https://www.scientificarchives.com/journal/journal-of-cellular-immunology

Journal of Cellular Immunology Review Article

The Endothelium: Global Integrator of Vascular-Immune Interactions

Daniel Bergey*

Department of Science, Great Basin College, Winnemucca, NV 89445, USA

*Correspondence should be addressed to Daniel Bergey; daniel.bergey@gbcnv.edu

Received date: February 18, 2019, **Accepted date:** June 10, 2019

Abstract

Vascular endothelial cells (ECs) form a one cell layer on the luminal surface of all blood and lymphatic vessels, the endocardium, blood-brain barrier, and renal glomerulus. EC function and phenotype can vary depending upon the tissue, vascular region, or given microenvironment. These versatile cells form the vanguard at the dynamic interface between the blood and tissue space, play central roles in the maintenance and regulation of vascular system homeostasis, the integration of immune cell signaling and trafficking, and diverse pathological processes including inflammation, tumor metastasis, and diabetes. ECs express class I and class II MHC molecules, interact with, and modulate, immune cell function by induced expression of adhesion molecules and cytokines, and recruit T cells into inflammatory sites by functioning as antigen presentation cells (APCs).

Introduction

Endothelial cells (ECs) are mesodermally-derived modified simple squamous epithelial cells that collectively form the vascular endothelium–the vast living shield that lines the luminal surface of all blood vessels, the lymphatic circuit, and heart. Endothelial cell phenotypes vary among different organs and tissues with regard to specific barrier characteristics, and can be altered by environmental stimuli [1,2].

Specialized endothelial cells in the blood-brain barrier, glomeruli, and retina regulate movement of small molecules and nutrients into and out of the circulation. This highly specialized lining, a single cell thick, is uniquely positioned to integrate signaling and nutrient transport between blood and surrounding tissues, and provides a non – thrombogenic surface to help prevent inappropriate blood clotting. The endothelium is now rightly recognized as a distinct, highly specialized (endocrine) organ – the largest organ in fact – consisting of an estimated 10^{13} cells and total surface area somewhere between 1,000 m^2–7,000 m^2 [3,4].

Besides its fundamental role in cardiovascular system homeostasis, angiogenesis, initiation and regulation of inflammation, and immune cell trafficking (an essential immune response function), the endothelium is the last barrier that metastatic tumor cells must breach before they can initiate new tumors in secondary organ sites [5].

Damage or disruption to the endothelium monolayer can lead to vascular leakage, vasoconstriction or vasodilation, promote a prothrombotic microvasculature environment, and initiate inflammatory reactions which set the stage for endothelial dysfunction. In fact, the basis for most forms of cardiovascular disease, such as hypertension, diabetes, chronic heart or kidney failure, and aggressive viral infections are manifestations of endothelial dysfunction [6].

This brief review will focus primarily on endothelial cell function in the immune response. See [7-9] for excellent recent reviews on the role of the endothelium in vascular integrity and disease.

Endothelial Cell Heterogeneity

The endothelial lining of capillaries can be continuous, fenestrated, or discontinuous, depending on the

specific function and location of the underlying tissue. Endothelial cell phenotypes differ among different organs, among different vascular regions within the same organ, and between endothelial cells of the same organ and blood vessel type. Integrating such an extensive range of anatomical and physiological demands requires exceptional functional versatility and phenotypic diversity. ECs can therefore function as fenestrated endothelium seen in liver sinusoids to facilitate rapid exchange of cells, molecules, and metabolites [10], or as tight vascular endothelium found in the central nervous system (CNS) that forms part of the blood–brain barrier, a critical interface between blood and neural tissue within the brain and spinal cord, that regulates homeostasis of the brain microenvironment [11,12].

Although the particular functions of an EC strongly depend on its anatomical location, the functional repertoire of ECs can be efficiently modulated by inflammatory stimuli, including microbial pathogens and their products, or inflammatory mediators derived from various other cell types.

For example, cerebrovascular endothelial cells (CVEs) are the major component of the blood-brain barrier that limit the passage of soluble and cellular substances from the blood into the brain. Although CEVs in the CNS are capable of presenting antigens and activating T cells, the ability of these cells to function as antigen-presenting cells in CNS inflammatory responses is still controversial [13].

