Common Injuries and Repair Mechanisms in the Endothelial Lining

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Abstract

Objective: Endothelial cells (ECs) are important metabolic and endocrinal organs which play a significant role in regulating vascular function. Vascular ECs, located between the blood and vascular tissues, can not only complete the metabolism of blood and interstitial fluid but also synthesize and secrete a variety of biologically active substances to maintain vascular tension and keep a normal flow of blood and long-term patency. Therefore, this article presents a systematic review of common injuries and healing mechanisms for the vascular endothelium.

Data Sources: An extensive search in the PubMed database was undertaken, focusing on research published after 2003 with keywords including endothelium, vascular, wounds and injuries, and wound healing.

Study Selection: Several types of articles, including original studies and literature reviews, were identified and reviewed to summarize common injury and repair processes of the endothelial lining.

Results: Endothelial injury is closely related to the development of multiple cardiovascular and cerebrovascular diseases. However, the mechanism of vascular endothelial injury is not fully understood. Numerous studies have shown that the mechanisms of EC injury mainly involve inflammatory reactions, physical stimulation, chemical poisons, concurrency of related diseases, and molecular changes. Endothelial progenitor cells play an important role during the process of endothelial repair after such injuries. What’s more, a variety of restorative cells, changes in cytokines and molecules, chemical drugs, certain RNAs, regulation of blood pressure, and physical fitness training protect the endothelial lining by reducing the inducing factors, inhibiting inflammation and oxidative stress reactions, and delaying endothelial caducity.

Conclusions: ECs are always in the process of being damaged. Several therapeutic targets and drugs were sought to protect the endothelium and promote repair.

Key words: Endothelium; Vascular; Wound Healing; Wounds and Injuries

INTRODUCTION

In recent years, cardiovascular disease has become the leading cause of disability and death among both urban and rural residents in China, driven largely by aging, diabetes, hypertension, hyperlipidemia, obesity, and smoking. However, vascular endothelial injury is also ubiquitous in atherosclerosis, hypertension, diabetic vascular complications, and several cardiovascular and cerebrovascular diseases. Endothelial cells (ECs) are important components of blood vessels, as they are arranged in a single vertical layer and are common targets in the development of cardiovascular disease. They not only form a barrier against allogenic material but also possess endocrine and immunological competence. Furthermore, they play an important role in vascular homeostasis, including by participating in vasoconstriction and vasodilation to control blood pressure, coagulation, atherosclerosis, and angiogenesis. Missing or dysfunctional ECs will expose damaged blood vessels to a variety of pathogenic factors so that the endogenous and extrinsic coagulation pathway is activated, and local thrombosis produces vessel stenosis or occlusion. At the same time,
various inflammatory dielectrics, cytokines, and chemokines\(^8\) are produced around the damaged vessels. Under the stimulation of these factors, smooth muscle cells proliferate, leading to endothelial hyperplasia and complications of hemadostenosis which can endanger the patient’s life.

However, it is unclear which key factors or links among them trigger endothelial injury and repair. Therefore, several studies have explored the characteristics and mechanisms of endothelial injury, as well as investigating the roles of the harmful or beneficial substances secreted by a damaged endothelium. The current research on endothelial injury chiefly focuses on inflammatory reactions, physical stimulations, chemical poisons, concurrency of related diseases, and molecular changes. On the other hand, ECs also possess the ability to proliferate and repair themselves. A variety of restorative cells, changes to cytokines and molecules, chemical drugs, certain RNAs, regulation of blood pressure, and physical fitness training can be beneficial to endothelial wound repair [Figure 1]. The research progress in both endothelial injury and repair is described below.

