Pivotal micro factors associated with endothelial cells

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Abstract
Objective: Recent studies have shown the important influence of various micro factors on the general biological activity and function of endothelial cells (ECs). Vascular endothelial growth factor (VEGF) and angiogenin (ANG) are classic micro factors that promote proliferation, differentiation, and migration of ECs. The underlying pathophysiologic mechanisms and related pathways of these micro factors remain the focus of current research.

Data sources: An extensive search was undertaken in the PubMed database by using keywords including “micro factors” and “endothelial cell.” This search covered relevant research articles published between January 1, 2007 and December 31, 2018.

Study selection: Original articles, reviews, and other articles were searched and reviewed for content on micro factors of ECs.

Results: VEGF and ANG have critical functions in the occurrence, development, and status of the physiological pathology of ECs. Other EC-associated micro factors include interleukin 10, tumor protein P53, nuclear factor kappa B subunit, interleukin 6, and tumor necrosis factor. The results of Gene Ontology analysis revealed that variations were mainly enriched in positive regulation of transcription by the RNA polymerase II promoter, cellular response to lipopolysaccharides, negative regulation of apoptotic processes, external side of the plasma membrane, cytoplasm, extracellular regions, cytokine activity, growth factor activity, and identical protein binding. The results of the Kyoto Encyclopedia of Genes and Genomes analysis revealed that micro factors were predominantly enriched in inflammatory diseases.

Conclusions: In summary, the main mediators, factors, or genes associated with ECs include VEGF and ANG. The effect of micro factors on ECs is complex and multifaceted. This review summarizes the correlation between ECs and several micro factors.

Keywords: Endothelial cells; Vascular endothelial growth factor; Interferon; Genes

Introduction
Cardio-cerebrovascular disease, the pathogenesis of which mainly involves atherosclerosis (AS), is a leading cause of disability and death, with acute coronary syndrome (ACS) being one of the more common cardio-cerebrovascular diseases. ACS is a group of clinical syndromes with a pathological basis of rupture or invasion of coronary atherosclerotic plaques and subsequent complete or incomplete occlusive thrombosis, including acute ST-segment-elevation myocardial infarction, acute non-ST-segment-elevation myocardial infarction, and unstable angina pectoris. Injury of vascular endothelial cells (ECs) is the initial factor in AS development. Therefore, a review of the literature on ECs is necessary.

During the past few years, researchers have established that ECs represent a metabolically active organ rather than a passive barrier between blood and tissues. ECs are vital bioactive and endocrine organs with critical functions in controlling vascular metabolism.[²] ECs situated between vascular tissues and blood can not only accomplish the metabolism of interstitial fluid and blood but also synthesize and secrete many vasoactive substances that maintain normal blood flow and long-term vessel patency as well as regulate blood pressure and anticoagulation-coagulation balance.[³]

The main micro factors associated with ECs include vascular endothelial growth factor (VEGF), angiogenin (ANG), interferons (IFNs), and several others; these factors are secreted by inflammatory leukocytes and some non-leukocytic cells and act as intercellular mediators. They differ from classic hormones in that they are produced by a number of tissue or cell types rather than by specialized glands. Other micro factors include nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB), p53, single-nucleotide polymorphisms (SNPs),

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mesenchymal stem cells (MSCs), arginine-to-proline amino acid substitutions (Arg72Pro), beta-2 adrenergic receptor ($\beta_2$AR), zinc-finger protein transcription factor (ZFP) 580, tumor necrosis factor-alpha (TNF-$\alpha$), and Kruppel-like transcription factor 6 (KLF6). In specific immune and inflammatory responses, these micro factors are produced by many cell types such as monocytes, macrophages, natural killer cells, T cells, B cells, fibroblast cells, and ECs. After binding to the high-affinity receptors of their corresponding target cells, these micro factors can perform biological functions such as regulation of cell growth, cell differentiation, and immune responses.\[4-6\] These micro factors regulate both innate and adaptive immune responses.\[6\] The micro factors addressed in the present review can be categorized as interleukins (ILs), IFNs, TNF, colony-stimulating factors, chemokines, growth factors, and other factors. Recent studies have shown that various micro factors have significant effects on the structure, function, and repair of ECs.\[7-9\] Figure 1 presents the flow diagram of the process for selecting references for review in the present study.