Endothelial Glycocalyx

The surface of ECs consist of a proteoglycan-rich complex lining the luminal surface of blood vessels, whose soluble components are in a dynamic equilibrium with the bloodstream. This glycocalyx, also called endothelial surface layer (ESL), forms a vascular sheath that maintains the integrity of the critical interface between blood and endothelial lining. However, this lining is fragile and highly vulnerable to damage from a multitude of sources, including physical trauma, inflammation, oxidative stress, hypovolemia, hemorrhagic shock, diabetes, sepsis, and ischemia-reperfusion (I/R) injury (caused by the ensuing surge of elevated levels of reactive oxygen species and proinflammatory neutrophils) [14,15].

Degradation of the integrity of the glycocalyx by various causes noted above can damage endothelial cells, resulting in pathophysiological dysfunction of this important barrier including increased permeability, platelet aggregation, loss of vascular integrity and responsiveness. Inflammation and other forms of oxidative stress due to increased levels of reactive oxygen or nitrogen species is a major contributor to glycocalyx disruption [16-18].

Increased neutrophil adhesion to the endothelium is an additional consequence of a damaged glycocalyx in the vasculature of the myocardium after I/R injury [19]. See Kalogeris et al. [20] for review of ischemia/reperfusion causes and consequences .

Innate Immune Response Overview

The innate immune system is the first line of defense that recognizes and responds to a wide range of microorganisms. Microbial recognition by immune cells occurs via specialized host-cell receptors called pattern-recognition receptors (PRRs), which can be soluble or membrane-bound. PRRs recognize and bind microbe-specific molecular structures called microbe-associated molecular patterns (PAMPs) [21]. Al-Soudi et al. [22] provide an excellent review of the role of endothelium in innate and adaptive immunity.

PRRs are expressed on key immune cells such as neutrophils, macrophages, and dendritic cells that serve as first responders for the immune system. When host PRRs interact with PAMPs, inflammation cascades in host cells are activated which, in turn, stimulate maturation of antigen-presenting cells (APCs), and upregulate expression of relevant immune-related cell surface and soluble molecules. These events enable APCs to initiate adaptive immunity.

Among the PRRs are a diverse group of surface molecules called Toll-like receptors (TLRs), which recognize distinct classes of pathogen structures and activate an array of host defense-related responses including phagocytosis, leucocyte chemotaxis, cytotoxicity, pro-inflammatory gene expression, and adaptive immune signaling [23,24].

Although the surface receptors expressed by ECs to recognize microbe-derived alarm signals are not well characterized, ECs are known to express various several classes of innate immune receptors including NOD-like receptors, RIG-I like receptors, as well as Toll-like receptors (TLRs) [25].

ECs have been shown to express members of the IL-1/Toll receptor receptor family, which likely mediates the response to endotoxin, and subsequent interaction with plasma lipopolysaccharide (LPS) via soluble CD14 and LPS-binding protein, both present in plasma. In addition, ECs express cytokine receptors which can recognize their respective ligands and modulate EC function [26,27].

Pathogen recognition can induce EC production of inflammatory mediators. For example, exposure of ECs to peptidoglycan fragments from Staphylococcus epidermidis causes a rapid, transient increase in both IL-6 and toll-like receptor TLR2 [28] and activation of endothelial TLR2 receptors by bacterial lipoproteins

upregulates a suite of cytokines such as IL-6, IL-8, ICAM1, which promote inflammation and neutrophil recruitment [29].

In addition, TLR activation can increase microvascular EC permeability, and the expression of intermediate products in the clotting cascade. Similar to the potential thrombogenic effect of neutrophil extracellular traps [30], microvascular thrombi could serve to trap microorganisms and thus inhibit the spread of infection. On the other hand, excessive EC inflammation and immune signaling could rapidly escalate leading to increased vascular leakage and a prothrombotic environment with subsequent sepsis. See [31] for summary of EC-immune cell signaling.

