[Frontiers in Bioscience 12, 1963-1972, January 1, 2007]

# Activated protein C in sepsis and beyond: Update 2006

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## 1. ABSTRACT

Activated protein C (APC), a plasma serine protease, is best known for its ability to inhibit blood clot formation. APC acts as an anticoagulant by degrading coagulation cofactors Va and VIIIa, thereby attenuating the coagulation cascade. Over the past 15 years, impressive research advances have provided novel insights into the diverse biological activities of this molecule. APC is now viewed not only as an anticoagulant but also as a signaling molecule that provides a pivotal link between the pathways of coagulation, inflammation, apoptosis, and vascular permeability. The protective effect of APC supplementation in patients with severe sepsis likely reflects the ability of APC to modulate multiple pathways implicated in sepsis pathophysiology. This review attempts to summarize key studies that support the therapeutic potential of APC in conditions beyond sepsis such as stroke, ischemia-reperfusion injury, lung injury, asthma, pancreatitis, wound healing, and angiogenesis. A comprehensive PUBMED literature review up to May 2006 was conducted.

## 2. INTRODUCTION

### 2.1. Sepsis

Sepsis is initiated by a focus of infection from which microbes and/or microbial toxins released into the blood stream trigger systemic and uncontrolled activation of inflammatory and coagulation pathways (1). Sepsis is the leading cause of death in non-coronary intensive care unit (ICU) patients and is a leading cause of morbidity and mortality in the Western world (2). Severe sepsis, defined as sepsis associated with at least one dysfunctional organ, afflicts approximately 700,000 people in the United States annually, with an estimated mortality rate of 30% to 50% (2). The incidence of sepsis is projected to increase by 1.5% per annum due to increased use of chemotherapeutic agents, aging of the population, and the increase in antibiotic resistance (2).

Over the past 20 years, many potential treatments for sepsis have shown early promise, yet failed to improve survival in phase 3 clinical trials. These agents attempted to treat sepsis through attenuation of inflammatory

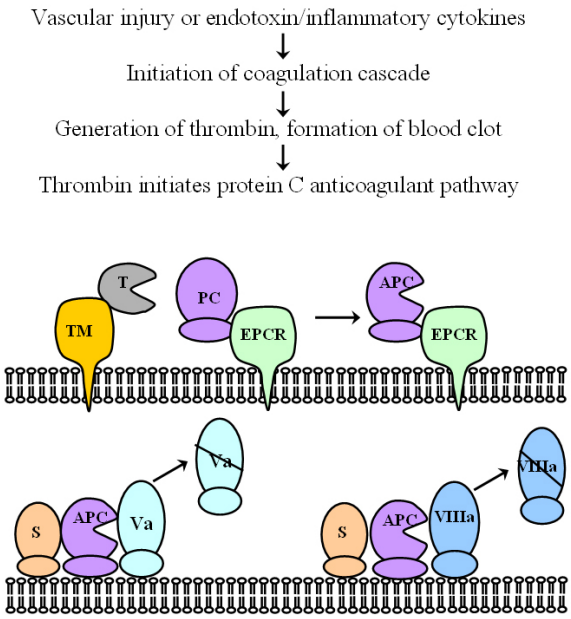


**Figure 1.** The protein C anticoagulant pathway. Activated protein C (APC), a physiological anticoagulant, is generated from the inactive precursor protein C "on demand" in response to thrombin formation. Briefly, vascular injury or endotoxin/inflammatory cytokines initiates the coagulation cascade, ultimately resulting in thrombin generation and blood clot formation. Excess thrombin then triggers the protein C pathway which provides feedback inhibition of coagulation. The protein C pathway is initiated when thrombin (IIa) binds to thrombomodulin (TM) on the endothelial cell surface. The thrombin-thrombomodulin complex rapidly converts zymogen protein C (PC) to its active form APC. Protein C activation is augmented by the endothelial cell protein C receptor (EPCR) which binds circulating protein C and presents it to the thrombin-thrombomodulin complex. APC then dissociates from EPCR and, in combination with its cofactor protein S (PS), acts as an anticoagulant by degrading factors Va and VIIIa, key cofactors in coagulation.