On the one hand, ECs play a vital role in maintaining micro factors that are located in tissues.\[10\] On the other hand, many micro factors act on ECs, affecting their structure, and function.\[11\] The vital aspects that characterize the function of micro factors—from induction of prothrombotic activity on the luminal surface to the transfer and functional activation of mobile elements and from the release of chemoattractants for different cell populations to the expression and functional activation of adhesion molecules of different classes—are mainly determined by the early metabolic response of ECs.\[12,13\]

**Effect of Vascular Endothelial Growth Factor on Endothelial Cells**

VEGF is the strongest factor that promotes angiogenesis.\[14,15\] It enhances mitosis and proliferation of ECs, increases the permeability of blood vessels, and facilitates the migration of ECs.\[16-18\] Members of the VEGF family include VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor.\[19\] VEGF-A signaling is the primary factor that initiates physiological sprouting angiogenesis and prompts crucial differentiation activities as well as the growth of endothelial progenitor cells (EPCs) and vascular ECs, mainly through the VEGF receptor 2 (VEGFR-2). VEGF-C can combine with the lymphatic-system-specific VEGFR-3; it is, therefore, critical for the formation of the lymphatic system. The remaining isoforms of the VEGF family include VEGF-D, which binds to VEGFR-2 and -3, and VEGF-B and placental growth factor, both of which bind to VEGFR-1. VEGF-A is one of the more important members of the family because of its ability to induce monocytes to activate, adhere, migrate, increase EC permeability, enhance endometrium hyperplasia, and aggravate AS.\[20\]

VEGFRs are transmembrane proteins with intrinsic tyrosine kinase activity in their cytoplasmic domains.\[21\] They appear to have minor functions in adult coronary vascularization, vascular remodeling, and the lymphatic system. VEGFR-2 contains 19 tyrosine residues.\[22\] The
extent to which the multitude of tyrosines in its cytoplasmic tail is differentially phosphorylated remains unclear. The binding mechanism of different SH2 domain-containing proteins, which leads to activation of gene induction patterns and receptor-specific intracellular signaling, is also unclear. Furthermore, the various effects of different receptors and growth factors are associated with receptor-distinctive signaling pathways, and differences exist in the spatial and temporal expression of the receptors. These effects govern the proliferation, growth, differentiation, tube formation, and maturation aspects of EC repair and regeneration.

To confirm the characteristics of VEGF-related gene induction and signaling pathways, some researchers have comparatively explored the gene repertoire and downstream pathway of VEGFR-2 and epidermal growth factor receptor, which is a non-endothelial-specific growth factor receptor. These studies have indicated that erythrocyte glutathione reductase-1 is a critical transcription factor for VEGF-mediated gene induction in ECs.\(^{[26,27]}\)

The genesis and development of many human diseases are associated with long non-coding RNAs, a novel type of RNA molecule. Recent researches have emphasized the significance of mono-ethylene glycol 3 (MEG3) in the maintenance of normal function of ECs and repair of damaged ECs through processes mediated by VEGF.\(^{[28,29]}\) However, whether MEG3 is beneficial for EC regeneration is unclear, as are the specific underlying pathophysiological mechanisms associated with VEGF. Experiments have shown that DNA methylation can control the high expression levels of MEG3 in primary ECs and that, under hypoxic conditions, hypoxia-inducible factor-1a can regulate MEG3 expression in ECs.\(^{[30]}\) Additionally, MEG3 silencing distinctly decreases VEGFR-2 mRNA levels but does not affect the expression levels of VEGFR-1, Delta-like ligand 4 (DLL4), Hes family BHHL transcription factor 1 (Hes1), or notch receptor 1 (Notch-1). Low MEG3 expression also inhibits endothelial angiogenesis and migration, both of which are induced by VEGF.\(^{[31]}\) Moreover, under normoxic and hypoxic conditions, MEG3 knockdown decreases the formation of ECs and spheroid sprouting of primary ECs. These findings indicate that MEG3 regulated by hypoxia-inducible factor-1a is necessary for increasing VEGFR-2 levels in ECs and that it plays an important role in EC angiogenesis, which is mediated by VEGF-A.\(^{[32,33]}\)

