Density-dependent control of MAdCAM-1 and chronic inflammation. Focus on “Mechanisms of MAdCAM-1 gene expression in human intestinal microvascular endothelial cells”

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MAdCAM-1 is an endothelial adhesion molecule that is expressed chiefly in the gut but also in several other organs and plays important roles in the control of leukocyte homing, especially during the intestinal inflammation of Crohn’s disease and ulcerative colitis. Despite a general acceptance of its importance, since the initial description of MAdCAM-1 by Briskin et al. (2) in 1993, there have been only 256 articles published about it, as opposed to 3,544 about VCAM-1, 9,479 about ICAM-1, 4,358 about E-selectin, and 4,257 about P-selectin at the time of this writing. The reasons for this include the limited expression of MAdCAM-1 to a few tissues, the fact that there are few in vitro systems in which to examine MAdCAM-1 (compared with the nearly ubiquitous expression of the other adhesion molecules in most endothelium), and most importantly, the difficulty of conclusively demonstrating causal roles for MAdCAM-1 in disease. Recent studies now indicate that MAdCAM-1 may be a necessary, if not sufficient, adhesive determinant for regulating chronic inflammation of the intestine (13) and the inflamed cerebrum (4, 5), and it currently is receiving more examination.

Although few studies have examined the regulated expression of MAdCAM-1 (11), an improved understanding of its regulation could have a strong impact on how MAdCAM-1 could be targeted in these diseases. In the current article in focus (Ref. 10; see p. C206 in this issue), Ogawa et al. describe some important differences in human intestinal microvascular endothelial cell (HIMEC) MAdCAM-1 expression that distinguish it from several of the other adhesion molecules expressed by endothelial cells. For example, MAdCAM-1 appears to be phosophatidylinositol 3-kinase (PI3-K) dependent, whereas ICAM-1 and E-selectin apparently are not. A further finding of this study by Ogawa et al. is the dependence of MAdCAM-1 expression on culture age (duration) and density, indicating that increased cell-cell contact may control the responsiveness of HIMEC to cytokines and LPS. This density-dependent activation appears to reflect a PI3-K-mediated Akt activation that is maximal at higher cell densities. NF-κB activation, while clearly necessary, was seen to be independent of cell density.

Most studies of endothelial cells have been performed with confluent cells, the assumption being that subconfluent cells do not represent any meaningful physiology. Very few studies have examined density-dependent adhesion molecule expression in endothelium, and more study of this topic is also warranted. Previously, Litwin et al. (8), using human umbilical vein endothelial cells (HUVEC), described an expression profile for E-selectin, VCAM-1, and ICAM-1 (but not PECAM-1) that was nearly opposite that found in HIMEC for MAdCAM-1. In Litwin’s study, E-selectin expression was low and transient in confluent cells and required cytokine exposure. However, E-selectin expression in HUVEC cells at low density was relatively high and did not require cytokine exposure to induce adhesion molecule expression. E-selectin was also expressed at the front of wounded monolayers (most immediately released from confluency), with E-selectin expression decreasing as the distance from the wounded margin increased. Down-regulation of E-selectin was also seen following PECAM-1, but not VE-cadherin, ligation. That report also showed contributions from cell-matrix interactions using cyclic RGD peptides (which block cell substrate adhesion) to decrease E-selectin expression.

A similar type of response was reported by Margiotta et al. (9), who reported that endothelial cells weakly adhered to their substratum (cells adhered to polytetrafluoroethylene) exhibited a higher than normal expression of ICAM-1 and elevated leukocyte adhesion. Therefore, matrix and cell-cell adhesive interactions may be important influences in regulating adhesion molecule expression and leukocyte adhesion, and adhesive responses of the endothelium may be even more complex than previously thought.

MAdCAM-1 is not only an organ- and stimulus-specific adhesive determinant but also is density dependent, suggesting that its highly restricted expression is decisively related to particular phases in inflammation. The ability of MAdCAM-1 to be induced by inflammatory stimuli is increased by cell-cell contact and, on the basis of studies like that of Litwin et al. (8), may be reciprocally regulated compared with other endothelial adhesion molecules (E-selectin, VCAM-1, and ICAM-1). There are several possible implications of such regulation. First, because there may be repeated rounds of angiogenesis accompanying the extensive intestinal tissue remodeling during inflammation (as is also perhaps true for inflammation in other organs), MAdCAM-1 expression in “mature” (higher density) cultures could indicate that MAdCAM-1 might act as a “trigger” early in inflammation, whereas other adhesion molecules might sustain later phases of chronic inflammation, when endothelial cell matrix binding or cell density is altered.

The potential relationship between well-organized tight junctions (occludin, ZO-1) and full expression of MAdCAM-1 is consistent with maturation-dependent sensitivity to stimuli that is controlled by cell-cell junctions. Laprise et al. (6) recently reported such a linkage, in which the state of assembly of adherens junctions controls Akt/PKB activation and is linked with a more highly differentiated culture phenotype in epithelia. It is not known whether tight junctions also participate in this same type of junctional regulation of culture phenotype, but it appears that they may (7). Therefore, an
implicit but unstated conclusion of this study could be that adhesion molecule expression, as a characteristic of culture differentiation, is controlled by the number and type of cell–cell junctional contacts (which are proportional to cell density). The number and activation of these junctions in turn controls cytoplasmic second messages and affects cell responses to paracrine, autocrine, and environmental signaling.

Ultimately, because MAdCAM-1 is dramatically elevated during chronic gut inflammation and is associated with tissue remodeling (especially the remodeling microvasculature), it will be interesting to see whether the vascular endothelial growth factors released during inflammation enhance MAdCAM-1 expression through effects on cell density or alter signaling through PKB/Akt-mediated, but possibly density-independent, mechanisms.

REFERENCES