mediators or by the neutralization of endotoxin (3). More recently, the focus has shifted to anticoagulants because current thinking is that coagulopathy also contributes to organ failure and death in sepsis. However, neither antithrombin (4) nor tissue factor pathway inhibitor (5), both of which are natural anticoagulants, has demonstrated a survival benefit in patients with severe sepsis. These results have forced a re-examination of the assumption that inflammation and coagulation are independent determinants of organ failure and outcome in sepsis. Indeed, one of the concepts that has radically changed the view of sepsis is the idea that inflammation, coagulation, and apoptosis act together in the disease process. It has been proposed that an imbalance in these pathways may ultimately lead to widespread inflammation, thrombosis, cell death, organ failure, and ultimately death (6-8).

In a landmark study, a large phase 3 placebo-controlled, randomized trial (the PROWESS study) demonstrated the efficacy and safety of recombinant activated protein C (rAPC) for severe sepsis (9). Patients were randomized to receive either rAPC or saline for 4-days. Compared with placebo, rAPC produced a reduction in the relative risk of death of 19.4% and an absolute reduction in the risk of death of 6.1% ($p$=0.005).

### 2.2. Anticoagulant properties of APC

APC, a plasma serine protease, is best known for its ability to inhibit blood clot formation (6). APC acts as an anticoagulant by degrading clotting factors Va and VIIIa, thereby attenuating the coagulation cascade. *In vivo*, APC is generated in the circulation "on demand" from its inactive precursor protein C. The signal that triggers the conversion of protein C to APC is thrombin. A schematic diagram of the APC anticoagulant pathway is shown in Figure 1. Briefly, vascular injury or inflammatory cytokines/endotoxin initiates the coagulation cascade, ultimately resulting in thrombin generation and blood clot formation. Excess thrombin then complexes with thrombomodulin (TM), a receptor on endothelial cells. The thrombin-TM complex rapidly converts protein C to its active form APC. APC generation is augmented 10- to 20-fold by the endothelial cell protein C receptor (EPCR). EPCR binds circulating protein C and presents it to the thrombin-thrombomodulin complex. The importance of the anticoagulant properties of APC is highlighted by the fact that patients with congenital or acquired deficiencies in the APC anticoagulant pathway are prone to venous and arterial thrombosis (10-15).

### 2.3. Modulation of cell functions by APC

In addition to its anticoagulant properties, APC has been shown to modulate cell functions including inflammation, apoptosis, and vascular permeability. The diverse biological activities of APC on various cell types are summarized in Table 1. With respect to its anti-inflammatory properties, APC has been shown to downregulate the production of TNF by monocytes (16-18) and to suppress expression of leukocyte adhesion molecules in endothelial cells (19), presumably by inhibiting NF-kB nuclear translocation (17) and/or downregulating the transcription of NF-kB subunits (19). In animals challenged with endotoxin, APC inhibited the production of pro-inflammatory cytokines (20, 21) and inhibited leukocyte accumulation in injured tissue (22). Likewise, the PROWESS trial revealed that recombinant APC infusion reduced levels of interleukin (IL)-6, a pro-inflammatory cytokine (9).

How does APC, a plasma serine protease, modulate cell functions? To date, the only known cellular receptor for APC is the endothelial cell protein C receptor (EPCR), a 46 kDa single-chain transmembrane glycoprotein homologous to the MHC class1/CD1 family of molecules (23). EPCR was originally identified on vascular endothelial cells and has since been detected in numerous other cell types including neutrophils, monocytes, neurons, fibroblasts, and keratinocytes (see Table 1). With respect to apoptosis, the anti-apoptotic effect of APC on vascular endothelial cells was dependent