T Cell Activation

T cell precursors originate from hematopoietic stem cells in bone marrow, where they begin their development. Immature T cells leave bone marrow, enter the blood and migrate to the thymus where they complete their final maturation and development, which includes intense thymic screening and selection of those T cells that can recognize one specific antigenic structure via their T cell receptor (TCR). Only 2-5% of all immature T cells entering the thymus survive selection. Once mature T cells leave the thymus they begin circulating throughout the body hunting for their cognate antigen displayed on the surface of an antigen presenting cell (APC) complexed with an MHC (major histocompatibility complex) molecule. The signaling events that can lead to optimal T cell activation are summarized below

Signal One

If an appropriate APC-displayed antigen is recognized by a given T cell, the TCR binds to the antigen as it is "presented" by the MHC complex on the surface of the APC. Formation of the TCR-MHC/Ag complex initiates activation (priming) of T cells. This initial T cell priming typically takes place in the secondary lymphoid tissues (e.g., lymph nodes, spleen, tonsils, or Peyer's patches in the gut).

Signal Two

In addition to TCR recognition and interaction with the MHC/Ag complex, various secondary (co-stimulatory) signals are required for T cells to become optimally activated and begin responding to the threat in an immunologically meaningful way. For helper T cells, the first of these secondary signals is provided by CD28, a receptor molecule constitutively expressed on T cells that binds to corresponding ligand B7 (CD80 or CD86) expressed on activated APCs. These secondary interactions (CD28/B7) stimulate the production of millions of genetically identical T cells (clonal expansion) that can recognize the initial antigen. To restrict a potentially uncontrollable T cell response, the interaction of the CD28 receptor on the T cell with B7 ligand expressed by the activated APC also induces production of CTLA-4 (CD152), which in turn competes directly with CD28 for the B7 ligand. This elegant molecular feedback loop thereby limits production of activation signals to the T cell, which harnesses and starts to de-escalate the immune response.

TCRs on T cells must interact with MHC/Ag displayed on APCs with both high specificity and high avidity to activate effective immune responses. "Effective" interaction also includes T cell recognition of co-stimulatory antigen-induced molecules on APCs that ensure T cells are activated only by those APCs that have previously encountered the antigen, and responded appropriately. TCR interaction with APC-displayed MHC/Ag in the absence of co-stimulation inactivates T cells so they cannot respond effectively, and thus become anergic.

Signal Three

Once the T cell has interacted with an appropriate MHC/Ag complex, and co-stimulatory signals (signal 2) have been induced, further T cell activation is directed by the expression of specific cytokine profiles, which dictate the final type of response effector the T cell will become. For example, activated helper ($CD4^+$) T cells can be directed to proceed toward one of three primary developmental pathways: Th1 type (cells exposed to the cytokine IL-12); Th2 (exposed to IL-4); or IL-17 (exposed to IL-6 and IL-23). Each one of these $CD4^+$ T cell variants performs specific functions in the tissue, which further customizes the immune response to better match the initial threat. Other cells present at the site of inflammation, such as epithelial and endothelial cells, neutrophils, and mast cell are also capable of releasing cytokines and other immune signals which further influences the course of T cell activation and proliferation during a given immune response [32].

Antigen Presentation by the Endothelium

Lymphatic endothelial cells (LECs) are typically the first to encounter antigen, immune cells, and cytokines in lymph nodes. It is not surprising therefore that LECs express MHC I and II molecules on their cell surface, which enable them to function as APCs.

Endothelial cells are capable of both activating, and suppressing, the immune response. Activation is discussed here. See [22,32-34] for more on role of ECs in tumor protection and immune inhibition.

Antigen presentation potential is determined by the

ability of cells to express class II MHC and co-stimulatory molecules. Due to their strategic location between circulating T cells and peripheral tissue sites of antigen exposure, ECs are ideally positioned to function as APCs [35-37].

For example, class II-MHC/Ag complexes regulate T cell activation and proliferation through production of cytokines, the co-stimulation of resting memory $CD4^+$ T cells to produce Th-1 and Th-2 cytokine profiles [38], whereas, inhibitory signals mediated through PD-L1 expression on human umbilical vein endothelial cells (HUVECs) inhibit IL-2 and interferon (IFN)-γ production by T cells stimulated with phytohemagglutinin [39].

