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Inflammation and oxidative stress in angiogenesis and vascular disease

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Abstract

Recent evidence suggests that processes of inflammation and angiogenesis are interconnected, especially in human pathologies. Newly formed blood vessels enable the continuous recruitment of inflammatory cells, which release a variety of proangiogenic cytokines, chemokines, and growth factors and further promote angiogenesis. These series of positive feedback loops ultimately create a vicious cycle that exacerbates inflammation, transforming it into the chronic process. Recently, this concept of reciprocity of angiogenesis and inflammation has been expanded to include oxidative stress as a novel mechanistic connection between inflammation-driven oxidation and neovascularization. Production of reactive oxygen species (ROS) results from activation of immune cells by pro-inflammatory stimuli. As oxidative stress can lead to chronic inflammation by activating a variety of transcription factors including NF- κ B, AP-1, and PPAR- γ , inflammation itself has a reciprocal relationship with oxidative stress. This review discusses the recent findings in the area bridging neovascularization and oxidation and highlights novel mechanisms of inflammation and oxidative stress driven angiogenesis.

Keywords

Angiogenesis; Inflammation; Oxidative stress

Introduction

Although vasculature in adult mammals is mainly quiescent, new blood vessel formation is required for timely tissue repair and remodeling after injury. At the same time, angiogenesis promotes a number of pathophysiological conditions associated with inflammation, solid tumor growth, and metastasis, as well as eye diseases. The process of angiogenesis involves migration, proliferation, differentiation, and adhesion of multiple cell types, including endothelial, mural, and inflammatory cells [1–3]. Whereas developmental angiogenesis mostly depends on conventional angiogenic signals, such as vascular endothelial growth factor (VEGF) and Notch, pathological angiogenesis appears to be closely associated with inflammation and inflammation-generated oxidative stress [4–7]. A number of novel mechanistic components contributing to neovascularization have been recently identified, however, the link coupling inflammation-dependent oxidation or inflammation-independent oxidation to the angiogenic process remains largely unknown. In this review, we summarize

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Conflicts of Interests Statement

The authors declare no conflict of interests. A patent describing the role of CEP has been submitted.

recent findings in this area and discuss their implications in the context of antiangiogenic therapeutic strategies.

Angiogenesis and inflammation

Inflammation is a host defense mechanism enabling the body to respond to injury and pathogenic challenges. Acute inflammation provides an immediate response against infectious agents with the so-called “search and destroy” mechanism, and involves rapid recruitment and activation of neutrophils, eosinophils, and natural killer (NK) cells [3, 6, 7]. The main weapon used by these cells against pathogens is the generation of reactive oxygen species, followed by an infiltration of leukocytes to remove remaining pathogens [8, 9]. In contrast to this protective mechanism, chronic inflammation causes substantial tissue damage which might create procarcinogenic conditions [6, 10]. In this situation, pathological angiogenesis promotes a continuous recruitment of inflammatory cells, thereby exacerbating inflammation and damage [11]. A number of inflammatory cells, including neutrophils, eosinophils, mast cells, NK cells, macrophages, and dendritic cells (DCs), are involved in inducing and promoting angiogenesis, while alternatively activated (or M2) macrophages seem to play a crucial role in tumor angiogenesis [3, 12]. Under hypoxia condition, inflammatory cells secrete a plethora of proangiogenic factors, including VEGF, tumor necrosis factor- α (TNF- α), and other cytokines, increasing vascular permeability and facilitating additional recruitment of immune cells [7, 11, 13, 14]. Multiple types of leukocytes and macrophages also contribute to the proteolytic remodeling of the extracellular matrix (ECM) by releasing matrix metalloproteinases (MMPs), cathepsins, plasminogen, and urokinase, thereby allowing blood vessel formation [2, 10]. Angiogenesis is indirectly enhanced by chemokines, such as CXCL12, CXCL8, and CXCL1, especially those derived from neutrophils, which further potentiate inflammation [3, 15]. However, one of the main functions of activated inflammatory cells is the generation of ROS, which serves as an important stimulus of angiogenic signaling [8, 9].