**Protective Factors Related to Endothelial Repair**

**Endothelial progenitor cells**

Since the initial discovery of endothelial progenitor cells (EPCs), researchers have made meaningful progress toward a strict functional description and a better interpretation of EPCs, which have been successfully used to stimulate vascular repair and angiogenesis in some experimental settings.\(^9\)\(^-\)\(^{13}\) Moreover, EPC-containing products (such as bone marrow or mobilized peripheral blood), which are a kind of human autologous cell therapies, have proven to be viable and valid options in the treatment of atherosclerotic disease. Furthermore, significantly higher levels of circulating \(CD34^+KDR^+\) cells are consistent with the number of EPCs improving endothelial repair. Thus, CD34\(^+\)KDR\(^+\) cells may become the key to successful therapies that require targeting several parallel mechanisms for a long time. They are also integral to novel molecular strategies and translational developments of cerebrovascular treatments in patients with type 2 diabetes mellitus.\(^14\) Since circulating CD34\(^+\) cells have been reported to be beneficial to endothelial repair (and thus to vascular repair and the development of atherosclerosis), this factor could be a biomarker for the activity of the vicious between endothelial damage and hypertension common in elderly men.\(^15\)

What’s more, external electric muscle stimulation (EMS) reduced symptoms of vascular lesions induced by diabetic neuropathy and decreased diastolic blood pressure. A single EMS remedy fortified the function of certain molecules which can mediate differentiation and attachment on the surface of hematopoietic stem cells (HSCs) during blood circulation. A new assumption is that the EMS-induced increase in surface attachment molecules on HSCs allows the HSCs to leave blood circulation and that the EMS remedy boosts the effect of EPCs and HSCs.\(^16\) However, the downregulation of Notch1 also enhanced the proliferation, differentiation, migration, and adhesion of EPCs, along with the capacity to form human vein ECs.\(^17\) In spite of a number of studies revealing correlations between circulating EPC phenotypes and patient traits and prognosis, the pathophysiological effect of circulating EPC concentrations is still unclear.

**Other correlative cells**

Endothelial repair can be considered from the cell’s perspective as a result of the lesions originating from ECs. Recent evidence illuminates the presence of two EPC subtypes: endothelial colony-forming cells (ECFCs) and early outgrowth cells (EOCs). Their different morphological and phenotypic characteristics, and more importantly, the release of the...
antiaggregating agents prostacyclin 2 and nitric oxide (NO) in each EPC subtype, are implicated in their respective roles in endothelial function and thus may be linked to the better efficiency of ECFCs in inhibiting endothelial injury during endothelial regeneration,[20,21] First, in vascular regenerative medicine, human amniotic epithelial cells (hAECs) are a promising means for endothelial repair. Váczi et al.[20] concluded that, without immunosuppression, hAECs were capable of intruding into the vascular wall but were incapable of enhancing vascular condition. She emphasized that this process can achieve the aim of morphological implantation and cannot gain the functional benefits, highlighting the necessity to research other theories of endothelial repair. In addition, Hasdemir et al.[21] proposed that, after a radiation injury, adipose-derived stem cells have an underlying capacity for strengthening hemokinesis, which might be accompanied with endothelial repair and needs further study. More recently, angiogenic T cells (Tang) have been recently discovered to cooperate with EPCs in endothelial repair. The main aim of Rodríguez-Carrio et al.'s research[22] was to analyze the Tang and EPC numbers in relation to traditional cerebrovascular risk factors. The increase of Tang has a protective effect on the endothelium. At present, cell replacement therapy is an idealized and novel strategy for endothelial injury, but there are also numerous obstacles and difficulties such as immunological rejection, ethical issues involving embryos, and a limited number of cells.

**Cytokines or molecules**

From a microscopic perspective, molecular expression plays an important role in endothelial repair. In the case of irradiation in rats, severe endothelial injury was produced, but treatment with human bone morphogenic protein-2 (HBMP-2) combined with mesenchymal stromal cells (MSCs) accelerated repair. By regulating hypoxia-inducible factor-1 α expression[23] (which influences endothelial formation and recovery), and by upregulating the expression of the endothelial NO synthase (eNOS) pathway,[24] HBMP-2 exerts its effect. These findings suggest that novel methods for adding molecules or cytokines to MSCs should be evaluated for remedying chronic radiation-induced damage to the endothelium.