Microvascular ECs in humans constitutively express MHC class I and II molecules *in vivo*, and MHC expression patterns in the endothelium of different vascular beds have been shown to vary in response to different environmental signals [40-42].

MHC class I and class II molecules can be induced in ECs by IFN-γ, human peripheral venular ECs express class II MHC constitutively. In general, microvascular ECs express class II MHC at sites of inflammation such as autoimmune reactions and allograft rejection [43-46].

MHC class II was shown to be expressed on microvasculature in unstimulated, untransplanted human hearts and was up-regulated following tissue rejection [47]. In addition, Biedermann and Pober [48] demonstrated that microvascular ECs were capable of activating $CD4^+$ and $CD8^+$ T cells.

ECs also affect antigen presentation indirectly. For example, productive trafficking of dendritic cells (DC) requires strategic communication with both vascular and lymphatic endothelium. Circulating monocytes (DC precursors) express adhesion molecules and respond to various chemokines (e.g., stromal cell-derived factor) constitutively expressed in tissues, or induced by inflammatory processes. After antigen activation, recruitment from tissues, and exposure to immune signals DCs enter the blood or lymph and home to lymphoid tissues where they practice their specialty, antigen presentation.

Vascular and lymphatic ECs are thought to play active roles in directing T cell and DC trafficking, though the specific molecular mechanisms involved remain unclear. The intimate proximity of ECs with T cells at the blood-tissue interface creates an ideal environment for extensive immune surveillance and requisite cellular interactions that could trigger a primary adaptive immune response. Although it is not known with certainty whether this specific type of activation of T cells by ECs occurs, it is well established that ECs are independently competent antigen presenting cells. For example, ECs have been shown to effectively present antigen to re-stimulate memory/effector T cells [48,49]. During this process, T cell membrane extensions protrude and form micro-contacts with antigen-presenting endothelial cells. It has been proposed that these T cell/EC micro-contacts serve as sensory projections to facilitate antigen recognition by T cells [50-53].

Cytokines

All vascular cells are capable of functioning as targets for, or sources of, cytokines which communicate with immune cells as well as many other cell and tissue types in the body. ECs display diverse biochemical and physiological responses depending on the particular cytokine profile they are exposed to. The course and rate of immune regulation is influenced by the nature of the eliciting stimulus, the extent of EC activation, and the particular EC microenvironment [54,55]. Together, these factors determine whether participating ECs ultimately facilitate, or impede, immune cell activation and trafficking [31].

In addition, ECs derived from different vascular beds respond differently to cytokines. For example, TNF induces ICAM-1 expression on both arterial and venous adult human iliac ECs. However, VCAM-1 is expressed only on TNF-activated venous ECs which are, consequently, more effectively at binding VLA-4^+ (CD49a/CD29) T cells. Moreover, iliac arterial and venous ECs, co-stimulate IL-2 and IFN-γ secretion, but not IL-4 secretion, by human peripheral blood T cells or $CD4^+$ T cell clones [56].

During innate immune responses, inflammation-related signals such as tumor necrosis factor (TNF) activate ECs and upregulate their expression of cell surface adhesion molecules, such as P-selectin and PECAM-1, which stimulate leukocyte adhesion and transmigration across the basement membrane and into tissue spaces [57].

T cell differentiation and migration to target tissues are essential for activation of adaptive immunity, and immune homeostasis requires localization of regulatory (suppressive) T cells (Tregs) to sites where immune reactions are occurring [58].

Naive T cells recirculate primarily in secondary lymphoid tissue (e.g., spleen, lymph nodes, mucosa-associated lymphoid tissues), whereas antigen primed T cells and activated Tregs migrate to antigen-rich non-lymphoid tissue where they manifest their effector and regulatory responses [59,60].

In lymph nodes, antigen priming induces expression of

surface receptors on T cells that mediate their trafficking to specific tissue and organ sites. This tissue-specific "homing" is further enhanced by the interaction of T cell receptors with relevant antigen displayed on endothelial cells.

