Review

Angiogenesis and Inflammation in Peritoneal Dialysis: The Role of Adipocytes

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Key Words

Adipocytes • Peritoneal dialysis • Angiogenesis • Inflammation

Abstract

Chronic inflammation and angiogenesis are the most common complications in patients undergoing maintenance peritoneal dialysis (PD), resulting in progressive peritoneum remodeling and, eventually, ultrafiltration failure. Contributing to the deeper tissue under the peritoneal membrane, adipocytes play a neglected role in this process. Some adipokines act as inflammatory and angiogenic promoters, while others have the opposite effects. Adipokines, together with inflammatory factors and other cytokines, modulate inflammation and neovascularization in a coordinated fashion. This review will also emphasize cellular regulators and their crosstalk in long-term PD. Understanding the molecular mechanism, targeting changes in adipocytes and regulating adipokine secretion will help extend therapeutic methods for preventing inflammation and angiogenesis in PD.

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Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is a well-established renal replacement therapy for patients with end-stage renal disease (ESRD). Peritoneal dialysis (PD) is a life-sustaining therapy used by 100,000 patients worldwide, accounting for approximately 10 to 15% of the dialysis population [1]. PD has several advantages over hemodialysis (HD), including a simpler and less invasive procedure and a more continuous removal of waste products. Additionally, it contributes to retention of residual renal function, which results in an improved quality of life. Patients who undergo CAPD have lower mortality than HD after the first 2 years of PD therapy [2]. Unfortunately, recurrent peritonitis and progressive peritoneal tissue remodeling, as well as angiogenesis, ultimately

leads to ultrafiltration failure (UFF), which results in discontinuation of PD therapy. Frail PD patients are more likely to be hospitalized, and they require a long stay for each hospital admission [3]. In developed countries, the proportion of dialysis patients undergoing PD significantly declined in the last 15 years [4]. Thus, overcoming complications and UFF have become key issues that require urgent solutions to maintain the longevity and efficiency of PD.

In PD, the peritoneum is used as a semi-permeable membrane, allowing for diffuse exclusion of uremic toxins and exchange of solutes between the circulation and PD fluid (PDF) [5]. The peritoneum consists of three layers. The most superficial layer is a mesothelial monolayer, which covers a basement membrane and submesothelial compact zone. This zone contains extracellular matrix (ECM), collagen and a few fibroblasts. The deepest layer comprises loose adipose tissue with peritoneal capillaries and peritoneal lymphatic vessels [6]. Long-term instillation of PDF causes morphological alterations in the peritoneal membrane, which are characterized by detachment of the mesothelial layer, increased ECM deposition, fibrosis and angiogenesis.

As the local blood circulation is supplied by mesenteric and celiac arteries, peritoneal microvessels play a crucial role in PD. Although PMCs directly contact the PDF, microvessels are an important location for the exchange of water, toxins, oxygen, and inflammatory mediators between the peritoneal membrane and cavity [7]. Angiogenesis increases the effective surface area for exchange and lymphangiogenesis raises the lymphatic absorption rates. The enhanced vascular network decreases the glucose-driven osmotic pressure of the PDF, leading to UF loss. Furthermore, vascular wall changes, such as thickening and increased permeability, increase small solute transport and thus reduce the time spent on exchanging waste products [8]. Furthermore, inflammation and angiogenesis occur simultaneously in the peritoneum, and efforts to alleviate inflammation also reduce angiogenesis [9].

Interestingly, a new study suggested that peritoneal adipocytes could also contribute to this pathological process. Manipulating crosstalk among adipose tissue, macrophages, mesothelial cells (MCs), and endothelial cells (ECs) may represent a novel therapeutic strategy for preventing the peritoneal inflammation and angiogenesis that lead to UFF [10]. In this review, the focus will be on the role of adipocytes on inflammation and accompanying angiogenesis in PD.

Molecular network of angiogenesis, fibrosis and inflammation in PD

Angiogenesis is an event induced by almost all injury and repair processes. PD-induced angiogenesis is mediated by inducing cytokines, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), as well as inhibitors, including angiogenesis inhibitor, endostatin (ES) and others [11, 12]. Local VEGF production during PD seems to play a central role in the processes leading to peritoneal neoangiogenesis and functional decline. One study showed VEGF is widely expressed in PMCs and has much lower expression in other cells [13]. Vascular endothelial growth factor receptor 2 (VEGFR2) is the specific receptor distributed on the surface of ECs. It binds VEGF and recruits EC migration to anoxic and avascular areas. As the ECs proliferate and differentiate, angiogenic remodeling occurs where the vessels enlarge and mature.