Apolipoprotein A-I (apoA-I) mimetic peptide has many antiatherogenic features which improve the impaired endothelial proliferation and migration resulting from oxidized low-density lipoprotein, by reducing EC apoptosis and upregulating the expression of heme oxygenase-1 (HO-1) and eNOS. Moreover, the antioxidation, proproliferation, and promigration abilities of apoA-I were cut down by the inhibitors of both eNOS and HO-1.[25] Next, increasing high-density lipoprotein (HDL) concentrations by inhibiting the cholesteryl ester transfer protein reduces intimal thickening and regenerates functional endothelia in damaged aortas in a scavenger receptor-B1-dependent and phosphatidylinositol-4,5-bisphosphate 3-kinase/ Akt-dependent manner.[26] In summary, the results suggest that apoA-I and cholesteryl ester transfer protein inhibition might be commendable candidates for the protection of ECs and the prevention of atherosclerotic disease.

Along similar lines, novel zinc finger transcription factor (ZFP580) facilitates not only the differentiation of EPCs into ECs by upregulating the availability of NO and the expression of eNOS but also endothelial formation.[27] This may demonstrate a new theory of ZFP580 in EPC evolution and its meaningful value in the remedy of vascular damage. Adepu et al.[28] research shows that early injury in transplanted kidneys causes repair stimulations, specifically tubular syndecan-1 expression for endothelial neogenesis. Syndecan-1 is a transmembrane heparan sulfate proteoglycan involved in regenerative growth and cellular adhesion. Increased serum syndecan-1 concentrations might be a repair factor relevant to endothelial function. Moreover, bone marrow-derived cellular therapies are a new and developing strategy to improve therapeutic endothelial neogenesis in atherosclerotic disease. Specifically, ixmyelocel-T is manufactured from a small sample of bone marrow aspirate, forming an expanded autologous multicellular therapy. Ledford et al.[29] reported that ixmyelocel-T cooperates with ECs in a paracrine manner, leading to endothelial protection and angiogenesis. This result shows that ixmyelocel-T could be beneficial for improving endothelial repair in ischemic cardiovascular and cerebrovascular diseases. In a word, ixmyelocel-T treatment may offer a novel insight into remedial vasculogenesis in patient populations requiring an increased number of reborn cells.

**Chemical drugs**

Endothelial-protective chemical drugs, including lipid-lowering medicines, anti-human immunodeficiency virus (HIV) drugs, hypoglycemic drugs, hypotensor, and Vitamin D, play a role in endothelial repair mainly by treating concomitant diseases, which can achieve better results. First, in terms of lipid-lowering medicines, present clinical worries center on restraining the proliferation of smooth muscle cells by utilizing drug-eluting stents. It is unfortunate that this approach can also suppress endothelial proliferation and prevent EC repair. However, Hussner’s data offered enough proof and a theoretical basis for using atorvastatin in stents to avoid this dilemma.[30] Furthermore, Li et al.[31] researched the capacity of atorvastatin to guard ECFCs, a subtype of EPCs, and to demonstrate a potential protective effect from hydrogen peroxide (H$_2$O$_2$)-induced oxidative injury. Furthermore, Rosuvastatin improved re-endothelialization by regulation of EPCs, proposing that facilitating endothelial recovery offers a fresh therapeutic strategy for vascular repair.[32]

Second, one study demonstrates that anti-HIV drugs can promote the repair of impaired endothelia. Recovery of the serum concentration of EPCs was higher in darunavir-remedied individuals than those remedied with rilpivirine, suggesting promising endothelial repair methods.[33] Third, hypoglycemic medicine can effectively reduce blood glucose concentrations, weaken the damage of high sugar on ECs, and form an endothelial protection mechanism. Metformin has an underlying
endothelium-protective function through promoting the level of EPCs and EC and markedly affecting hypoglycemic function.\[34\] Similarly, irisin was proven to promote endothelial regeneration in diabetic mice that received EPC transplants after vascular damage.\[33\] Fourth, store-operated calcium entry (SOCE), a major mode of extracellular calcium entry, plays a part in all kinds of cell activities. SOCE inhibition can have a favorable influence on EPCs after exposure to oxidative stress caused by oxidizing agents and may provide an underlying method to compete with endothelial damage.\[36\]

