Targeting endothelial adhesion molecule mRNA to control inflammation: novel insights into potential anti-inflammatory effects of IL-19. Focus on “Interleukin-19 decreases leukocyte-endothelial cell interactions by reduction in endothelial cell adhesion molecule mRNA stability”

David W. Scott and Rakesh P. Patel
Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama

Activation of vascular endothelial cells is required for trafficking of leukocytes to sites of inflammation, a process underlying innate immunity and numerous acute and chronic diseases. Typically, activation refers to an inflammatory stimulus-dependent upregulation of adhesion molecule expression such as ICAM-1, VCAM-1, E-selectin, or P-selectin through NF-κB-mediated transcription (7). These proteins facilitate leukocyte rolling, adhesion, and transmigration through interactions with cognate leukocyte receptors such as LFA-1, Mac-1, VLA-4, and PSGL-1 (6).

Interleukin-19 (IL-19) is a member of the IL-10 cytokine family and, like other members of this family (including IL-20 and IL-24), promotes an anti-inflammatory Th2 response in T-lymphocytes (1, 8). A separate series of investigations have demonstrated that IL-19 is expressed in smooth muscle and endothelial cells from diseased but not healthy arteries (5, 10), but the precise role that IL-19 plays in these cells is unknown, with the potential that this cytokine suppresses vascular smooth muscle and endothelial cell activation noted. This brings about the intriguing possibility that IL-19 can suppress inflammation outside of the immune system, and by directly exerting effects on the vasculature by controlling endothelial and/or smooth muscle cell phenotype and responses to inflammation. However, the underlying mechanisms and potential implications for inflammatory diseases remain unknown.

In their current work, England and colleagues (4) provide evidence that begins to clarify this gap in knowledge and show that IL-19 modulates endothelial cell inflammatory signaling in vitro and in vivo, by inhibiting protein adhesion molecule expression and subsequent leukocyte-endothelial cell interactions. Surprisingly, this anti-inflammatory effect of IL-19 was not via inhibition of NF-κB, but rather by preventing the phosphorylation and subsequent nuclear-to-cytosolic translocation of the mRNA stability factor HuR (3). As a result, the newly transcribed adhesion molecule mRNA has a decreased half-life, resulting in lower levels of adhesion molecule protein expression, which leads to reduced leukocyte adhesion. Importantly, the findings complement this group’s previous finding that IL-19 decreases HuR expression in vascular smooth muscle cells (2). Several interesting questions emanate from the current study (4): 1) Do other members of the IL-10 cytokine family have similar posttranscriptional effects on adhesion molecule expression via HuR regulation? 2) Are other mRNA stability factors involved? 3) How does IL-19 regulate HuR phosphorylation in the endothelial cells, compared with regulation of HuR expression in smooth muscle cells? 4) What is the molecular basis for cell type specificity?

Perhaps the most intriguing implication is that endogenous IL-19 may function to resolve inflammation, although it should be stated that, in the study by England et al., only effects of IL-19 pretreatment on TNF-α-dependent endothelial activation were tested. Notwithstanding this issue, the fact that IL-19 is only expressed in activated endothelial cells, and not basally, does suggest a potential protective and anti-inflammatory role. Furthermore, the study by England et al. lays the groundwork to test the hypothesis that therapeutic targeting of the IL-19-HuR axis may provide a novel means to modulate the inflammatory response. Clearly, further studies delineating mechanisms and testing whether IL-19 can accelerate adhesion molecule degradation by promoting RNA instability, after endothelial activation has already occurred, are required.

From a broader perspective, it is interesting to note that the canonical NF-κB upregulation of adhesion molecule transcription and translation has long been established and many studies have attempted to identify strategies to antagonize adhesion molecule function, by either preventing interactions with cognate receptors (e.g., use of blocking antibodies) or inhibiting NF-κB signaling, to limit the inflammatory response. Despite positive proof-of-concept data in cell culture and preclinical experimental models, no clinical strategy has yet emerged to control inflammation by targeting the NF-κB-dependent endothelial adhesion molecule expression. As a result, interest in antiadhesion therapies as a strategy to control inflammation has waned considerably. However, recent studies are beginning to demonstrate that other mechanisms independent of the NF-κB pathway may also regulate adhesion molecule function, including postranscriptional regulation by IL-19 (4) and posttranslational modification by N-linked sugars (9). Thus, vascular inflammation is not simply modulated at the level of adhesion molecule gene transcription. The identification of postranscriptional and posttranslational processing of these proteins provides a fresh impetus to the idea that targeting adhesion molecules may be useful in limiting inflammatory diseases in humans.

DISCLOSURES
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AUTHOR CONTRIBUTIONS
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REFERENCES


