

20-HETE Mimetics or Inhibitors in the Treatment of Cancer Patients with Sepsis and Septic Shock

Review Article

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Abstract

Patients with a variety of malignancies have a greater tendency to acquire infections than patients with non-malignant disorders. Sepsis and septic shock are common complications in patients with cancer. As the most common causes of morbidity and mortality in intensive care units worldwide, the societal and economic costs of cancer, sepsis, and septic shock are staggering. The molecular pathophysiology of cancer, sepsis, and septic shock remains controversial despite decades of study. 20-Hydroxyeicosatetraenoic acid (20-HETE), a ω -hydroxylation product of arachidonic acid that is produced by cytochrome P450 (CYP) enzymes, mainly by CYP4A and CYP4F isoforms, has been implicated in the regulation of proto-oncogenic, mitogenic, and angiogenic responses both *in vitro* and *in vivo* as well as inflammation that can support tumor progression. Therefore, selective 20-HETE inhibitors has been suggested to be a new class of compounds with antitumor and antiangiogenic activity. On the other hand, studies from our laboratory and others have provided substantial evidence that administration of a synthetic analog of 20-HETE, N-[20-hydroxyeicosa-5(Z),14(Z)-dienoyl]glycine, a 20-HETE mimetic, prevents vascular hyporeactivity, hypotension, tachycardia, inflammation, and mortality presumably due to increased CYP4A1 expression and formation of 20-HETE associated with decreased vasodilatory and proinflammatory mediator production in a rodent model of septic shock. This review will focus on the rationale for the use of 20-HETE mimetics or inhibitors for the treatment of cancer patients with sepsis and septic shock.

Key Words: Cancer; Septic Shock; 20-HETE.

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Overview of Sepsis and Septic Shock

Infection is a pathological process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. The systemic inflammatory response syndrome concept is valid to the extent that a systemic inflammatory response can be triggered by a variety of infectious and noninfectious conditions. Signs of systemic inflammation can occur in the absence of infection among patients with burns, pancreatitis, and other disease states. Sepsis is a syndrome characterised by a systemic inflammatory response to infection that leads to acute organ failure and potentially rapid decline to death. Septic

shock, the most severe complication of sepsis, accounts for approximately 10% of all admissions to intensive care unit (ICU). Septic shock in adults refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mmHg (or, in children, <2 standard deviation below normal for their age), a mean arterial pressure <60, or a reduction in systolic blood pressure of >40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension [reviewed in [1,2].

Sepsis and septic shock are viewed as a complex chain of systemic events in response to invading pathogens involving inflammatory and antiinflammatory processes, humoral and cellular reactions, respiratory, gastrointestinal, renal, and circulatory dysfunctions leading to organ dysfunction and finally to multiple organ dysfunction syndrome and death. The pathogenesis of sepsis and septic shock has long been investigated and, although it is still not fully understood, seems to be due to circulating substances released by pathogens (e.g., endotoxins) and host immunoinflammatory responses (e.g., cytokines, reactive oxygen and nitrogen species, and eicosanoids). Despite intensive basic research worldwide and numerous clinical trials, sepsis and septic shock remain the most important causes of morbidity and mortality in patients admitted to the ICU. Patients with septic shock present typically in their sixth or seventh decade of life, and the average age of these patients has been reported to continue to increase constantly. Predisposing factors include male sex, nonwhite ethnic origin in North Americans, comorbid diseases, malignancy, immunodeficiency or immunocompromised state, chronic organ failure, alcohol dependence, and genetic factors. Patients with diabetes mellitus, malignancy, human immunodeficiency virus (HIV)

infection, or disrupted skin, especially trauma victims, or surgical patients, are more likely to develop severe sepsis. In the United States, the number of cases of severe sepsis and septic shock has been estimated to reach 934,000 and 1,110,000 cases by the years 2010 and 2020. Severe sepsis and septic shock also consume considerable health care resources with the average cost per case. The average costs per case are reported to be \$22,100, with annual total costs of \$16.7 billion nationally. These annual costs will most likely increase in the upcoming years because of the overall aging population, emergence of newer antimicrobial-resistant bacteria, and increasing use of invasive therapeutic measures [reviewed in [1]].

