead to inactivation of PTP1B, possibly as a result of compartmentalization of signaling. The mechanism by which PTP1B regulates endothelial cell junctions to promote TEM, is as yet unidentified.

Regulation of IgCAM Signaling

Complex as it already is, the signaling by endothelial IgCAMs after leukocyte adhesion is clearly subject to additional levels of regulation (Figure 2). Proteolysis, eg, by metalloproteases (see for example Garton et al) is a well known fate for (endothelial) CAMs and soluble forms of ICAMs as well as VCAM-1 have been detected in sera from patients with inflammatory disorders, including atherosclerosis or some forms of cancer. Unfortunately, however, neither the source nor the potential role of these fragments is currently very clear. Interestingly, a recent study showed cleavage and inactivation of VCAM-1 by thrombin, suggesting a connection between the coagulation cascade, involving a series of proteases, and regulation of integrin-ligand interactions.

On binding of LFA-1 to ICAM-1 or after antibody-mediated clustering, ICAM-1 is incorporated into detergent-insoluble membrane domains, referred to as lipid rafts. These domains may serve as signaling platforms that include, next to ICAM-1, several other transmembrane proteins as well. It has been reported that tetraspanin proteins can be localized to such platforms, although these can be distinct from lipid rafts. Tetraspanins are integral membrane proteins that are involved in a variety of different cellular processes and appear to act by regulating the distribution and activity of membrane-associated proteins, such as integrins. Barreiro et al showed that tetraspanins associate to ICAM-1 and VCAM-1 in the docking structures and mediate the IgCAM clustering on the apical surface of the endothelium. Importantly, these authors showed that functional expression of 2 tetraspanins, CD9 and CD151, are required for proper leukocyte TEM.

The notion that IgCAMs take part in multiprotein signaling units on the endothelial cell surface is probably very likely, but has so far received relatively little attention. Although the endothelial CAMs are capable of stimulating various relevant signaling cascades, the limited size of their C-terminal domains (Table) does suggest that interactions in cis with membrane spanning molecules that harbor, eg, enzymatic activity, would allow more efficient signal transmission, as was shown for NCAM and the FGFR-receptor. The formation of docking structures with their high concentrations of actin and adhesion and signaling molecules may well provide an excellent platform to further promote such interactions (Figure 2). This topic is of particular interest for future studies in this field.

Finally, there is increasing interest in the role of shear forces in the control of endothelial signaling and for the role for shear in TEM. For VCAM-1 as well as for E-selectin, Cuvelier et al showed that shear stress is an important factor controlling their signaling competence. This was studied in HUVECs across which eosinophils, neutrophils, or myeloid leukemia cells were migrating, in a shear-dependent fashion. In particular calcium signaling and activation the p42/p44 MAPkinases, which followed adhesion of eosinophils or of the leukemic cells, were found to depend on the presence of shear. Similar findings were reported when spheres coated with antibodies to VCAM-1 or E-selectin were used, which further shows that the modulation of adhesion-driven extracellular signal regulated kinase (ERK) activation by shear is at the level of the endothelium, and not necessarily at the level of the adherent and spreading leukocyte. This data are in line with the idea that shear may in fact promote transendothelial migration, as suggested by the group of Alon. The IgCAM CD31 has recently been identified as part of the endothelial shear-sensing complex, which further comprises the VEGFR2 and VE-cadherin. Whether eg, VCAM-1 or ICAM-1 could be part of a similar, shear-sensitive, signaling complex is currently unknown.

Concluding Remarks

Our insights in the key mechanisms that control leukocyte TEM have significantly increased over the past years, and much attention has been paid to the role of the endothelium in this process. The initiation of various signaling pathways in endothelial cells, after the firm adhesion of leukocytes and the
parallel formation of cup structures which play an important yet poorly understood role, and the somewhat bizarre phe-
nomenon of transcellular migration all have generated many new questions that need to be addressed. The relevance of various adapter and signaling molecules that colocalize and sometimes even associate with clustered IgCAMs need to be rigorously established. The interplay between kinase/ phosphatase-driven signaling and cytoskeletal changes in the control of cell-cell contact is another poorly understood, but important aspect of TEM. Additional key issues, such as the differential roles of the integrin ligands ICAM-1 and VCAM-1, the modulation of their adhesive and signaling roles by, eg, shear stress, and the contribution of cell type-
and tissue-specificity in the efficiency of TEM, provide us with sufficient research questions for the coming years.

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Disclosures

None.

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