During adaptive immune response, a diverse repertoire of adhesion molecules and chemokines expressed on the surface of ECs interact with corresponding counter-receptors on migrating lymphocytes to direct their entry into tissue spaces [61]. Differential expression of these molecules in endothelial cells of different organs enables selective recruitment of distinct lymphocyte subsets. Antigen priming induces T lymphocytes to express unique subsets of adhesion molecules and chemokine homing receptors. The specific cellular interactions and conditions in the local microenvironment that occur during priming enable antigen-exposed T cells to recognize and interact with organ-specific ECs, and migrate to distinct target tissues [62-64].

Co-stimulatory molecules

Co-stimulatory molecules such as CD80 and CD86 are required for optimal activation of naïve T cells, but ECs have generally been shown to express few if any co-stimulatory molecules. Biliana et al. reported constitutive expression of CD86 and ICOS ligand (ICOS-L) co-stimulatory molecules in human islet microvascular ECs, and demonstrated that functional CD86 expression facilitated adhesion and migration of previously activated memory $CD4^+$ T cells. To date however, there has been no conclusive report demonstrating expression of both classic T cell co-stimulators CD80 and CD86 in EC cells [65,66].

Given the apparent lack of significant co-stimulatory molecule expression by ECs, it is surprising that interaction of antigen-presenting ECs with cognate T cells promotes migration of the engaging T cells, rather than inducing expected T cell anergy [67].

ECs are considered "semiprofessional" or non-classical APCs because they have not been shown to have the capacity to prime naive T cells, but are capable of enhancing the activation of previously primed T cells, especially with respect to production of cytokine signals [68,69].

It is becoming increasingly clear that the endothelium plays many significant and complex roles in overall organismal homeostasis, including regulating and maintaining vascular system integrity, mediating immune cell trafficking, presenting antigen to T cells, and modulating immune responses. Given its vast internal surface area at the critical blood-tissue interface, and its remarkable phenotypic plasticity, the endothelium is ideally suited to provide continuous, real-time immune surveillance and response coordination. As we learn more about this dynamic and versatile internal shield, its central role as a global integrator of vascular-immune interaction will become increasingly evident, and provide fertile therapeutic potential for disease treatment and prevention.

References

1. Aird WC. Spatial and temporal dynamics of the endothelium. Journal of Thrombosis and Haemostasis. 2005 Jul;3(7):1392-406.

2. Aird WC. Endothelial cell heterogeneity. Cold Spring Harbor perspectives in medicine. 2012 Jan 1;2(1):a006429.

3. Augustin HG, Kozian DH, Johnson RC. Differentiation of endothelial cells: analysis of the constitutive and activated endothelial cell phenotypes. Bioessays. 1994 Dec;16(12):901-6.

4. Cahill PA, Redmond EM. Vascular endothelium–gatekeeper of vessel health. Atherosclerosis. 2016 May 1;248:97-109.

5. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation. 2007 Mar 13;115(10):1285-95.

6. Tousoulis D, Simopoulou C, Papageorgiou N, Oikonomou E, Hatzis G, Siasos G, Tsiamis E, Stefanadis C. Endothelial dysfunction in conduit arteries and in microcirculation. Novel therapeutic approaches. Pharmacology & therapeutics. 2014 Dec 1;144(3):253-67.

7. Gimbrone Jr MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circulation research. 2016 Feb 19;118(4):620-36.

8. Boulanger CM. Endothelium. Arteriosclerosis, thrombosis, and vascular biology. 2016 Apr;36(4):e26-31.

9. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascular pharmacology. 2018 Jan 1;100:1-9.

10. Rubin LL, Staddon JM. The cell biology of the blood-brain barrier. Annual review of neuroscience. 1999 Mar;22(1):11-28.

11. Crispe IN. The liver as a lymphoid organ. Annual review of immunology. 2009 Apr 23;27:147-63.

12. Daneman R, Prat A. The blood–brain barrier. Cold Spring Harbor perspectives in biology. 2015 Jan 1;7(1):a020412.

13. Wheway J, Obeid S, Couraud PO, Combes V, Grau GE. The brain microvascular endothelium supports

T cell proliferation and has potential for alloantigen presentation. PloS one. 2013 Jan 8;8(1):e52586.