The pathophysiological events in sepsis and septic shock are initiated by entry of an invasive Gram-negative or Gram-positive bacteria into the circulation through the gut, lung, skin, or genitourinary tract during the course of an infection triggers pathophysiological events of sepsis. In addition, the number of cases of severe sepsis or septic shock due to fungal infections has significantly increased. It has been reported that multidrug-resistant bacteria and fungi account for 25% of cases of severe sepsis and septic shock. Viruses and parasites are also isolated in 2% to 4% of cases. On the other hand, a causative organism is not identified in 20% to 30% of cases, because of the relatively low sensitivity of blood cultures or use of antibiotics. In 25% of individuals who have severe sepsis or septic shock, multiple sites of infection can account for the clinical presentation. Twenty percent of individuals have severe sepsis or septic shock with infection site unknown [reviewed in [1]].

Since sepsis and septic shock are the result of complex interactions between the infecting microorganism and host immune, inflammatory, and coagulation responses, the management of the life-threatening conditions is a complex and dynamic process. In general, treatment of sepsis and septic shock is focused on supporting failing organ systems with interventions including (1) improving supportive care (e.g., oxygenation/ventilation strategies, optimize fluid/vasopressor use, and early goal-directed therapy), (2) antimicrobial therapy, (3) targeting bacterial virulence factors (e.g., antiendotoxin antibodies and endotoxin removal columns), and (4) targeting host response factors (e.g., corticosteroids, anticytokine drugs, and anticoagulants) [reviewed in [1,2]]. The Surviving Sepsis Campaign, a collaboration of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and the International Sepsis Forum, whose recommendations on the management of sepsis are considered widely, will publish an updated version of the International Guidelines for Management of Severe Sepsis and Septic Shock originally published in 2004 and last updated in 2008 [3] [for the most recent recommendations and guidelines from the Surviving Sepsis Campaign, visit www.survivingsepsis.org]. These recommendations are intended to provide guidance for the clinician caring of a patient with severe sepsis and septic shock. However, it should be noted that recommendations from these guidelines cannot replace the decision-making capability of the clinicians when they are provided with a patient's unique set of clinical variables.

Clinical Characteristics and Outcomes of Cancer Patients with Sepsis and Septic Shock

In particular, septic shock remains a frequent and feared complication in patients with malignancies because of the underlying immunosuppression related to the disease itself or imposed by treatments, including combined regimens of chemotherapy

and radiotherapy, high dose steroids, and hematopoietic stem cell transplantation [4-6].

In comparison to general patients with sepsis or septic shock, cancer patients experience prolonged lengths of stay and higher morbidity and mortality [7,8]. In a recent prospective cohort study, Rosolem et al. [9] evaluated the characteristics and outcomes of patients with severe sepsis/septic shock (91%) associated with solid tumor (77%) or hematologic malignancies (23%) over a 55-month period. They demonstrated that the most frequent sites of infection were the lung, abdomen, and urinary tract, Gram-negative bacteria were responsible for more than half of the episodes of infection, and 38% of patients had polymicrobial infections. In addition, ICU, hospital, and 6-month mortality rates were 51%, 65%, and 72%, respectively. They also observed that organ dysfunctions were associated with increased mortality. Therefore, the findings of this study confirm that sepsis remains a frequent complication in patients with cancer and associated with high mortality.