Various exogenous factors strengthen peritoneal angiogenesis. Local catheter repetitive stimulation and bacterial peritonitis are considered extrinsic factors. Intriguingly, a study found that VEGF, bFGF, and ES expression as well as the number of neocapillaries were increased in pre-dialysis uremics and PD patients compared to control subjects [14], which indicates that uremia is an independent risk factor for microvessel formation.

Normally, the human peritoneal cavity contains approximately 100 ml of fluid, which works as a lubricating liquid. During CAPD, approximately 2 liters of PDF is instilled with 5 exchanges per day, which is approximately 20 times the baseline level of fluid. Conventional PDFs have a low pH value, a high glucose concentration in lactate-buffered solution, and contain glucose degradation products (GDPs), which are formed during heat sterilization of

the fluids. GDPs cause the formation of advanced glycation end-products (AGEs), which are critical to determining the biocompatibility of different PDFs. Prolonged exposure to GDP solutions enhances cytotoxic damage and proangiogenic responses in PMCs [15], stimulating the release of VEGF, which in turn enhances vascular permeability and angiogenesis [16, 17]. Meanwhile, GDPs could also reduce the expression of intercellular tight junction proteins, including ZO-1, occludin and claudin-1, in MCs [18]. Exogenous VEGF suppresses ZO-1 expression, while neutralizing the anti-VEGF antibody reverses the effect of GDPs on ZO-1 expression in PMCs. These findings suggest that the action of GDPs on ZO-1 expression is regulated through VEGF. It is more important to realize ZO-1 is one of the biomarkers of EMT, a process by which MCs undergo a progressive loss of the epithelial phenotype and acquire fibroblast-like characteristics. MCs that have undergone EMT augment the ability to invade and migrate into the submesothelial zone, leading to angiogenesis, fibrosis and ultrafiltration failure. In addition to undergoing morphological changes, the non-epithelioid MCs produce higher levels of VEGF than the non-EMT cells [13]. MCs that undergo EMT promote angiogenesis via VEGF and fibrosis via ECM formation [19]. TGF- β 1, the vital induced factor of EMT and subsequent fibrosis, is up-regulated among EMT progress [20], which participates in a positive feedback loop and enhances the production of ECM, leading to further neovascularization [13, 21]. AGE receptor (RAGE) activation also participates in VEGF-induced angiogenesis and TGF- β -induced EMT [22]. The receptor has been considered a scavenger receptor in AGE removal and clearance with binding of AGE to the receptor. The anti-RAGE antibody partially prevents blood tube formation and submesothelial fibrosis in vivo [23], demonstrating the pivotal interaction between AGEs/GDPs and RAGE in neoangiogenesis.

Inflammation, the most common complication in ESRD patients, may be progressively exacerbated upon initiation of PD. This process is well recognized as alleviated secretion of C-reactive protein (CRP) and inflammatory factors, such as interleukins (ILs) and TNF- α . Notably, the microinflammatory state in PD patients may potentially trigger the pro-angiogenesis response [24]. A sequence of molecules or inflammatory factors produced by different cells compose the angiogenic network (Table 1). Among all cytokines, IL-6 plays a key role in modulating inflammation and angiogenesis. First, it is positively associated with other inflammatory factors, such as TNF- α , IL-10, and IL-18 [25]. Second, IL-6 also induces the

Table 1. Pro-angiogenic cytokines in PD

Types of cytokines	Cytokines	Cellular source in peritoneum	Relevance to PD	References
Angiogenic factors	VEGF	Mast cells ECs MCs	VEGF and VEGFR are decisive molecules for angiogenesis.	[26, 27]
	Angiopoietin2	ECs	Angiopoietin2 signaling involved in TNF- α induced peritoneal angiogenesis.	[28, 29]
	IL-6	Macrophages ECs MCs	IL-6 is positively correlated with VEGF in plasma and dialysate.	[30-33]
Inflammatory factors	IL-1	Macrophages MCs	IL-1 increases vessel-like structures by enhancing VEGF production, and augments proliferation when added to ECs.	[34-36]
	IL-8	Macrophages Mast cells MCs	IL-8 enhances EC proliferation and capillary tube formation.	[37, 38]
	TNF- α	Macrophages Mast cells MCs	TNF- α causes neoangiogenesis both in vitro and in vivo.	[29, 39]
Chemokines	MCP-1	Macrophages ECs	MCP-1-induced protein enhances endothelial cell proliferation, migration, and other pro-angiogenic genes, leading to capillary-like tube formation.	[40, 41]
Adhesion molecules	ICAM-1	ECs	Induced by IL-6 and TNF- α after EC injury, promoting new capillary formation.	[32, 42]
	VCAM-1			[32, 43]
Growth factors	TGF- β	Mast cells MCs	TGF- β triggers the expression of VEGF via EMT and conversely amplifies its own secretion.	[26, 44, 45]