**Table 1.** Modulation of cell functions by APC

| Cell Type | Cell functions modulated by APC | Mechanism of action | Reference |
|---|---|---|---|
| Endothelial cells from large vessels | - APC inhibited apoptosis<br>- APC exerts anti-inflammatory effects via suppression of NFκB pathway<br>- APC inhibits expression of adhesion molecules<br>- APC upregulates COX-2 and $PGI_2$<br>- APC enhanced endothelial cell barrier integrity<br>- APC induced endothelial cell proliferation by MAPK activation *in vitro* and angiogenesis *in vivo*<br>- APC induced release of microparticle-associated EPCR | - Anti-apoptotic effect requires EPCR and PAR-1<br>- Upregulation of COX-2 and $PGI_2$ requires EPCR and PAR-1<br>- Barrier protective effect requires EPCR, PAR-1, and S1P receptor-1<br>- Induction of proliferation requires EPCR | 19;24;25;28 ;29;80-83 |
| Endothelial cells from microvasculature | - Gene expression profiling demonstrated that APC downregulated BH4-synthesis, IL-6, IL-8, MCP-1, and ICAM-1 in inflamed endothelial cells<br>- APC also inhibited activities of transcription factors c-Fos, FosB, and c-Rel | | 84 |
| Brain endothelium | - APC prevented apoptosis in hypoxic human brain endothelium by inhibiting tumor suppressor protein p53, normalization of the Bax/Bcl-2 ratio, and reduction of caspase-3 signalling<br>- APC induces an intracellular $[Ca^{2+}]$ signal | - Cytoprotective effects of APC require EPCR and PAR-1<br>- APC regulates $[Ca^{2+}]$ by binding to EPCR and signaling via PAR-1 | 26;38 |
| Lung endothelium | - APC mediates endothelial cell barrier protection<br>- APC increases cortical myosin light chain (MLC) phosphorylation in concert with cortically distributed actin polymerization | - APC, via EPCR and PI 3-kinase, transactivates $S1P_1$, leading to endothelial cell barrier protection | 29 |
| Neurons | - APC prevented N-methyl-D-aspartate-induced apoptosis by blocking caspase-3 activation, nuclear translocation of AIF, and induction of p53<br>- APC prevented staurosporine-induced apoptosis by blocking caspase-8 activation and AIF nuclear translocation<br>- APC blocked tPA-induced apoptosis of neurons | - Neuronal protective effects of APC *in vitro* and *in vivo* require PAR-1 and PAR-3 | 30;39 |
| Monocytes | - APC inhibited LPS-induced TNF production via suppression of the NF-κB pathway and AP-1<br>- APC decreased tissue factor expression in unstimulated and phorbol ester-stimulated cells<br>- APC inhibited the LPS-induced release of chemokines MIP-1α and MCP-1<br>- APC induced release of microparticle-associated EPCR<br>- APC inhibited camptothecin-induced apoptosis | - Anti-apoptotic effect of APC requires EPCR and PAR-1 | 16-18;82;85;86 |
| Neutrophils | - Both APC and protein C inhibited neutrophil chemotaxis triggered by IL-8, formyl-Met-Leu-Phe, antithrombin or C5a<br>- Neutrophils from bronchoalveoloar lavage fluid of volunteers receiving rhAPC demonstrated decreased chemotaxis *ex vivo* | - EPCR is required for the inhibitory effects of APC and protein C on cell migration | 59;87 |
| Keratinocytes | - APC stimulated proliferation, migration, and wound closure<br>. APC attenuated calcium-induced apoptosis<br>- APC upregulated IL-6 and IL-8 production, and suppressesNF-κB activity<br>. APC upregulated VEGF, and enhances expression and activation of MMP-2 | - Keratinocyte proliferation and induction of MMP-2 by APC may act through EPCR, PAR-1, and MAP kinase activity | 77;78;88 |
| Skin fibroblasts | - APC upregulated MMP-2, VEGF, and MCP-1 | | 79 |
| Gastric epithelial cells | - APC inhibited secretion of MCP-1 and IL-1β by gastric epithelial cells cultured in *H. pylori* homogenates | . Effect of APC on IL-1β secretion is EPCR-dependent<br>. Effect of APC on MCP-1 and IL-1β secretion is PAR1-dependent | 89 |
| Lymphocytes | . Both APC and protein C inhibited lymphocyte migration towards IL-8, RANTES, MCP-1, and substance P | . Effects of APC and protein C is dependent on EPCR and epidermal growth factor receptor | 90 |

on the endothelial cell protein C receptor (EPCR) as well as protease activated receptor-1 (PAR-1)(24-26). PAR-1 is a member of the G-protein-coupled receptors that convert extracellular proteolytic cleavage events into intracellular signals (27). Current thinking is that EPCR binds to APC and serves as a co-receptor for APC-mediated proteolytic activation of PAR-1. EPCR and PAR-1 are also required for the ability of APC to enhance endothelial barrier integrity (28,29). In mouse cortical neurons, the neuroprotective effect of APC required protease activated receptor 1 (PAR-1) and 3 (PAR-3) (30).