Although sepsis and septic shock in patients with cancer remain associated with high morbidity, mortality, costs, and use of ICU resources, the outcomes in these patients including those presenting with severe infectious complications seem to be improving. Indeed, Pene et al. [10] performed a retrospective observational study to assess temporal trends in the ICU management and outcome of cancer patients (solid tumors or hematologic malignancies) with septic shock between 1998 and 2005. The authors demonstrated that short-term survival rates were significantly higher in cancer patients with septic shock admitted to the ICU during 2002-2005 compared with the previous 4-year period (1998-2001). They attributed the increases in survival to both a better selection of patients and improvements in the care and management, including new therapeutic strategies for sepsis. In another retrospective study, Larche et al. [11] evaluated critically ill cancer patients admitted to ICU for septic shock and looked for determinants of 30-day mortality, with a particular attention to outcome changes over a 6-year period (1995-2000). The authors demonstrated that earlier ICU admission and antibiotic treatment of critically ill cancer patients with septic shock was associated with higher 30-day survival. In a prospective observational study, Taccone et al. [12] reported that patients with cancer were more often admitted to the ICU for sepsis and respiratory complications than other ICU patients and the outcome of patients with solid cancer was similar to that of ICU patients without cancer, whereas patients with hematological cancer had a worse outcome. In another prospective observational cohort study, Namendys-Silva et al. [13] reported that survival in cancer patients having solid tumors (68.3%) and hematological malignancies (31.7%) with septic shock admitted to the ICU increased over the 2008-2010 study period. They also demonstrated that the most frequent sites of infection were abdominal (57.3%) and respiratory (35.8%), the most common source of infection were abdominal with predominance Gram-negative bacilli (50%), and more than half of the patients (63.4%) had three or more organ dysfunctions (frequently for the respiratory, cardiovascular, coagulation, and renal systems) on the day of their admission to the ICU. In a recent retrospective cohort study, Zuber et al. [14] evaluated the characteristics and outcomes of septic shock patients with malignancies over a 12-year period (1997-2008). The authors reported that the ICU and hospital mortality rates dramatically dropped over the time (from 70.4% and 72.1% in 1997 to 52.5% and 56.1% in 2008, respectively). Recently, in a large cohort study, Legrand et al. [15] demonstrated that survival increased over the 1998-2008 study

period in neutropenic patients having acute leukemia, lymphoma, and solid tumors with sepsis or septic shock. They also reported that combination antibiotic therapy with an aminoglycoside and early catheter removal may improve survival in the patients.

Biosynthesis and Biologic Effects of 20-Hydroxyeicosatetraenoic Acid (20-Hete)

20-HETE is an ω -hydroxylation product of arachidonic acid (AA) that is produced by cytochrome P450 (CYP) enzymes, mainly by the CYP4A and CYP4F isoforms in the kidney, heart, liver, brain, lung, and vasculature [1,16-18]. In the vasculature, 20-HETE causes vasoconstriction in several vascular beds, including renal, cerebral, aortic, mesenteric, and coronary arteries [19-23]. Activation of protein kinases, such as mitogen-activated protein kinase (MAPK), MAPK kinase (MEK), and extracellular signal-regulated kinase (ERK) which contribute to the regulation of vascular tone, have been shown to mediate the vasoconstrictor effect of 20-HETE [24-26]. As opposed to its vasoconstrictor effect, 20-HETE has also been reported to produce vasodilation in the vasculature including renal and coronary arteries [27-29]. These vasodilatory responses of 20-HETE have been attributed to nitric oxide (NO) release [30], conversion of 20-HETE to 20-OH-PGE2 and 20-OH-PGF2 α by cyclooxygenase (COX) [21,27,31], and increased formation of PGE2 [32] and PGI2 [27-29,31]. In addition, 20-HETE has been shown to activate nuclear factor- κ B (NF- κ B) signaling and induce expression of cellular adhesion molecules and cytokines, thereby promoting inflammation [32,33]. It has also been reported that NO inhibits renal CYP ω -hydroxylase activity and the production of 20-HETE [34,35]. Moreover, a NO-induced fall in the endogenous production of 20-HETE has been found to contribute to the cyclic guanosine monophosphate (cGMP)-independent vasodilator effects of NO in renal and cerebral microcirculations [34,36]. In addition, CYP4A- and CYP4F-derived 20-HETE has been reported to be involved in lipopolysaccharide (LPS)-induced acute systemic inflammation as a proinflammatory mediator [37,38]. Changes in the production of 20-HETE have also been observed in numerous pathological conditions including hypertension, ischemic vascular, cerebral, cardiac, and renal diseases, diabetes, inflammation, polycystic kidney diseases, toxemia of pregnancy, and cancer [1,16-18,39-42].