Toll-like receptors in angiogenesis

It has been discovered that TLRs act as guardians of innate immunity, revealing several classes of pathogens either on the plasma membrane or on the endosomal membranes after pathogen phagocytosis [16–18]. TLR expression is not restricted to leukocytes, but has been reported in multiple cell types, including endothelial cells, implying that the role of the TLR pathway may not be limited to immune response [16, 19]. Recent evidence suggests that the TLR pathway significantly contributes to angiogenesis. It has been shown that LPS, a well-known TLR4 ligand, interacts with adenosine A_{2A} receptor (A_{2A}R) agonists through the TLR4 pathway, resulting in a markedly increased production of VEGF in macrophages [20]. LPS is also known to directly stimulate endothelial sprouting *in vitro* through a TRAF6-mediated activation of NF- κ B and JNK [21]. On the other hand, it has been demonstrated that MALP-2, a TLR2/6 ligand, promotes angiogenesis in a TLR2/6 dependent manner by inducing the secretion of a granulocyte-macrophage colony stimulating factor (GM-CSF) [22]. In addition, it has been reported that poly(I:C), a TLR3 ligand, induces the hypoxia inducible factor 1 α (HIF-1 α) activation and VEGF secretion in a TLR3 dependent manner *in vitro* [23]. An increasing body of evidence shows that TLRs also recognize endogenously generated molecular patterns, i.e. denatured or death-associated molecular patterns (DAMPs) [24, 25]. Interestingly, recent studies have shown that the high-mobility group B1 (HMGB1) and oxidation-generated ω -(2-carboxyethyl)pyrrole (CEP) activate TLR signaling and promote angiogenesis [19, 26]. Given that TLRs are required to trigger a defensive inflammatory response to infection, the ongoing investigation of the role of the TLR pathway in angiogenesis bridges inflammation and angiogenesis.

Novel mechanisms of oxidation-driven angiogenesis

One of the signature cellular processes observed during inflammation is respiratory burst, which results in the generation and accumulation of extracellular ROS aimed to protect against invading pathogens [27–29]. At the same time, ROS, in a form of superoxide anion or hydrogen peroxide, seem to act as bona fide messengers to control multiple cellular functions such as cell cycle, proliferation, and apoptosis [30–36]. However, excessive formation of ROS creates an imbalance in aerobic cells and tissues known as “oxidative stress,” which is associated with ageing and numerous pathologies, including heart and vascular diseases [8, 37–43]. One of the well established roles of ROS in human pathologies is lipid peroxidation, a main contributor to atherosclerosis [5]. Both intracellular and extracellular ROS have been implicated in the process of angiogenesis in a number of pathophysiological settings [38, 44, 45]. First, intracellular ROS were shown to be involved in VEGF-dependent signaling in endothelial cells [46]. In a tumor microenvironment, the NADPH oxidase-dependent ROS increase HIF-1 α -dependent VEGF secretion, which, in turn, promotes angiogenesis and facilitates tumor growth [47]. During the wound healing process, ROS released by inflammatory cells (neutrophils and macrophages) and fibroblasts not only act against invading bacteria, but also induce the basic fibroblast growth factor (bFGF) and VEGF expression and signaling [37]. Thus, increasing evidence suggests that ROS are able to promote angiogenesis through known VEGF- or bFGF-dependent pathways.

Intriguingly, several recent studies identified ROS as main mediators of novel VEGF-independent pathways of angiogenesis. Newly generated ROS were shown to cause oxidation of readily available polyunsaturated fatty acids present within phospholipid membranes. This process, often observed at the sites of injury or inflammation, leads to local accumulation of carboxyalkyl pyrrole (CAPs) protein adducts [19, 48, 49]. There are three main members of the CAPs family: 2-(ω -carboxyheptyl)pyrrole (CHP), 2-(ω -carboxyethyl)pyrrole (CEP), and 2-(ω -carboxypropyl)pyrrole (CPP) [50]. Among them, CEP has attracted considerable attention as a potential biomarker for advanced age-related macular degeneration [49, 51, 52]. *In vitro*, exogenously provided CEP had a proangiogenic effect comparable to that of VEGF [19, 53]. During the wound healing process, endogenous CEP accumulated in a transient fashion and its generation was aided by inflammatory cells (neutrophils and macrophages). Molecular patterns of CAPs are recognized by TLR2/1 complex on endothelial cells and trigger MyD88-dependent signaling to promote neovascularization at the wound site, which, in turn, accelerate wound healing and subsequent tissue regeneration (Figure 1). In tumors with substantial inflammation, such as melanomas, CEP seems to continuously accumulate [19].

It is clear that the cascade of these events occurs in a well-coordinated and interconnected fashion. Inflammation gives rise to ROS, triggering lipid oxidation to generate CEP. In turn, CEP induces angiogenesis leading to enhanced blood flow and additional recruitment of inflammatory cells, which release angiogenic factors at the wound site to further facilitate wound healing or tumor growth. The evidence that CEP neutralization impairs wound healing and diminishes tumor angiogenesis indicates that CEP-TLR2/1-dependent neovascularization is as important as the VEGF pathway in conditions associated with inflammation. Yet, CEP-TLR2/1 induced angiogenesis is independent on VEGF signaling in endothelial cells, but involves Rac1 activation, a key factor that regulates endothelial cell migration and adhesion [19]. Toll-like receptors are known primarily for their role as innate immunity receptors [16–18]; however, CEP-TLR2/1 induced angiogenesis provides the first link between oxidative stress, innate immunity, and vascularization [19].

Another recent finding implicates an alternative mediator of oxidative stress induced pathological angiogenesis, ATM kinase. ATM, a protein kinase from the phosphoinositide 3-kinase-related protein kinase (PIKK) family, is known for its role in the regulation of cell cycle and DNA repair and damage [54, 55]. This essential role of ATM has been recently extended to its function as a redox sensor regulating oxidative stress-associated signaling pathways.