**Effect of Angiogenin on Endothelial Cells**

ANG is a single-stranded peptide comprising 123 amino acids (molecular weight: ~14,000 Da).\(^{[34]}\) Approximately 35% of its amino acids are similar to those of pancreatic RNase. In rabbit cornea, 50 ng of ANG can promote EC formation. ANG is not active against some traditional ribonuclease substrates such as poly(C) RNA of wheat germ. However, ANG is inhibited by RNase inhibitors from human placenta, and it cannot combine with heparin.\(^{[35,36]}\)

The primary biological function of ANG is to promote EC formation. The four types of ANG (ANG-1, ANG-2, ANG-3, and ANG-4) bind to the tyrosine kinase-2 receptor.\(^{[37,38]}\) ANG-1 plays a vital role in vascular remodeling events, possibly by co-activating recombinant TEK tyrosine kinase, endothelial 1 (Tie1) and, in combination with the Tie2 receptor, optimizing the manner in which ECs bind to supporting cells.\(^{[39]}\) However, ANG-2 might antagonize ANG-1 activity by blocking the binding of ANG-1 to Tie2. Some studies have focused on the recognition of natural feedback inhibitors of EC activation\(^{[39-41]}\) and shown that such inhibitors can be used to inhibit the induction of angiogenic genes.

A previous study has shown that the ANG-1/Tie2 signaling system can promote EC migration.\(^{[42]}\) The results of in vitro experiments on small-tube formation have demonstrated that the ANG-1/Tie2 signaling system can facilitate EC formation in the blood vessel lumen.\(^{[43]}\) The experimental results suggest that a fibroblast medium can boost EC migration and small-tube generation, mainly because of the presence of the fibroblast matrix. Cartilage oligomeric matrix protein COMP-ANG-1 facilitates EC migration and small-tube generation in a dose-dependent manner. However, the addition of Tie2 inhibitors to an EC nutrient solution leads to significant inhibition of EC migration and tube formation.\(^{[44]}\) These findings demonstrate that the ANG-1/Tie2 signaling system can accelerate angiogenesis by promoting EC migration and tube formation.\(^{[45]}\)

Research has shown that, when ECs are stimulated with different concentrations of COMP-ANG-1, the expression of Notch-1 receptor and its DLL4 ligand are up-regulated in a dose-dependent manner, while the expression of their downstream target genes (e.g., Hey1, Hey2, and Hey5) is also increased.\(^{[46]}\) Similarly, different concentrations of COMP-ANG-1 stimulate ECs and inhibit the Tie2 receptor. ECs that have been stimulated by COMP-ANG-1 show similar Notch-1 receptor and DLL4 ligand expression levels as non-stimulated ECs.\(^{[47,48]}\) Likewise, there is no obvious difference in the expression levels of the downstream target genes (such as Hey1, Hey2, and Hey5) between stimulated and non-stimulated ECs. Stimulation of ECs with different concentrations of COMP-ANG-1 leads to an increase in EC migration and tube formation.\(^{[49,50]}\) Such ECs can settle Notch-1 signaling pathways, and they show no difference in EC migration and tube formation relative to ECs that have not been stimulated by COMP-ANG-1.\(^{[51]}\) Therefore, we can conclude that the ANG-1/Tie2 signaling system might regulate EC regeneration through Notch-1 signaling pathways.