Role of 20-Hete and Effects of 20-Hete Analogs in Sepsis and Septic Shock

Although changes in 20-HETE production have been well studied in several pathophysiological conditions, little information is available concerning the role of 20-HETE in the pathogenesis of inflammatory diseases such as septic shock in humans and animals. Recent studies from our laboratory and others provided substantial evidence that CYP4A- and CYP4F-derived 20-HETE is a one of the key mediator of vascular hyporeactivity, hypotension, inflammation, and mortality in rodent models of septic shock induced by LPS.

Our recent studies with the use of a stable synthetic analog of 20-HETE, N-[20-hydroxyeicosa-5(Z),14(Z)-dienoyl]glycine, 5,14-HEDGE, which mimics the effects of endogenously produced 20-HETE, (30 mg/kg, s.c., 1 h after LPS injection), and a competitive antagonist of vasoconstrictor effects of 20-HETE, 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid, 20-HEDE (also known as WIT002), (30 mg/kg, s.c., 1 h after LPS injection) sug-

gest that CYP4A-derived 20-HETE is a one of the key mediator of LPS (*Escherichia coli* LPS; 10 mg/kg, i.p.)-induced changes in the renal and cardiovascular systems in rats and mortality in mice [43-46]. Moreover, our data also demonstrate that increased expression of CYP4A1 and CYP2C23 and formation of vasoconstrictor eicosanoids (i.e., 20-HETE) and antiinflammatory mediators (i.e., epoxyeicosatrienoic acids; EETs) associated with suppression of MEK1/ERK1/2/NF- κ B kinase (IKK) α /inhibitor of κ B (I κ B)- κ /NF- κ B and inducible NO synthase (iNOS)/soluble guanylyl cyclase (GC)/protein kinase G (PKG) pathways, COX-2, gp91phox (also known as NOX2), and soluble epoxide hydrolase (sEH) as well as production of NO and vasodilator prostanoids (i.e., PGI2 and PGE2), peroxynitrite, and proinflammatory cytokines (i.e., tumor necrosis factor [TNF]- α and interleukin [IL-8]) participate in the protective effect of 5,14-HEDGE against vascular hyporeactivity, hypotension, tachycardia, inflammation, and mortality in the rodent models of septic shock. In the light of the important role of 20-HETE in the regulation of renal and cardiovascular hemostasis as well as inflammatory process, our findings strongly suggest that further studies with stable 20-HETE mimetics in animal models of endotoxemia could provide a novel approach to treat hypotension, tachycardia, inflammation, and mortality which lead to multiple organ failure and death in patients with septic shock.

In contrast to our findings, Anwar-Mohamed et al. [37] demonstrated that CYP4A1 mRNA expression was increased in the heart of inflamed animals at 6, 12, and 24 h by 400%, 900%, and 6000%, respectively, after injection of LPS (*E. coli* LPS, O127:B8, 1 mg/kg, i.p.) to Sprague-Dawley rats. Similarly, but with a lower magnitude, renal mRNA expression of CYP4A1 was increased only at 24 h by 100% after injection of LPS (*E. coli* LPS, O127:B8, 1 mg/kg, i.p.) to rats. The LPS-induced changes in the expression of CYP4A1 as well as enhanced expression of TNF- α and IL-6 genes in cardiac and renal tissues were also associated with increased production of 20-HETE in the heart microsomes of inflamed animals by 40% *ex vivo*. The authors suggested that acute inflammation causes alteration in cardiac CYP-mediated AA metabolism in favor of 20-HETE formation. However, Theken et al. [38] reported that 20-HETE formation in the kidney, but not in the heart, decreased 6 or 24 h after injection of LPS (*E. coli* LPS, O111:B4, 1 mg/kg, i.p.) to C57BL/6 mice leading to the conclusion that acute activation of the innate immune response alters CYP expression and eicosanoid metabolism in an isoform-, tissue-, and time-dependent manner. Thus, the contradiction between previously published studies and our results could be attributed to differences in type and strain of animals, dose regimen, strain of LPS, and time points for measurement of enzyme expression and activity which might reflect the differences in the response to LPS treatment.