expression of chemokines and adhesion molecules, such as monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), as well as angiogenic markers, such as VEGF and angiotensin-2 (Ang-2).

Adipocytes become activated in PD

Compared with hemodialysis, there is an increasing trend in the body mass, BMI, muscle mass and visceral fat percentage in PD patients [46]. Body mass starts to increase after 6 months of PD therapy, and most of the increased body mass consists of visceral fat [47]. A new explanation to consider is that PD-induced obesity is significantly related to the BMI, duration of dialysis, and whether patients received dialysis and is less related to glucose absorption [48]. Although some studies of PD patients have reported an inverse relationship between weight and mortality [49-51], the visceral fat content increases in long-term PD.

A nest of mature adipocytes and a stromal-vascular fraction compose the adipose tissue. Anatomically, these features are abundant in mesenteric or omental peritoneum, but they contribute less to the parietal, intestinal and diaphragmatic peritoneum. As above, the peritoneal adipose tissue is deeply buried under a mesothelial monolayer and submesothelial layer. However, when the mesothelial monolayer is injured, dialysate could also reach the adipose tissue. An ultrastructural study revealed that some omental adipocytes stretch out from the mesothelial surface and directly contact the dialysate [10]. Adipose tissue is not only an energy storage depot, it has autocrine, paracrine, and endocrine functions. Adipocytes secrete various cytokines and adipokines, including leptin, adiponectin, resistin, TNF- α , IL-6, visfatin, TGF- β , VEGF and other molecules [52], which form a network that regulates various physiological processes. Chronic PD patients are characterized by elevated plasma levels of adipokines [53]. Although a majority of previous work has focused on peritoneal mesothelial cells, more attention has been paid to the role of peritoneal adipocytes during PD therapy. It is reasonable to speculate that during direct or indirect contact with dialysate, peritoneal adipocytes will be “activated” and are associated with angiogenesis and inflammation.

Adipokines primarily promote angiogenesis via regulating VEGF

The pro-angiogenic function of adipocyte-derived cytokines involves VEGF. Inflammatory adipokines, such as TNF- α , IL-6, and MCP-1, are strongly related to VEGF as explained in Table 1. TNF- α has been shown to mediate endothelial dysfunction and promote calcification of vascular cells. Increased TNF- α level results in a dose-dependent VEGF in peritoneal mesothelium [54]. IL-6 and soluble IL-6 receptor (sIL-6R) not only directly promote VEGF, but also induce the synthesis and secretion of MCP-1, which in company with VEGF, recruits monocytes and lymphocytes [55].

Among all other adipokines, leptin receives substantial attention because it is the most abundant hormone secreted by adipocytes, and it is also known as a pro-inflammatory cytokine. This 16-kDa protein is a uremic toxin because the serum leptin concentration is markedly higher in patients with chronic renal failure or undergoing dialysis [56]. Moreover, it cannot be removed by hemodiafiltration. Leptin could directly phosphorylate VEGFR2 and activate the p38 mitogen-activated protein kinase/protein kinase B/cyclooxygenase-2 (p38MAPK/Akt/COX-2) signal axis to stimulate angiogenesis [57]. In addition, as it is a positive modulator of IL-1 α , TNF- α and IL-6 secretion [58, 59], leptin has emerged as an indirect pro-angiogenic mediator. Leptin receptor, Ob-Rb, has been found in MCs. Glucose notably increases the synthesis of adipocyte-derived leptin and Ob-Rb in a dose-dependent manner [54].

TGF- β , a VEGF associated inflammatory factor, is directly released by adipocytes via up-regulating proto-oncogene c-Fos [35]. Additionally, it is amplified by adipocyte-derived leptin, activating the Janus kinase-signal transducers and activation (JAK-STAT) signal transduction pathway [60]. Resistin also promotes the expression of VEGF via phosphatidylinositol 3 kinase/protein kinase B-Sp1 (PI3K/Akt-Sp1) pathway activation [61]. Visfatin influences vasodilatation and promotes the proliferation of ECs independent of VEGF [62].