**Effects of Other Cytokines on Endothelial Cells**

The expression of certain molecules plays a vital role in the repair of ECs. In one study, when ECs were treated with indoxyl sulfate and extracellular microvesicles, the expression levels of NFKB and p53 increased but the concentration of NFKB inhibitory protein alpha (IkBa) decreased in EPCs. These findings indicate that IkBa, NFKB, and p53 play specific roles in EC repair.\(^{[52]}\) IFNs, a type of cytokine, are a group of secretory proteins (mainly glycoproteins) produced by monocytes and
lymphocytes upon stimulation by viruses or other IFN inducers. IFNs are categorized as types I, II, and III on the basis of their cell sources and receptors. A previous study combined tumor-angiogenesis-specific polypeptides with human IFNa. These polypeptides can bind to integrin avb3 and aminopeptidase N, which are expressed on the surface of ECs with high efficiency. IFNa2a and IFNa2b are then induced to gather in the new blood vessels of tumor tissues, where they play a vital antitumor role and inhibit tumor angiogenesis. IFN could prompt ECs to express the major histocompatibility complex-II antigen.

A recent report described changes in VEGFR-2/CD133/CD34 levels in EPCs (which are indispensable for endothelial repair) and in CD31/annexin V levels in endothelial microvesicles are indicators of endothelial lesions. Additionally, an experiment demonstrated the reparative effect of CD34: Using CD34 antibodies to cover a sirolimus-eluting coronary stent can effectively reduce injuries induced by metal instruments.

TNFα is a cell-signaling protein (cytokine) involved in systemic inflammation and one of the cytokines involved in the acute-phase responses of inflammation. TNFα can decrease intimal hyperplasia effectively through its role in the NFκB pathway. NFκB is a protein complex that controls DNA transcription, cytokine production, and cell survival. Its effect can be partially abolished by an inhibitor of nuclear factor kappa-B kinase xi, an NFκB inhibitor. TNFα can inhibit EC proliferation, differentiation, migration, and adhesion. It can also promote cell apoptosis. However, microRNA-19b has the opposite effect on EC apoptosis. The general biological roles of microRNAs and TNFα in coronary artery diseases have been investigated. MicroRNA-19b performs a vital function in weakening TNF-α-induced EC apoptosis, and this function is strongly associated with the Apafl/caspase-dependent pathway.

Tumor protein p53 (Tp53), also known as p53, is an isoform of a protein encoded by homologous genes in various organisms, such as Tp53 in humans and Tp53 in mice. The SNP is a variation in a single nucleotide that occurs at a specific position in the genome, where each variation is present to some appreciable degree within a population. In the case of Arg72Pro, a common protein in exon 4 and codon 72 of the p53 gene can produce arginine or proline residues. The human Tp53 gene harbors a common SNP at codon 72; this mutation yields Arg72Pro, which modulates the apoptotic activity of the p53 protein. A study has revealed that the Tp53, Arg72Pro, and SNP regulate neovascularization and endothelial repair. The Pro allele of Tp53 is associated with the ability of ECs for functional recovery from stroke and vascular repair. Moreover, inhibition of Rho-associated protein kinase improves endothelial repair in stented arteries by enhancing EC proliferation and migration through the bidirectional flow. Liu et al. discovered a new method for improving endothelialization through erythropoietin (EPO)-induced EPC activation, ARA290, a specific agonist of the EPO receptor/CD131 complex, induces specific improvement in the biological activity of endothelial colony-forming cells, which are a subpopulation of EPCs. Alternate EPO-mediated signaling through the EPO receptor/CD131 heteromeric receptor is responsible for the endothelium-protective functions of EPO in a variety of injuries, especially ischemic diseases. B2AR is a cell-membrane-spanning β2AR that interacts with (binds to) epinephrine, a hormone, and neurotransmitter (ligand synonym, adrenaline). Epinephrine signaling increases cyclic adenosine monophosphate levels through adenylyl cyclase stimulation by trimeric G proteins and mediates physiological responses such as muscle relaxation and bronchodilation by means of downstream L-type calcium-channel interaction. Ke et al. have shown that β2AR up-regulation improves the capabilities of EPCs and strengthens their ability for endothelial repair in vivo through the β2AR/Akt/endothelial nitric oxide synthase pathway. Up-regulation of β2AR gene expression through gene transfer might be a novel therapeutic target for endothelial repair. Unexpectedly, biofunctionalization with RGD/chemokine (C-X-C motif) ligand 1 (CXCL1) has been reported to dramatically decrease thrombus formation and improve re-endothelialization in apolipoprotein E−/− arteries relative to bare-metal nitinol stents. Therefore, RGD/CXCL1 might play an indispensable role in endothelial repair. However, CXCL-10 up-regulation reduces angiogenic capacity in patients with systemic lupus erythematosus. Thus, an antagonistic relationship might exist between CXCL1 and CXCL-10, which should be a point of focus in future research.