Role of 20-Hete and Effects of 20-Hete Analogs in Cancer

In recent years, increasing evidence has implicated that the 20-HETE producing CYP4A/4F enzymes also play an important role in the regulation of neovascularization process, including vasculogenesis and angiogenesis, that can support tumor progression.

In 1997, Goodman et al. [47] reported that CYP arachidonic acid epoxidase and ω -hydroxylase activities were markedly reduced in the tumor tissues, whereas, in the juxtatumor tissue, CYP ω -hydroxylase activity was significantly increased. In this study,

mRNA levels for \square -hydroxylase transcripts were significantly decreased in the adenocarcinoma compared with juxtatumor. The decrease in CYP4A2 mRNA levels correlated with a decrease in the arachidonic acid \square -hydroxylation metabolite, 20-HETE. The production of 20-HETE was significantly higher in juxtatumor in agreement with \square -hydroxylase mRNA. The authors concluded that increased generation of mitogenic activities by \square -hydroxylase and 20-HETE in the juxtatumor may be a contributing factor in the development and growth of neoplastic tissues.

Chen et al. [48] examined the effects of inhibiting the formation of 20-HETE with N-hydroxy-N \square -(4-butyl-2-methylphenyl)-formamide (HET0016), a selective inhibitor of CYP4A and thus 20-HETE synthesis, on the mitogenic response of vascular endothelial growth factor (VEGF) in human umbilical vein endothelial cells (HUVECs) in vitro, and on growth factor-induced angiogenesis in the cornea of rats in vivo. In this study, HET0016 abolished the mitogenic response to VEGF in HUVECs and the angiogenic response to VEGF, basic fibroblast growth factor (bFGF), and epidermal growth factor (EGF) in vivo by 80 to 90%. Dibromododecenyl methylsulfonamide (DDMS), a structurally and mechanistically different inhibitor of 20-HETE synthesis, also abolished angiogenic responses when tested with VEGF. In addition, administration of the stable 20-HETE agonist, 20-hydroxyeicosa-5(Z),14(Z)-dienoic acid (WIT003) induced mitogenesis in HUVECs and angiogenesis in the rat cornea in vivo. When administered locally into the cornea, HET0016 reduced the angiogenic response to human glioblastoma cancer cells (U251) by 70%. The authors concluded that a product of CYP4A product, possibly 20-HETE, plays a critical role in the regulation of angiogenesis and may provide a useful target for reduction of pathological angiogenesis.