14. Cancel LM, Ebong EE, Mensah S, Hirschberg C, Tarbell JM. Endothelial glycocalyx, apoptosis and inflammation in an atherosclerotic mouse model. Atherosclerosis. 2016 Sep 1;252:136-46.

15. Wang L, Huang X, Kong G, Xu H, Li J, Hao D, Wang T, Han S, Han C, Sun Y, Liu X. Ulinastatin attenuates pulmonary endothelial glycocalyx damage and inhibits endothelial heparanase activity in LPS-induced ARDS. Biochemical and biophysical research communications. 2016 Sep 16;478(2):669-75.

16. Rubio-Gayosso I, Platts SH, Duling BR. Reactive oxygen species mediate modification of glycocalyx during ischemia-reperfusion injury. American Journal of Physiology-Heart and Circulatory Physiology. 2006 Jun;290(6):H2247-56.

17. Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. Cardiovascular research. 2010 May 11;87(2):300-10.

18. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. InInternational review of cell and molecular biology 2012 Jan 1 (Vol. 298, pp. 229-317). Academic Press.

19. Kurzelewski M, Czarnowska E, Berêsewicz A. superoxide-and nitric oxide-derived species mediate. Journal of physiology and pharmacology. 2005;56(2):163-78.

20. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Ischemia/reperfusion. Comprehensive Physiology. 2011 Jan 17;7(1):113-70.

21. Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity. 2011 May 27; 34(5):637-50.

22. Al-Soudi A, Kaaij MH, Tas SW. Endothelial cells: From innocent bystanders to active participants in immune responses. Autoimmunity reviews. 2017 Sep 1; 16(9):951-62.

23. Jiménez-Dalmaronia MJ, Gerswhin ME, Adamopoulos IE. The critical role of toll-like receptors-From microbial recognition to autoimmunity: A comprehensive review. Autoimmunity Reviews 2016 January 1; 15:1-8

24. Den Haan JM, Arens R, van Zelm MC. The activation of the adaptive immune system: cross-talk between antigen-presenting cells, T cells and B cells. Immunology letters. 2014 Dec 1; 162(2):103-12.

25. Opitz B, Eitel J, Meixenberger K, Suttorp N. Role of Toll-like receptors, NOD-like receptors and RIG-I-like receptors in endothelial cells and systemic infections. Thrombosis and haemostasis. 2009; 102(12):1103-9.

26. Salvadora B, Arranz A, Francisco S, Córdoba L, Punzón C, Llama M, Fresno M. Modulation of endothelial function by Toll like receptors. Pharmacol. Res. 2013. 108; 46-56.

27. Sturtzel C. Endothelial Cells. In The immunology of Cardiovascular Homeostasis and Pathology. 2017. pp. 71-91.

28. Robertson J, Lang S, Lambert PA, Martin PE. Peptidoglycan derived from Staphylococcus epidermidis induces Connexin43 hemichannel activity with consequences on the innate immune response in endothelial cells. Biochemical Journal. 2010 Nov 15; 432(1):133-43.

29. Wilhelmsen K, Mesa KR, Prakash A, Xu F, Hellman J. Activation of endothelial TLR2 by bacterial lipoprotein upregulates proteins specific for the neutrophil response. Innate immunity. 2012 Aug; 18(4):602-16.

30. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M, Myers DD, Wrobleski SK, Wakefield TW, Hartwig JH, Wagner DD. Extracellular DNA traps promote thrombosis. Proceedings of the National Academy of Sciences. 2010 Sep 7; 107(36):15880-5.

31. Cheung KC, Ward EJ, Fu H, Marelli-Berg FM. Endothelial Cells: Immunological Aspects. eLS. Jan 22; 2018; 1-13.

32. Obst R. The timing of T cell priming and cycling. Frontiers in immunology. 2015 Nov 5; 6:563.

33. Rita M, Young MR. Endothelial cells in the eyes of an immunologist. Cancer Immunology, Immunotherapy. 2012 Oct 1; 61(10):1609-16.