In molecular genetics, KLFs are described as a set of zinc-finger DNA-binding proteins that regulate gene expression. KLFs are divided into three subgroups. Group 2 KLFs (KLF1, 2, 4, 5, 6, and 7) are transcription activators. The KLF6 protein is encoded by the KLF6 gene in humans. In a previous study, mobilization of KLF6 into the nucleus was shown to regulate various target genes related to angiogenesis, vascular repair, and remodeling after endothelial injury. Matrix metalloproteinase 14 (MMP14) targets endoglin to release soluble endoglin and is associated with the endothelial repair. Expression of KLF6 leads to enhancement of MMP14 activity. KLF6 then cooperates with MMP14 to improve EC proliferation; this cooperation is increased in case of vascular injury. These findings suggest that KLF6 promotes MMP14 activity and plays a pivotal role in the gene expression network that is stimulated during the endothelial repair.

VEGF might contribute to vascular endothelial repair and function as a protective factor. Song et al. attempted to provide sufficient evidence for the existence of this phenomenon. They found that VEGF observably improves the quantity and activity of EPCs. Moreover, treatment with VEGF reduces the apoptosis rate of ECs. However, carbamylated high-density lipoproteins inhibit the activation of VEGFR-2 and signaling pathways of the scavenger receptor class B type I in ECs. Furthermore, these lipoproteins suppress the repairability of ECs. Using the online tool STRING (https://string-db.org/cgi/input.pl), we obtained details regarding the protein-protein interaction network of interleukin-10, Tp53, VEGF-A, ANG, nuclear factor kappa B subunit, interleukin 6, and TNF [Figure 2].
ZFPs are transcription factors composed of a zinc-finger-binding domain and any of a variety of transcription factor effector domains that exert their modulatory effect in the vicinity of any sequence to which the protein domain binds. The novel ZFP580 facilitates the differentiation of EPCs into ECs by not only up-regulating the expression of nitric oxide and endothelial nitric oxide synthase but also by up-regulating EC formation. This might represent a new theory on the role of ZFP580 in EC evolution and its clinical value in the resolution of vascular damage. Additionally, the DLL4/Notch signaling pathway and ephrin-B2 expression both play necessary roles in every step of endothelial neogenesis. The ephrin-B2 expression is remarkably augmented in the EPCs of patients with pre-eclampsia. While ephrin-B2 over-expression negatively affects EPC functions, including their ability to increase the number of ECs and promote endothelial repair, decreasing ephrin-B2 expression has the opposite effect. Activation of DLL4/Notch signaling results in increased expression of ephrin-B2 and subsequent inhibition of EPC activity. Down-regulation of the DLL4/Notch signaling pathway and ephrin-B2 expression might be a novel therapeutic strategy for endothelial repair. Furthermore, cyclooxygenase-2 (COX-2) expression has been found to be markedly up-regulated because of thrombin receptor (protease-activated receptor-1) activation, and this can enhance chemotactic gene activation at an ischemic location through a COX-2-dependent approach in endothelial colony-forming cells.