In a parallel study, Guo et al. [49] reported that HET0016 inhibits U251 cell proliferation in a dose-dependent manner. In this study, HET0016 also suppressed 56% of U251 proliferation and significantly increased the proportions of the cells arrested in the G0/G1 phase of the cell cycle. Exposure to HET0016 reduced protein tyrosine and ERK1/2 phosphorylation. Furthermore, HET0016 significantly inhibited the U251 proliferation and phosphorylation of both the EGF receptor and ERK1/2 induced by EGF. These authors concluded that HET0016 may be the prototype of compounds with antitumor activity in glioma since it prevented U251 proliferation by inhibiting 20-HETE synthesis. Subsequently, the authors demonstrated that HET0016 reduced the proliferation of 9L rat gliosarcoma cells in vitro by 55% after 48 h of incubation, and this was associated with a fall in ERK1/2 and stress-activated protein kinase/c-Jun NH2-terminal kinase phosphorylation and increased apoptosis [50]. In this study, HET0016 inhibited EGF and platelet-derived growth factor (PDGF)-induced proliferation and diminished phosphorylation of PDGF receptors. The 20-HETE analog, WIT003, increased 9L cell proliferation. In vivo, chronic administration of HET0016 (10 mg/kg/day i.p.) for 2 weeks reduced the volume of 9L tumors by 80%. This was accompanied by a 4-fold reduction in the mitotic index, a 3- to 4-fold increase in the apoptotic index, and a \square 50% decrease in vascularization in the tumor. HET0016 treatment increased mean survival time of the animals from 17 to 22 days. Liquid chromatography/mass spectrometry experiments indicated that neither 9L cells grown in vitro nor 9L tumors removed produce 20-HETE when incubated with arachidonic acid. The normal surrounding brain tissue, however, avidly makes 20-HETE, and this activity is selectively inhibited by HET0016. The authors suggested that HET0016 may be the prototype of a class

of antigrowth compounds that may be efficacious for treating malignant brain tumors. They also concluded that HET0016 may act in part by inhibiting the formation of 20-HETE by the surrounding tissue in vivo, however, its antiproliferative effects on 9L cells in vitro seem unrelated to its ability to inhibit the formation of 20-HETE. The same group also showed U251 cells transfected with CYP4A1 cDNA (U251 O) increased the formation of 20-HETE from less than 1 to over 60 pmol/min/mg proteins and increased their proliferation rate by 2-fold [51]. In this study, compared with control U251, U251 O cells were rounded, smaller, showed a disorganized cytoskeleton, exhibited reduced vinculin staining, and were easily detached from the growing surface. There was a marked increase in dihydroethidium staining, suggesting increased oxidative stress. The expression of phosphorylated ERK1/2, cyclin D1/2, and VEGF was markedly elevated in U251 O. The hyperproliferative and signaling effects seen in U251 O cells are abolished by selective inhibition of CYP4A and 20-HETE formation with HET0016, by small interfering RNA against the enzyme, and by the 20-HETE antagonist, 20-HEDE. In vivo, implantation of U251O cells in the brain of nude rats resulted in a \square 10-fold larger tumor volume (10 days postimplantation) compared with animals receiving mock-transfected U251 cells. The authors concluded that elevations in CYP4A-induced 20-HETE synthesis in a human glioma U251 cell line lead to an increased growth both in vitro and in vivo, suggesting that 20-HETE may have proto-oncogenic properties in U251 human gliomas.

Recently, Alexanian et al. [52] examined the ability of inhibitors of the synthesis or actions of 20-HETE to inhibit proliferation of human renal carcinoma cell lines. In this study, addition of HET0016 and the 20-HETE antagonist, 20-HEDE, inhibited the proliferation of 786-O and 769-P human renal cell carcinoma lines. HET0016 and 20-HEDE had little effect on the proliferation of primary cultures of normal human proximal tubule epithelial cells. 20-HEDE (10 mg/kg, s.c.) administered daily to athymic nude mice implanted subcutaneously with 786-O cells reduced the growth of the tumors by 84% compared to vehicle. The authors concluded that 20-HETE is required for proliferation of human renal epithelial cancers. More recently, the same group reported that the expression of CYP4A/4F genes is markedly elevated in thyroid, breast, colon, and ovarian cancer samples in comparison to matched normal tissues [53]. In this study, the levels of the CYP4F2 protein and of 20-HETE were also higher in ovarian cancer samples compared to normal control tissues. A stable 20-HETE agonist induced activation of the small-GTPase Ras in human proximal tubule epithelial cells. The authors concluded that the finding of elevated expression of CYP4A/F enzymes in human cancer tissue suggests that 20-HETE inhibitors and antagonists may be useful in the treatment of human cancer.