## 3. APC BEYOND SEPSIS

Recent experimental and preclinical studies suggest that APC may exert a protective effect in other clinical situations characterized by coagulopathy, inflammation, and vascular dysfunction.

### 3.1. Stroke

Despite tremendous efforts in stroke research, stroke remains the third most common cause of mortality in developed countries (31). Currently, intravenous recombinant tissue plasminogen activator (tPA) is the only drug indicated for the treatment of acute ischemic stroke (32). However, only 3% of all stroke patients receive recombinant tPA due to the narrow time-to-treat window (3 hours) and the potential for symptomatic brain hemorrhage (33). In addition, although tPA restores circulation to the brain by lysing blood clots, cell culture and animal studies suggest that tPA also exerts neurovascular toxicities (34). For example, tPA promotes neurodegeneration in mice (35) and triggers neuronal apoptosis *in vitro* (36).

The anticoagulant and anti-inflammatory properties of APC support the use of APC as a potential new therapy for stroke. In a murine model of transient focal cerebral ischemia, animals that received intravenous APC either 15 minutes before or 10 min after stroke induction had improved cerebral blood flow, reduced brain infarct volume and brain edema, and fewer fibrin-positive cerebral vessels (37). In addition, APC reduced ICAM-1 at the blood-brain barrier, thereby reducing ischemic injury by preventing adhesion of neutrophils to the ischemic vessel wall (37). Importantly, intracerebral bleeding was not observed in the APC-treated animals (37).

To determine if APC acts as a direct cell survival factor or whether its neuroprotective effects were secondary to its anticoagulant and anti-inflammatory properties, Cheng et al. examined the effects of APC on hypoxic human brain endothelium (26). APC was shown to prevent hypoxia-induced apoptosis by inhibiting p53 tumor suppressor protein, by normalizing the pro-apoptotic Bax/Bcl-2 ratio, and by reducing caspase-3 activation (26). In mouse cortical neurons, APC prevented apoptosis induced by two divergent inducers of apoptosis, N-methyl-D-aspartate (NMDA) and staurosporin, by blocking caspase activation and by inhibiting nuclear translocation of apoptosis-inducing factor (AIF) (30). The neuroprotective effect of APC required protease activated receptor 1 (PAR-1) and 3 (PAR-3) (30). In human brain microvascular endothelial cells, APC induces an intracellular [$Ca^{2+}$] signal in a PAR-1 and EPCR-dependent manner (38). However, the implications of the intracellular [$Ca^{2+}$] signal elicited by APC remains to be determined.

Recently, APC has been shown to block tPA-mediated vascular and neuronal toxicities *in vitro* and *in vivo* (39). APC inhibited tPA-induced caspase-8 activation of caspase-3 in hypoxic brain endothelial cells, and caspase-3-dependent nuclear translocation of AIF in NMDA-treated neurons. In addition, APC reduced tPA-mediated cerebral ischemic injury in a mouse model of middle cerebral artery occlusion followed by 24 hour reperfusion. In a rat embolic stroke model, administration of APC alone or in combination with tPA 4 hours after embolic stroke reduced infarct volume and improved neurological recovery (40). In contrast, tPA alone was not protective (40). Taken together, these studies suggest a substantial therapeutic benefit of APC as a stand-alone or combination therapy for stroke. Furthermore, APC may be beneficial in extending the time frame for treatment opportunity in ischemic stroke patients.

### 3.2. Ischemia-Reperfusion Injury

Ischemia-reperfusion (I/R) injury occurs when a tissue is temporarily deprived of blood supply and the return of the blood supply leads to additional cell or tissue injury (41). The intense inflammatory response triggered by I/R injury may lead to damage in remote organs that were not exposed to the initial ischemic insult. The systemic effects of I/R may manifest as systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS), both of which are devastating and often fatal in critically ill patients (42). I/R injury is commonly encountered in a variety of settings from disease states such as myocardial infarction, stroke, arterial disease, and shock, to interventions including cardiopulmonary bypass, organ transplantation, thrombolytic therapy, and coronary angioplasty (43).