Adipocytes bridge inflammation and angiogenesis in PD

As mentioned above, peritoneum failure could be induced by infectious or non-infectious inflammation. Despite being in clinical remission, PD patients still suffer from prolonged systemic chronic inflammation [63]. A series of studies have focused on its mechanisms, however, the cause of systematic inflammation in PD is not completely understood [64]. Patients undergoing CAPD have increased levels of pro-inflammatory cytokines, including IL-1 β , IL-6, TNF- α , and TGF- β , in both PD effluent and plasma [65]. The serum leptin level increases during acute infection, and even after apparent remission of peritonitis, in response to IL-1 and TNF- α [66]. Hyperleptinemia also induces IL-6 and TNF- α protein production by monocytes [58]. It may be posited that low-grade inflammation in the peritoneum activates fat cells, releases pro-inflammatory adipokines and accelerates angiogenesis. The positive feedback from the inflammatory response may cause a vicious cycle for angiogenesis.

Intriguingly, not all the adipokines destroy vascular function. The vascular protector inhibits capillary formation by restraining the inflammation reaction. Omentin inhibits norepinephrine synthesis and promotes EC-derived NO release via 5-AMP-activated protein kinase (AMPK)-mediated eNOS phosphorylation, inducing down-regulation of TNF- α [62].

Contrary to leptin, adiponectin has anti-angiogenic, anti-inflammatory and insulin-sensitizing functions [67]. It is negatively related to the adipose tissue mass [68] and a low plasma adiponectin level is associated with coronary artery disease and type-2 diabetes. Adiponectin inhibits adhesion molecule production by ECs, suppressing the attachment of monocytes, a precursor in the angiogenic process [69]. Moreover, adiponectin reduces the TNF- α -induced activation of NF- κ B; in turn, TNF- α downregulates adiponectin production [70]. This negative reciprocal interaction on their local production in adipose tissue suggests that adiponectin decreases in the peritoneum may aggravate local inflammation, creating a “vicious cycle” that lowers adiponectin release [71]. In vivo, neointimal thickening of injured arteries is accelerated in adiponectin-KO mice [72] and inhibited by exogenous adiponectin [73], revealing the key role of adiponectin in anti-angiogenesis.

Crosstalk among adipocytes, macrophages and endothelial cells

To better understand the molecular mechanism of inflammation and angiogenesis during PD, it is important to identify the different cell types that are involved and their potential cross-talk (Figure 1).

Fig. 1. Adipocytes in inflammation and angiogenesis during PD. Adipocytes lie deep beneath the monolayer peritoneal mesothelial cells and submesothelial zone, which contains collagen and fibroblasts. PD patients undergo chronic low-grade inflammation in dialysate and plasma. The adipocytes enhance and regulate adipokine secretion. On the one hand, they produce

pro-inflammatory and pro-angiogenic cytokines (e.g., leptin and resistin). On the other hand, anti-inflammatory cytokines are suppressed (e.g., adiponectin and omentin). Meanwhile, hypertrophic adipose directly releases inflammatory factors (e.g., IL-6 and TNF- α). The adipose-derived MCP-1 propagates inflammation by stimulating macrophage infiltration to interstitial space in fat tissue. The pro-angiogenic function focuses on VEGF, which acts on endothelial cells with inflammatory factors, inducing angiogenesis.

Hypertrophic adipocytes initiate inflammation

As mentioned above, with decreased residual renal function, the fat mass index increases, while the non-fat content decreases [74]. As mature fat cells account for 50–85% of the total cellular components in adipose tissue, obese patients seem to have a higher total adipocyte number than individuals who are not obese [75]. Approximately 10% of adipocytes are renewed annually, regardless of the BMI levels and ages. Beyond altering the quantity, it is more important to target the enlarged fat cells (hypertrophy) and then the increased fat storage in fully differentiated adipocytes and adipokine overproduction. They were found not only in the context of PD, but also in individuals with obesity-related metabolic disorders [76]. First, the adipocyte size is hyper-responsive to disordered adipokine secretion. Second, the hypertrophic adipocytes shift their balance towards producing cytokines, regulating the subsequent immune response [77]. Larged cells are more lipolytic, release more inflammatory promoters (ILs, leptin, resistin) and less inhibitors (adiponectin, omentin). Chemoattractants, such as MCP-1, are released for subsequent macrophage infiltration. Thus, the relative number of hypertrophic adipocytes might be the most pivotal determinant in the originating of inflammation. Additionally, these highly sensitive larged adipocytes were mediated by the NF- κ B pathway and could be prevented by NF- κ B inhibitors [78, 79], which indicates the activation would occur before or after inflammation events.