Fifth, in Reynolds et al.’s experimental research, calcitriol promoted endothelial repair in individuals with systemic lupus erythematosus (SLE). The results demonstrate that Vitamin D could be a new treatment to decrease atherosclerotic disease and protect the ECs from damage.\[37,38\] Recently, there have been some new reports that the prostacyclin has a certain role in the repair of endothelial injury, but it is not very clear and needs further study.\[39\]

**Other approaches to endothelial repair**

The repair of the endothelium involves a variety of aspects including certain RNAs, regulation of blood pressure, physical fitness training, number of blood platelets, and physical stimulation. Although the whole network of microRNAs (miRNAs) involved in the process is still largely unknown, present evidence shows that therapeutic replacement of 23 miRNAs, miR-126-5p, miR-155, and other miRNAs, which help maintain the vascular homeostasis of EPCs, may restore endothelial health and reduce atherosclerosis.\[14,40,41\]

Furthermore, hypertension might indicate an insufficient ability for adequate vascular maintenance, so lowering blood pressure is a protective strategy and a therapeutic prospect for repairing damaged vascular ECs.\[42-45\] Next, the number and activity of ECs in men and increased CD34+ cells in women are enhanced through exercise.\[46-49\] Finally, as to physical stimulation, external EMS,\[42\] shear stress,\[43\] and hypoxia\[50\] are vital nonpharmacologic methods to improve the activity of EPCs. These findings provide novel nonpharmacologic therapeutic methods for hypertension-interrelated endothelial neogenesis.

**Risk Factors Related with Endothelial Injury**

**Inflammatory reactions**

Numerous studies have demonstrated that the pathophysiological processes of various cardiovascular and cerebrovascular diseases, such as atherosclerosis, involve inflammatory responses.\[51,52\] Mitsides et al. proved that inflammation reactions were mediated through the interleukin-8 (IL-8) pathway forecasted microvascular endothelial injury, but fms-like tyrosine kinase-1 (Flt-1), which is a potential marker of angiogenesis and endothelial repair, might have a remarkable protective function. Further cognition of IL-8 and Flt-1 will be inevitable to improve the stationary state of vessels.\[53\] Except for IL-8, which can exert a harmful effect on ECs, there are some aspects relevant to the relationship between inflammation and endothelial injury. To start with, as a characteristic of rheumatoid arthritis, inflammation results in the activation of ECs, which can cause atherosclerosis by means of prompting leukocyte adhesion molecules to overexpress.\[54\] Endothelial dysfunction, induced by inflammation, interferes with endothelial repair courses. Accardi et al.\[55\] argued that inflamm-ageing, the chronic low-grade inflammation that is common in elderly populations, complicates general vascular condition and gives rise to atherosclerosis, the main predictor of cardiovascular and cerebrovascular diseases. As a matter of course, oxidative stress and inflammation play an essential part in the pathogenic mechanism of endothelial injury, generally due to the reduced availability of NO.

Finally, it is worth mentioning that the underlying influences of Tan II A on tumor necrosis factor (TNF)-α-motivated EPC proliferation, formation ability, and paracrine activity in vitro tubes, as demonstrated by Wang et al.\[56\] The results predicted that TNF-α damaged EPC proliferation competence and neovascularization capacity in vitro and boosted the EPC excretion of inflammation factors such as soluble CD40 ligand, monocyte chemoattractant protein-1, and IL-6. Nevertheless, these effects were able to be reversed by Tan II A. In other words, these results proved that Tan II A may possess the ability to defend EPCs from lesions triggered by TNF-α. Consequently, these findings may offer proof for the theoretical foundation of Tan II A and its underlying value to prevent and remedy early atherosclerotic disease related to EPC and endothelial injury. In brief, the infiltration and activity of inflammatory cells have been key factors in endothelial injury.