34. Cohen JN, Guidi CJ, Tewalt EF, Qiao H, Rouhani SJ, Ruddell A, Farr AG, Tung KS, Engelhard VH. Lymph node–resident lymphatic endothelial cells mediate peripheral tolerance via Aire-independent direct antigen presentation. Journal of Experimental Medicine. 2010 Apr 12; 207(4):681-8.

35. Hirschberg H, Braathen LR, Thorsby E. Antigen presentation by vascular endothelial cells and epidermal Langerhans cells: the role of HLA-DR. Immunological reviews. 1982 Sep; 66(1):57-77.

36. Johnson DR. Endothelial cell-mediated antigen presentation. Transfusion Medicine and Hemotherapy. 2006; 33(1):58-70.

37. Taflin C, Favier B, Baudhuin J, Savenay A, Hemon P, Bensussan A, Charron D, Glotz D, Mooney N. Human endothelial cells generate Th17 and regulatory T cells under inflammatory conditions. Proceedings of the National Academy of Sciences. 2011 Feb 15; 108(7):2891-6.

38. Rodig N, Ryan T, Allen JA, Pang H, Grabie N,

Chernova T, Greenfield EA, Liang SC, Sharpe AH, Lichtman AH, Freeman GJ. Endothelial expression of PD-L1 and PD-L2 down-regulates CD8+ T cell activation and cytolysis. European journal of immunology. 2003 Nov; 33(11):3117-26.

39. Pober JS, Collins T, Gimbrone Jr MA, Cotran RS, Gitlin JD, Fiers W, Clayberger C, Krensky AM, Burakoff SJ, Reiss CS. Lymphocytes recognize human vascular endothelial and dermal fibroblast Ia antigens induced by recombinant immune interferon. Nature. 1983 Oct; 305(5936):726-9.

40. Carman CV, Martinelli R. T Lymphocyte–endothelial interactions: emerging Understanding of Trafficking and Antigen-Specific immunity. Frontiers in immunology. 2015 Nov 24; 6:603.

41. Pober JS, Collins T, Gimbrone Jr MA, Libby P, Reiss CS. Inducible expression of class II major histocompatibility complex antigens and the immunogenicity of vascular endothelium. Transplantation. 1986 Feb 1; 41(2):141-6.

42. Pober JS, Tellides G. Participation of blood vessel cells in human adaptive immune responses. Trends in immunology. 2012 Jan 1; 33(1):49-57.

43. Goes N, Urmson J, Hobart M, Halloran PF. The unique role of interferon-γ in the regulation of MHC expression on arterial endothelium. Transplantation. 1996 Dec 27; 62(12):1889-94.

44. Manes TD, Pober JS. Antigen presentation by human microvascular endothelial cells triggers ICAM-1-dependent transendothelial protrusion by, fractalkine-dependent transendothelial migration of, effector memory CD4+ T cells. The Journal of Immunology. 2008 Jun 15; 180(12):8386-92.

45. Marelli-Berg FM, Frasca L, Weng L, Lombardi G, Lechler RI. Antigen recognition influences transendothelial migration of CD4+ T cells. The Journal of Immunology. 1999 Jan 15; 162(2):696-703.

46. Scott NA, Zhao Y, Krishnamurthy B, Mannering SI, Kay TW, Thomas HE. IFNγ-induced MHC class II expression on islet endothelial cells is an early marker of insulitis but is not required for diabetogenic CD4+ T cell migration. Frontiers in Immunology. 2018 Nov 28; (9) 2800.

47. Rose ML, Coles MI, Griffin RJ, Pomerance AR, Yacoub MH. Expression of class I and class II major histocompatibility antigens in normal and transplanted human heart. Transplantation. 1986 Jun; 41(6):776-80.

48. Biedermann BC, Pober JS. Human endothelial cells induce and regulate cytolytic T cell differentiation. The Journal of Immunology. 1998 Nov 1;161(9):4679-87.

49. Wagner CR, Vetto RM, Burger DR. The mechanism of antigen presentation by endothelial cells. Immunobiology. 1984 Dec 1;168(3-5):453-69.