Yu et al. [54] examined the role of CYP \square -hydroxylase in angiogenesis and metastasis of human non-small cell lung cancer (NSCLC). In this study, addition of WIT003 or overexpression of CYP4A11 with an associated increase in 20-HETE production significantly induced invasion and expression of VEGF and matrix metalloproteinase (MMP)-9. Treatment of A549 cells with HET0016 or 20-HEDE inhibited invasion with reduction in VEGF and MMP-9. The phosphoinositide-3-kinase (PI3K) or ERK inhibitors also attenuated expression of VEGF and MMP-9. Compared with control, CYP4A11 transfection significantly increased tumor weight, microvessel density (MVD), and lung metastasis by 2.5-fold, 2-fold, and 3-fold, respectively. In con-

trast, 20-HEDE or HET0016 decreased tumor volume, MVD, and spontaneous pulmonary metastasis occurrences. The authors concluded that CYP ω -hydroxylase promotes tumor angiogenesis and metastasis by upregulation of VEGF and MMP-9 via PI3K and ERK1/2 signaling in human NSCLC cells. More recently, the same group demonstrated that stable expression of CYP4Z1 a novel CYP4 family member, which is over-expressed in human mammary carcinoma and associated with high-grade tumors and poor prognosis, in T47D and BT-474 human breast cancer cells significantly increased mRNA expression and production of VEGF-A, and decreased mRNA levels and secretion of tissue inhibitor of metalloproteinase-2 (TIMP-2), without affecting cell proliferation and anchorage-independent cell growth in vitro [55]. In this study, the conditioned medium from CYP4Z1-expressing cells also enhanced proliferation, migration and tube formation of HUVECs, and promoted angiogenesis in the zebrafish embryo and chorioallantoic membrane of the chick embryo. In addition, there were lower levels of myristic acid and lauric acid, and higher contents of 20-HETE in CYP4Z1-expressing T47D cells compared with vector control. CYP4Z1 overexpression significantly increased tumor weight and microvessel density by 2.6-fold and 1.9-fold in human tumor xenograft models, respectively. Moreover, CYP4Z1 transfection increased the phosphorylation of ERK1/2 and PI3K/Akt, while PI3K or ERK inhibitors and siRNA silencing reversed CYP4Z1-mediated changes in VEGF-A and TIMP-2 expression. Conversely, HET0016 potently inhibited the tumor-induced angiogenesis with associated changes in the intracellular levels of myristic acid, lauric acid and 20-HETE. The authors suggested that increased CYP4Z1 expression promotes tumor angiogenesis and growth in breast cancer partly via PI3K/Akt and ERK1/2 activation.

Although the pro-angiogenic, proto-oncogenic, and mitogenic effects of 20-HETE have extensively been investigated in human carcinoma tissues and cell lines both in vitro and in vivo, little is known about the role of 20-HETE in cancer patients. In one study, Nithipatikom et al. [56] investigated the relationship between the concentrations of urinary free acids of 12-HETE and 20-HETE and the benign prostatic hypertrophy (BPH) and prostate cancer. In this study, urinary concentrations of 12-HETE and 20-HETE of BPH and prostate cancer patients were significantly higher than normal subjects. After removal of the prostate gland, the urinary concentrations of these eicosanoids decreased to concentrations similar to the normal subjects. The authors concluded that urinary free acids of 12-HETE and 20-HETE indicate an abnormality of the prostate gland.