**Physical stimulation**

Physical stimulation refers to external changes in the body or the natural environment, including knocking, pressure, pulling, fire, ice, radiation, metal ions, and body type changes. However, damage to ECs mainly includes the following aspects. Pradhan et al.\[57\] found that radiation during childhood cancer treatment boosts the risk for cardiovascular and cerebrovascular diseases among adult survivors, which is considered to be mediated by the injury to the ECs. ECFCs, a population of EPCs,\[58\] exhibited some changes after exposure to radiation. ECFCs and EPCs in the individuals receiving radiation therapy were significantly lower (P < 0.05) than those without radiotherapy. The elementary results of this research provide proof that ECFCs function as biological targets for endothelial damage. In addition, interventional therapy, mainly device implants, markedly decreases the incidence of restenosis and the necessity for vascular remodeling but is related with impaired ECs. Namely, the constant presence of a metal stent or spring coil may injure the proliferation of ECs. The hysteresis effect of intervention operation on endothelial damage was discussed by Tesfamariam.\[59\] Furthermore, another finding implied that zinc oxide nanoparticles restrain angiogenesis from ECFCs by downregulating the expression of receptors associated with angiogenesis including the vascular endothelial growth factor receptor (VEGFR), the VEGFR2, and the CXC chemokine receptor 4. The
influences are on the condition of levels of secreted Zn(II). [60]
Finally, it was surprising that obese patients presented with high concentrations of adipokines, plenty of endothelial microparticles, and a low number of EPCs, with more augmentation in adipokines after surgical stimulation, indicating an inflammatory situation that deteriorates after surgical stimulation and may influence endothelial repair. [61]
Physical stimulation, an important factor in endothelium damage, should be avoided as much as possible.

**Chemical poison**
The role of chemical toxicants in endothelial injury is also significant, including indoxyl sulfate, nicotine, reactive oxygen, H$_2$O$_2$, and oxidative stress. Carmona et al.’s findings [41] confirmed that indoxyl sulfate is associated with the poor prognosis of chronic kidney disease and cardiovascular disease owing to the injury of endotheliocytes, and that it is able to promote the formation of endothelial vesicles with varying molecules that maintain the homeostasis of EPCs. These particular traits of endothelial vesicles could be regarded as original biological targets for a diagnosis of atherosclerotic disease. In addition, as we all know, smoking is harmful to our health. Specifically, nicotine concentrations in hair were dramatically negatively interrelated with total antioxidant capacity levels of HDL and EPCs, after controlling for body mass index, age, sex, education, and consumption patterns. [62] Moreover, nicotine exposure during adolescence is disadvantageous to the vascular endothelium simply because intercellular adhesion molecule 1 is a biomarker for endothelial excitation and stress after damage to the endothelium. [63]

Oxidative stress also plays a primary part in the pathogenic mechanism of endothelial damage, generally owing to the attenuated availability of NO. [55] Furthermore, H$_2$O$_2$ can induce oxidative stress to weaken the protective condition of EPCs. [36] Amassing reactive oxygen species (ROS) can do some harm in the repair of impaired endotheliocytes, but the potential theory is undiscovered. EOCs play an important role in endothelial repair. Research findings show that p66$_{shc}$ overexpression induced by ROS, through the nicotinamide adenine dinucleotide phosphate/manganese superoxide dismutase (MnSOD) axis, impairs the paracrine angiogenic potential of aged EOCs to aggravate endothelial injury. [64]

In short, the damage from chemical poisons is widespread, causing ECs to be stripped, losing their invisible protective barrier, and forming atherosclerosis. These findings form the basis for novel therapeutic strategies to improve vascular repair after injury and combat atherosclerotic disease in the early stages.

**Other relevant factors in endothelial injury**
There are many connections between the upregulation of SM22alpha promoter, sympathoadrenal activation, Red Cell Distribution, aging, Vitamin D deficiency, and SOCE. Whether these factors or their interactions will produce injury to the endothelium needs to be studied further in the future [Table 1]. [65–70]

**Concurrence of Related Diseases on Endothelial Injury**
Diseases of some other systems can be accompanied by endothelial injury, such as chronic obstructive pulmonary disease, [71,72] sepsis, [73] SLE, [70] obstructive sleep apnea, [74] end-stage renal disease, [75] left ventricular hypertrophy, [75] Blackfoot disease, [76,77] and type 2 diabetes [78,79] [Table 1]. It may be that many diseases are connected to endothelial injuries to varying degrees, but uncovering those connections will require tireless scientific efforts.