Macrophage infiltration into adipocytes spreads inflammation

There are two types of macrophages in adipose tissue: M1 (classically activated) macrophages and M2 (resident or alternatively activated) macrophages. M1 macrophages are characterized by expression of CD11c surface marker, inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokines such as TNF- α , IL-6, while M2 macrophages produce arginase and anti-inflammatory cytokines such as IL-10 and IL-1Ra [80]. Macrophage infiltration is correlated with both adipocyte size and BMI [81]. Hypertrophic adipocytes initiate the infiltration of monocytes/macrophages. The enlarged adipocytes are related to IL-6, MCP-1, free fatty acid (FFA) and oxidative stress conditions [82]. In PD, circulating mononuclear cells and MCP-1 play a vital role in endothelial cell dysfunction. Monocytes from dialysate or circulating blood persist in a pro-inflammatory state and transmigrate to peritoneal adipose tissue by promoting adherent molecules, which are secreted by both monocytes and vascular endothelial cells. After this process, the monocytes differentiate into inflammatory (M1) macrophages.

Infiltrating inflammatory macrophages produce inflammatory cytokines and synergistically act with adipocytes, leading to massive amplification of the inflammatory process. Resident macrophages can be activated with reinforced monocytes recruitment; however, they express a low level of pro-inflammatory molecules. It seems that PD-related inflammation causes a shift in the polarized state of adipose tissue macrophages from M2, which has anti-inflammatory function, to M1, which contributes to a pro-inflammatory state [83]. Intriguingly, over 90% of all macrophages in adipose tissue from obese mice or humans surround dead adipocytes [84]. In line with this view, conversion of the M1/M2 balance relies on the recruitment of inflammatory monocytes from the circulation to macrophage clusters that surround dead adipocytes instead of on the resident M2 macrophages that are directly transformed to M1 in situ, where there are interstitial spaces among adipocytes [85]. Inhibition of M1 cell differentiation or permeation through adipocytes offers a therapeutic approach for PD-related complications.

Activation of ECs amplifies the inflammatory response and promotes angiogenesis

Endothelial cells could be activated by inflammatory cytokines, VEGF, and the aforementioned adipose-derived secretions. This is much more an immune response than a process of ECs and macrophages feeding each other. A series of signaling pathways in ECs are invoked, and downstream cytokines, such as adhesion molecules and chemokines, are excreted. These factors, in a synergistic model, drive local macrophages into deep-seated adipose tissue and induce full activation of ECs. Therefore, peripheral blood monocytes are closely absorbed to ECs or even seep out of vessels and are thus polarized to different macrophage phenotypes among adipocytes, which provide sources for spreading inflammation [86]. Adipose tissue inflammation cross talks with endothelial cells via adipocyte-derived cytokines and promotes NF- κ B-dependent endothelial dysfunction [87]. Moreover, ECs are recruited to anoxic zones to form neovascularization via VEGF, which is partially enhanced by EC activation as well as a stimulus for inflammation factors and adipokines.

Conclusions

Patients in long-term PD undergo progressive inflammation and accompanying angiogenesis. Chronic local or systemic inflammatory responses promote new blood vessel formation. During this process, adipocytes participate in two-way regulating actions by producing substantial adipokines, inflammatory factors, and other molecules. On the one hand, inflammatory response and angiogenesis are stimulated by adipose-derived ILs, VEGF, leptin, and resistin. On the other hand, some adipokines participate as inflammatory inhibitors and vascular function protectors, such as adiponectin and omentin. Inflammation is initiated by enlarged adipose, propagated by macrophage infiltration and amplified by EC activation. All the multiple cytokines and cellular components compose a complex network. Targeting the changes in adipocytes as well as the regulated secretion of adipokines (or their activation/receptors) offers a therapeutic approach for suppressing inflammation and angiogenesis in PD. Further studies that aim to illustrate the molecular mechanisms of diverse adipokines and cells in the context of PD should be performed.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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