I/R injury is characterized by the release of inflammatory mediators, complement activation, oxygen radical formation, and increased leukocyte adhesion and transmigration through the endothelium (42). The endothelial cells in the microvasculature are particularly vulnerable to the damaging effects of both hypoxia (ischemia) and reoxygenation (reperfusion) (42).

In a rat model of skeletal muscle reperfusion injury, intravenous injection of APC attenuated tissue oxidative damage and edema (44). *In vitro* studies further demonstrated that APC reduced CD18 expression and reactive oxygen species (ROS) generation in TNF-stimulated neutrophils, suggesting that the protective effect of APC is mediated by a direct inhibitory effect on neutrophil activation (44).

In a rat model of I/R-induced renal injury, intravenous administration of APC inhibited the I/R-induced decrease in renal tissue blood flow and the increase in vascular permeability (45). Furthermore, APC inhibited renal levels of TNF, IL-8, and myeloperoxidase, suggesting that APC protects aginst I/R-induced renal injury by inhibiting leukocyte activation (45). APC also decreased tissue levels of TNF, IL-8, and myeloperoxidase in a rat model of spinal cord injury (46).

The effects of APC on I/R-induced organ damage have also been studied in a rat model of intestinal I/R injury (47). Specifically, APC-treated animals showed less thrombin generation, fibrin degradation products, fibrin deposition, and IL-6 compared with control animals. In contrast, heparin administration only modestly reduced the levels of fibrin degradation products and had no effect on IL-6 levels. These findings suggest that APC reduced I/R-induced intestinal injury by downregulating coagulation as well as inflammation.

APC has also been shown to exert a protective effect in hepatic I/R injury (48). APC was injected intravenously prior to occlusion of the portal vein. Serum

levels of cytokine-induced neutrophil chemoattractant (CINC) were lower in APC-treated animals compared with controls. Myeloperoxidase activity and the number of neutrophils accumulated in the liver 24 hours post I/R injury were also lower in APC-treated animals. Interestingly, DEGR-Xa (a competitive inhibitor of thrombin generation) inhibited I/R-induced increases in CINC as well as reduced hepatic accumulation of neutrophils. Taken together, these results indicate that inhibition of coagulation may attenuate cytokine production and leukocyte accumulation following I/R in rat liver.

### 3.3. Lung Fibrosis

Lung fibrosis is a chronic progressive disorder that leads to lung destruction and scarring (49) (50). It results from a variety of insults to the lung that include autoimmune, infectious, toxic, drug-induced, or traumatic injuries (49). Progressive lung fibrosis results from the loss of alveolar epithelial cells and the accumulation of activated fibroblasts and myofibroblasts, with overproduction of profibrotic cytokines, growth factors, and chemokines, and increased oxidative stress (49). Activation of the coagulation cascade and impaired fibrinolytic activity also play a major role in the pathogenesis of lung fibrosis (51). For example, tissue factor levels and fibrin deposition are elevated in the lungs of human patients with lung fibrosis (52), and mice overexpressing plasminogen activator inhibitor-1 (PAI-1) experienced greater bleomycin-induced fibrosis than wildtype mice (53).

Therapeutic interventions such as APC that inhibit inflammation, enhance fibrinolysis, and decrease coagulation may thus be an attractive strategy to limit the development of lung fibrosis. In a mouse model of bleomycin-induced lung fibrosis, intratracheal administration of APC reduced fibrotic lesions in the subpleural and central areas of the lung (54). Levels of TNF and IL-1β were decreased in the lungs of the APC-treated animals compared with controls (54). Intratracheal administration of APC also decreased the expression of platelet-derived growth factor (PDGF) in an EPCR-dependent manner (54). In human lung cell lines, primary bronchial epithelial cells, and macrophages, APC inhibited the expression and secretion of platelet-derived growth factor (PDGF). Futhermore, i*n vitro* studies have shown that APC prevents increases in human lung endothelial permeability and protects the cells from thrombin-induced vascular permeability (29).