ATM activation by ROS levels was shown to promote pathological neoangiogenesis. Remarkably, ATM seems to be involved uniquely in pathological angiogenesis, such as tumor angiogenesis or ischemia-induced neovascular remodeling, but not in physiological vascularization [56]. ATM activation seems to specifically promote endothelial proliferation, but not any other cell types including pericytes, a-smooth muscle cells, or inflammatory cells. Unexpectedly, ATM activation in endothelial cells does not result in phosphorylation of two main targets of ATM in DNA damage response, p53, or H2AX, but diminishes p38 α phosphorylation, a pathway involved in response to oxidative stress. Similar to TLRs, deletion of ATM inhibited angiogenesis even in the presence of VEGF inhibitors, indicating that this process is VEGF independent. Thus, this study establishes another VEGF-independent and oxidation-driven mechanism of angiogenesis.

As discussed above, CEP-TLR2/1 and ATM-p38 α seem to have indispensable roles in angiogenesis, from tissue regeneration and remodeling to tumor progression. These two novel VEGF independent signaling pathways establish new targets for treatment of angiogenesis-associated pathologies, such as tumors resistant to anti-VEGF therapy. Furthermore, these findings demonstrate how oxidation and inflammation are able to orchestrate neovascularization. This cross-talk between inflammation-induced oxidative stress and angiogenesis is emerging as an important mechanism underlying vascular complications in humans. However, the detailed mechanistic aspects of this interface remain to be elucidated. For example, it remains ambiguous how exactly CEP triggers TLR2/1 downstream signaling in endothelium versus other TLR expressing cells, leading to neovascularization in injured tissues and tumors. In addition, DAMPs are known to trigger multiple signaling pathways. Thus, it is possible that CAPs can be recognized by other pattern recognition receptors. In this regard, a recent study demonstrated that platelets respond to CAPs, including CEP, via TLR9 activation, thereby promoting platelet hyper-reactivity and thrombosis in pathologies associated with oxidative stress [57]. This evidence implies that CAPs serve as previously unrecognized pathological mediators involved in a number of oxidation and inflammation associated human diseases, now including atherosclerosis and thrombosis. In sum, these novel mechanisms underlying oxidation-driven processes might be applicable to more pathological situations than it was first anticipated. It is still not clear whether there is any cross-talk between oxidation-triggered and conventional signaling for both TLRs and ATM. Further analysis of the molecular mechanism of oxidation and inflammation induced angiogenesis will provide the necessary information for translating these findings into therapeutic approaches.

Therapeutic implications

Since tumor growth and metastasis critically depend on sufficient blood supply, the inhibition of tumor neovasculature is considered to be a crucial anticancer strategy in clinical oncology. A variety of proangiogenic factors, such as VEGF, bFGF, interleukin 8 (IL-8), G-CSF, and GM-CSF, are produced by tumor cells as well as tumor stroma, and aim to promote angiogenesis [2, 8]. Particularly, VEGF and its pathway, which specifically affects endothelial cells proliferation and migration during angiogenesis, serve as primary targets for antiangiogenic therapy [58, 59]. Several of anti-VEGF approaches are already approved for clinical use worldwide, indicating its substantial clinical efficacy [58, 59].

There are, however, several drawbacks for anti-VEGF therapy. First, VEGF blockers do not differentiate between pathological and healthy vasculature, thereby causing undesirable side effects, such as delayed wound healing, pulmonary hemorrhage, gastrointestinal perforation, and thrombotic events [60–63]. Thus, there is a need to target pathological vasculature while sparing normal blood vessels. In this regard, it is intriguing that ATM is specifically activated by oxidative stress in newly formed pathological vasculature, but not in normal healthy vessels [56]. Second, multiple cancers seem to show considerable resistance to anti-VEGF therapy [64, 65]. It has been shown that an extended VEGF blockade might result in tumor revascularization, which is independent of VEGF signaling [60, 66]. In most cases this resistance to anti-VEGF is associated with inflammation and infiltration of myeloid cells which create substantial oxygen tension. This, in turn, results in the accumulation of CAPs promoting angiogenesis in VEGF independent manner. Therefore, targeting oxidation-driven processes might overcome limitations of anti-VEGF therapy, especially in relation to tumor resistance.

In sum, it is important to continue the search for novel and VEGF-independent proangiogenic pathways, such as CEP/TLR2/MyD88 axis and ROS/ATM/p38 α pathway. In this respect, improved understanding of oxidation-driven and inflammation-dependent angiogenesis will pave the way toward improved antiangiogenic therapy.

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Figure 1.

Role of oxidation- driven processes in wound angiogenesis. During the inflammatory phase of wound healing, immune cells including neutrophils and macrophages, infiltrate into the injured area and become activated to produce ROS aimed to defend against pathogens. ROS oxidize readily available membrane phospholipids to produce CAPs (exemplified by CEP). CEP adducts are recognized by TLR1/TLR2 complex on endothelial cells to induce neovascularization and accelerate wound healing