MSCs are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells), and adipocytes (fat cells which give rise to marrow adipose tissue). MSCs that have been induced to up-regulate the expression of the angiotensin-converting enzyme 2 (ACE2) gene can increase their production of positive ACE2 protein for a long time and have a stepped-up capacity to facilitate endothelial recovery. These findings are expected to stimulate further experiments to elucidate the favorable influence of ACE2 on endothelial recovery.

The latest CANTOS study led by Dr. Paul Ridker, showed that treatment with canakinumab, a monoclonal antibody against interleukin 1b, can further reduce the risk of cardiovascular events after myocardial infarction by 15% in conjunction with standard drug therapy. This study concluded that anti-inflammatory therapy targeting the interleukin 1b innate immunity pathway with canakinumab (at a dose of 150 mg every 3 months) led to a significantly lower rate of recurrent cardiovascular events than placebo therapy, independent of the decrease in lipid levels. Therefore, anti-inflammatory therapy might slow the development and progression of AS.

Conclusions

In summary, the effect of cytokines on ECs is complex and multifaceted. The results of Gene Ontology analysis revealed that variations in biological processes were mainly enriched in positive regulation of transcription by the RNA polymerase II promoter, cellular response to lipopolysaccharides, negative regulation of apoptotic processes, positive regulation of transcription, DNA-templated, and other processes. Changes in cellular components were mainly enriched in the external side of the plasma membrane, cytoplasm, extracellular regions, and extracellular space. Variations in molecular function were enriched in cytokine activity, growth factor activity, identical protein binding, transcription regulatory DNA region binding, and other processes. The results of Kyoto Encyclopedia of Genes and Genomes analysis revealed that micro factors were prevalently enriched in inflammatory bowel disease, pertussis, Chagas disease, amoebiasis, hepatitis B, and so on. VEGF regulates the proliferation, tube formation, differentiation, and maturation aspects of EC regeneration and repair, which are associated with erythrocyte glutathione reductase-1 and MEG3. Some research has shown that the ANG-1/Tie2 signaling system can promote EC migration through Notch-1 regulation. Furthermore, some cytokines, such as IFNs, prompt ECs to participate in immune or inflammatory responses. Of course, many of the current studies have been performed in vitro, and the effect of cytokines on ECs in the body is likely to be more complex and not static. That is, the effect of micro factors on ECs is dependent not only on the relative concentrations of various micro factors in ECs and the different stages of immune or inflammatory responses but also on the condition of the ECs themselves. The relationships between the endothelium and micro factors are complex. Existing researches show that the reactivity of ECs to the same cytokines differs between arteries and veins, between the great and small blood vessels, and between the blood vessels of people of different ages. Many published reports have focused on micro factors under various disease conditions. However, it is critical to further study how the effects of various micro factors on ECs adjust and modify the effects of
cytokines on ECs. This will help elucidate the emergence and development of certain diseases and establish novel targets for their treatment.\(^{78,79}\)

Effective methods for early diagnosis and therapy of ACS could be discovered on the basis of research on EC-related macro factors. Future studies should pay more attention to the pivotal micro factors associated with ECs. Vascular endothelial injury is an important cause of AS, which is the pathological basis of ACS. Therefore, treating AS and delaying its progression is of great significance in preventing ACS. A study has found that micro factors, especially the ones related to vascular endothelial injury, participate in the development of AS and are closely related to complications such as ACS. The underlying mechanism might be that micro factors promote inflammation and activate blood coagulation systems and vascular injuries, thus promoting AS and inducing ACS. At the same time, micro factors might serve as biomarkers for new EC injuries and vasomotor dysfunction, and their circulating...
levels might reflect the extent of stimulation of cell proliferation. In conclusion, the study of micro factors related to vascular EC injury is of great significance for the treatment of ACS caused by AS.

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Conflicts of interest

None.

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