### 3.4. Acute Lung Injury

Acute lung injury (ALI) is a critical illness characterized by severe lung dysfunction (55). The risk factors for ALI can be categorized into direct (e.g. infection, trauma) or indirect (e.g. sepsis, disseminated intravascular coagulation, cardiopulmonary bypass) injury to the lungs (56). Acute respiratory distress syndrome (ARDS), the most severe manifestation of ALI, is associated with mortality rates of 34 to 58% (57). Although mechanical ventilation is the cornerstone of supportive therapy for ALI, this procedure may actually increase the risk of nosocomial infections and may also aggravate or even initiate pulmonary inflammation (58).

The pathological injury associated with ALI has three overlapping phases. The exudative phase is characterized by a marked influx of neutrophils and necrosis of epithelial and endothelial cells. The proliferative stage is accompanied by cell hyperplasia and the deposition of fibrin and collagen within the alveolar space. The last phase, the fibrotic phase, is associated with the deposition of excess extracellular matrix material in the lungs (55). Coagulopathy is also an important feature of ALI. Alveolar fibrin deposition is attributed to tissue-factor-mediated thrombin generation and inhibition of bronchoalveolar fibirnolysis due to an increase of plasminogen activator inhibitors (58).

In a rat model of LPS-induced pulmonary vascular injury, APC prevented LPS-induced increases in pulmonary vascular permeability and in pulmonary accumulation of leukocytes (22). In a double-blinded, placebo-controlled study of APC in a human model of endotoxin-induced pulmonary inflammation, administration of APC reduced leukocyte accumulation to the airspaces (59). Neutrophils recovered from bronchoalveolar lavage fluid of volunteers receiving APC exhibited reduced chemotaxis *ex vivo* (59). In healthy volunteers who received an instillation of endotoxin into the lungs, intravenous administration of APC decreased levels of thrombin-antithrombin complexes, soluble tissue factor, and PAI-1 activity in bronchoalveolar lavage fluid. These studies suggest that APC may be a potential therapeutic approach in limiting the coagulopathy and inflammatory injury associated with ALI.

### 3.5. Asthma

Asthma is a chronic inflammatory disorder of the respiratory tract that is associated with coughing, shortness of breath, chest tightness, and airway inflammation (60,61). The Th2 cytokines IL-4, IL-5, and IL-13 are major mediators of allergic inflammation in asthma, where IL-4 and IL-13 promote IgE secretion and IL-5 stimulates eosinophilic inflammation (62). With respect to the coagulation system, elevated thrombin levels are present in the sputum of patients with bronchial asthma, suggesting that there is activation of the coagulation in the airways of these patients (63). In addition, APC/thrombin and APC/PC ratios were decreased and soluble TM levels were increased in sputum of bronchial asthma patients compared with healthy subjects (64). *In vitro* studies further demonstrated that thrombin increased the expression of protein C antigen from lung epithelial cells, and TNF decreased the expression of protein C and EPCR in these cells (64). Thus, impaired protein C activation may contribute to the inflammatory and coagulation response in the airways of asthmatic patients.

Although inhaled corticosteroids are effective for the symptomatic control of asthma, use of these agents may be associated with side effects including growth impairment, decreased bone density, and development of glaucoma and cataracts (65). Recently, APC has been shown to exert an anti-inflammatory effect in a mouse model of asthma. Asthma was induced in BALB/c mice by exposure to aerosolized chicken egg ovalbumin. Inhalation

of APC significantly inhibited IgE secretion as well the secretion of Th2 cytokines (IL-4, IL-13, and IL-5). In addition, inhalation of APC was associated with inhibition of STAT6, which may explain the reduced production of Th2 cytokines and IgE. Reduced NFkB activation and nuclear translocation was also demonstrated by APC inhalation, which may illustrate a secondary mechanism that inhibits Th2 cytokine and IgE production. Furthermore, APC inhalation inhibited bronchioconstriction, which appears to be due to its effect on Th2 cytokine production, since these cytokines induce airway hyperresponsiveness (66). Exogenous supplementation of APC may thus represent a novel and safe anti-inflammatory treatment for asthma.