**Conclusion**
Endothelial injury is an important pathophysiological step toward atherosclerotic stenosis, [80] an overhealing reaction of the blood vessels to the injury. [81,82] Studies have shown that various factors can lead to damage of the endothelium, [83] including inflammatory reactions, physical stimulation,

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**Table 1: Other relevant factors on endothelial injury in the literature**

| References | Relevant risk factors | Main viewpoint |
|------------|-----------------------|---------------|
| Jing et al. 2015 [65] | SM22alpha promoter | In VSMC, the SM22alpha promoter, carried by a recombinant lentiviral vector, was used to successfully infect and selectively upregulate expression of p27 protein, which restrains intimal hyperplasia with inhibition of endothelial repair |
| Wang et al. 2015 [64] | SOCE | The decrease of SOCE led to EPC damage potentially by downregulating SOCC and impairing eNOS pathway |
| Ostrowski et al. 2017 [71] | Sympathoadrenal activation | Sympathoadrenal activation, injuring endothelial function, was dramatically correlated with hypocoagulability and endotheliopathy |
| Rodriguez-Carrio et al. 2015 [84] | RDW | RDW was related with endothelial progenitor cells consumption and incremental concentrations of various intermediaries connected to endothelial injury, thereby which unmask novel insight on the science of RDW as predictive factors |
| Bochenek et al. 2016 [84] | Aging | The damaged proliferation and migration of local endothelial cells as well as exhaustion of endogenous endothelial repair mechanisms become worse with age by impairing re-endothelialization |
| Reynolds et al. 2016 [79] | Deficiency of Vitamin D | Vitamin D shortage is associated with poor vascular repair and weakened endothelial function and may regulate inflammatory reaction |

VSMC: Vascular smooth muscle cells; EPC: Endothelial progenitor cell; SOCE: Store-operated calcium entry; SOCC: Store-operated calcium channel; eNOS: Endothelial nitric oxide synthase; RDW: Red cell distribution width.

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chemical poisons, concurrency of related diseases, aging, and a deficiency of Vitamin D. However, the exact mechanism of endothelial injury is not yet fully understood.

Repairing endothelial injury and recovering endothelial function are considered to be the keys to the prevention and treatment of atherosclerotic stenosis. Numerous studies have confirmed that several different sources of EPCs are transplanted to the damaged blood vessel; these EPCs can locate the vascular lesions, mediate vessels to be endothelial, and inhibit neointimal hyperplasia. Through the deepening of endothelial injury and repair research, especially in terms of changes in cytokines and molecules, chemical drugs, certain lipid pathways, certain RNAs, regulation of blood pressure, and physical fitness training, new targets for the protection of the vascular endothelium will be found to produce new drugs for the protection of damaged endothelia.

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Conflicts of interest
There are no conflicts of interest.

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血管内皮细胞的普遍状态：修复与损伤的抗衡

摘要

目的：内皮细胞是重要的代谢和内分泌器官，在调节血管功能方面起着重要的作用。血管内皮细胞位于血液和血管组织之间，不仅可以完成血液和组织液的新陈代谢，而且可以合成和分泌多种生物活性物质，以保持血管紧张度，维持正常的血液流动和长期通畅。因此，本文系统地综述了血管内皮细胞的普遍状态：修复与损伤的抗衡。

方法：通过计算机检索Pubmed数据库，搜索了2003年以后发表的相关研究论文，文章关键词包括“内皮细胞”、“血管”、“损伤”、“修复”。

结果：多种心脑血管疾病的发生发展与内皮细胞的损伤密切相关。然而，血管内皮细胞损伤的机制尚不完全清楚。大量研究表明，内皮细胞损伤的机制主要涉及炎症反应、物理刺激、化学毒物和分子改变。内皮祖细胞在损伤后的内皮细胞修复过程中起着重要作用。此外，多种具有修复功能的细胞、细胞因子和分子的变化、药物、某些RNA、血压调节和体能训练都对内皮细胞有保护作用，其作用是通过减弱诱发因素、抑制炎症和氧化应激反应、延缓内皮细胞衰老来实现的。

结论：内皮细胞一直处于损伤和抗损伤的过程中。鉴于内皮细胞在脑血管病发展中的重要作用，人们正在寻找保护内皮细胞和促进内皮细胞修复的治疗靶点和药物。