50. Xu L, Ding W, Stohl LL, Zhou XK, Azizi S, Chuang E, Lam J, Wagner JA, Granstein RD. Regulation of T helper cell responses during antigen presentation by norepinephrine-exposed endothelial cells. Immunology. 2018 May; 154(1):104-21.

51. Dengler TJ, Pober JS. Human vascular endothelial cells stimulate memory but not naive CD8+ T cells to differentiate into CTL retaining an early activation phenotype. The Journal of Immunology. 2000 May 15; 164(10):5146-55.

52. Carman CV. Mechanisms for transcellular diapedesis: probing and pathfinding by invadosome-like protrusions. J Cell Sci. 2009 Sep 1; 122(17):3025-35.

53. Sage PT, Varghese LM, Martinelli R, Sciuto TE, Kamei M, Dvorak AM, Springer TA, Sharpe AH, Carman CV. Antigen recognition is facilitated by invadosome-like protrusions formed by memory/effector T cells. The Journal of Immunology. 2012 Apr 15; 188(8):3686-99.

54. Johnson DR, Hauser IA, Voll RE, Emmrich F. Arterial and venular endothelial cell costimulation of cytokine secretion by human T cell clones. Journal of leukocyte biology. 1998 May; 63(5):612-9.

55. Zhang, C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res Cardiol. 2008 Sep; 103(5):398-406.

56. Hauser IA, Johnson DR, Madri JA. Differential induction of VCAM-1 on human iliac venous and arterial endothelial cells and its role in adhesion. The Journal of Immunology. 1993 Nov 15; 151(10):5172-85.

57. Privratsky JR, Newman PJ. PECAM-1: regulator of endothelial junctional integrity. Cell and tissue research. 2014 Mar 1; 355(3):607-19.

58. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Annual review of immunology. 2012 Apr 23; 30:531-64.

59. Walling BL, Kim M. LFA-1 in T cell migration and differentiation. Frontiers in immunology. 2018 May 3; 9-952.

60. Fu H, Wang A, Mauro C, Marelli-Berg F. T lymphocyte trafficking: molecules and mechanisms. Front Biosci. 2013 Jan 1;18:422-40.

61. Chimen M, Apta BH, Mcgettrick HM. Introduction: T cell trafficking in inflammation and immunity. InT-Cell Trafficking 2017 (pp. 73-84). Humana Press, New York, NY.

62. Ley K, Kansas GS. Selectins in T-cell recruitment to non-lymphoid tissues and sites of inflammation. Nature Reviews Immunology. 2004 May; 4(5):325-36.

63. Butcher EC, Picker LJ. Lymphocyte homing and homeostasis. Science. 1996 Apr 5; 272(5258):60-7.

64. Sigmundsdottir H, Butcher EC. Environmental cues, dendritic cells and the programming of tissue-selective lymphocyte trafficking. Nature immunology. 2008 Sep; 9(9):981-87.

65. Lewis M, Tarlton JF, Cose S. Memory versus naive T-cell migration. Immunology and cell biology. 2008 Mar;86(3):226-31.

66. Epperson DE, Pober JS. Antigen-presenting function of human endothelial cells. Direct activation of resting CD8 T cells. The Journal of Immunology. 1994 Dec 15; 153(12):5402-12.

67. Lozanoska-Ochser B, Klein NJ, Huang GC, Alvarez RA, Peakman M. Expression of CD86 on human islet endothelial cells facilitates T cell adhesion and migration. The Journal of Immunology. 2008 Nov 1;181 (9):6109-16.

68. Ma W, Pober JS. Human endothelial cells effectively costimulate cytokine production by, but not differentiation of, naive CD4+ T cells. The Journal of Immunology. 1998 Sep 1; 161(5):2158-67.

69. Greening JE, Tree TI, Kotowicz KT, van Halteren AG, Roep BO, Klein NJ, Peakman M. Processing and presentation of the islet autoantigen GAD by vascular endothelial cells promotes transmigration of autoreactive T-cells. Diabetes. 2003 Mar 1; 52(3):717-25.