### 3.6. Acute necrotizing Pancreatitis

Acute pancreatitis is a potentially lethal disorder with no specific medical treatment. Acute pancreatitis produces a spectrum of symptoms, ranging from a local inflammatory process to the more severe form (acute necrotizing pancreatitis) which is associated with a systemic inflammatory response and a mortality rate of 27-45%. Causes of acute pancreatitis include gallstones, alcohol, toxins, trauma, and bacterial and viral infections (67).

Patients with acute necrotizing pancreatitis have similar clinical and physiologic characteristics as patients with sepsis (68). There are similarities in hemodynamic abnormalities as well as in cytokine and inflammatory mediator profiles (68). In acute pancreatitis, inappropriate intracellular activation of digestive enzymes such as trypsin is the main initiating event of pancreatitis (69). The development of acute necrotizing pancreatitis is usually associated with pancreatic glandular necrosis (70). Acinar cell apoptosis, the release of cytokines, increased oxidative stress, tissue ischemia, and tissue necrosis are key factors in the progression of the condition, as well as in the development of associated extrapancreatic complications (68, 69).

NFkB, a transcription factor necessary for the production of pro-inflammatory molecules, plays a key role in acute pancreatitis. In an experimental mouse model of cerulein-induced pancreatitis, NF-kB-deficient mice show reduced organ damage compared with wildtype mice, suggesting that blockade of the inflammatory cascade may be a pharmacologic approach to attenuate acute pancratitis (71).

Given that APC inhibits NFkB activation (72), Yamenel et al. investigated the effects of APC in a rat model of acute necrotizing pancreatitis (73). This study demonstrated that APC improved the severity of pancreatic tissue histology and decreased the incidence of bacterial translocation from the intestine (73). Serum amylase, plasma IL-6, and plasma TNF levels were all significantly decreased in the APC-treated animals (73).

Further rationale for using APC in the treatment of acute necrotizing pancreatitis is that non-surviving patients had significantly lower levels of protein C than survivors (74). In an observational study of 31 patients with acute pancreatitis, protein C deficiency and decreased APC generation were associated with the development of multiple organ failure (75). In two case studies, administration of recombinant APC rapidly improved the progression of severe sepsis associated with acute necrotizing pancreatitis (76). APC supplementation may thus represent an alternative treatment option in patients with acute necrotizing pancreatitis.

### 3.7. Wound healing and angiogenesis

Recent studies indicate that APC has the potential to promote wound healing and angiogenesis. *In vitro*, APC regulated human skin keratinocyte function by stimulating proliferation, migration, wound closure, and by preventing apoptosis (77). These events likely relect, in part, the ability of APC to upregulate MMP-2, IL-6, and IL-8, and to inhibit NF-κB activity in human keratinocytes (77). EPCR has been shown to be strongly expressed by human skin keratinocytes. Furthermore, keratinocyte proliferation and induction of MMP-9 by APC requires EPCR, PAR-1, and MAP kinase activity (78).

In a rat healing model, a single topical application of APC enhanced wound healing compared to saline control (79). In a chick embryo chorioallantoic membrane assay, APC promotes re-epithelialization and angiogenesis (79). Using cultured human cells, APC promoted MMP-2 activity in fibroblasts and endothelial cells, upregulated VEGF in keratinocytes and fibroblasts, and upregulated MCP-1 in fibroblasts (79). APC also activated the MAPK pathway in endothelial cells, increased DNA synthesis, and induced proliferation (80). When applied topically to the mouse cornea, APC induced an angiogenic response comparable to that of vascular endothelial growth factor (VEGF) (80).

## 4. CONCLUSIONS

APC is the first effective biological agent that decreases the mortality rate in patients with severe sepsis. The therapeutic efficacy of APC likely reflects its ability to modulate the cellular functions of many cell types. Recent experimental and preclinical studies warrant future clinical investigations to test the use of recombinant APC to improve clinical outcomes in conditions beyond sepsis.

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**Key Words:** Activated protein C, EPCR, PAR Receptors, Sepsis, Coagulation, Inflammation, Apoptosis, Vascular Dysfunction, Review

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