Conclusion

The current management of cancer patients with sepsis and septic shock relies on immediate treatment with antibiotics and strong supportive care to control hypotension, tachycardia, cardiac output, and tissue oxygenation to maintain organ function. However, the failure of conventional therapy is that the pathophysiology of septic shock is the result of a highly complex set of processes in which the host response becomes dysregulated and causes cellular damage, tissue damage, and, ultimately, organ failure. Accumulating evidence suggest that the importance and contribution of 20-HETE generated via CYP4A and CYP4F to renal and cardiovascular diseases associated with inflammation and cancer is beginning to emerge. Although inhibitors of 20-HETE synthesis such as HT0016 and DDMS as well as its competitive antagonist 20-HEDE have been proposed to be useful in the treatment of cancer, in the light of the important role of NO, prostanoids, and

20-HETE in hypotension, inflammation, MOF, and mortality, the interaction of NOS, COX, and CYP4A/4F pathways should be considered when developing new strategies for drug development in the treatment of cancer patients with sepsis and septic shock. More importantly, further studies with stable mimetics of 20-HETE, such as 5,14-HEDGE, in experimental models of cancer in endotoxemic animals could provide a novel approach to treat hypotension, inflammation, and mortality which lead to MOF and death in cancer patients with septic shock admitted to the ICU.

References

- [1]. Tunctan B, Korkmaz B, Sari AN, Kacan M, Unsal D et al. (2012) A novel treatment strategy for sepsis and septic shock based on the interactions between prostanoids, nitric oxide, and 20-hydroxyeicosatetraenoic acid. *Anti-inflamm Antiallergy Agents Med Chem* 11: 121-150.
- [2]. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 36: 296-327.
- [3]. Friswell AC (2012) Surviving Sepsis Campaign Previews Updated Guidelines for 2012. *Pulm Rev* 17: 1, 5.
- [4]. Thirumala R, Ramaswamy M, Chawla S (2010) Diagnosis and management of infectious complications in critically ill patients with cancer. *Crit Care Clin* 26: 59-91.
- [5]. Cohen J, Drage S (2011) How I manage haematology patients with septic shock. *Br J Haematol* 152: 380-391.
- [6]. Tan SJ (2002) Recognition and treatment of oncologic emergencies. *J Infus Nurs* 25: 182-188.
- [7]. Danai PA, Moss M, Mannino DM, Martin GS (2006) The epidemiology of sepsis in patients with malignancy. *Chest* 129: 1432-1440.
- [8]. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B; CUB-Réa Network (2003) Current epidemiology of septic shock: the CUB-Réa Network. *Am J Respir Crit Care Med* 168: 165-172.
- [9]. Rosolem MM, Rabello LS, Lisboa T, Caruso P, Costa RT et al. (2012) Critically ill patients with cancer and sepsis: clinical course and prognostic factors. *J Crit Care* 27: 301-307.
- [10]. Pene F, Percheron S, Lemiale V, Viallon V, Claessens YE et al. (2008) Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. *Crit Care Med* 36: 690-696.
- [11]. Larche J, Azoulay E, Fioux F, Mesnard L, Moreau D et al. (2003) Improved survival of critically ill cancer patients with septic shock. *Intensive Care Med* 29: 1688-1695.
- [12]. Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y et al. (2009) Characteristics and outcomes of cancer patients in European ICUs. *Crit Care* 13: R15.
- [13]. Namendys-Silva SA, Gonzalez-Herrera MO, Texcocano-Becerra J, Herrera-Gomez A (2011) Clinical characteristics and outcomes of critically ill cancer patients with septic shock. *QJM* 104: 505-511.
- [14]. Zuber B, Tran TC, Aegerter P, Grimaldi D, Charpentier J et al. (2012) Impact of case volume on survival of septic shock in patients with malignancies. *Crit Care Med* 40: 55-62.
- [15]. Legrand M, Max A, Peigne V, Mariotte E, Canet E et al. (2012) Survival in neutropenic patients with severe sepsis or septic shock. *Crit Care Med* 40:43-49.
- [16]. Kroetz DL, Xu F (2005) Regulation and inhibition of arachidonic acid omega-hydroxylases and 20-HETE formation. *Annu Rev Pharmacol Toxicol* 45: 413-438.
- [17]. Miyata N, Roman RJ (2005) Role of 20-hydroxyeicosatetraenoic acid (20-HETE) in vascular system. *J Smooth Muscle Res* 175: 175-193.
- [18]. Roman RJ (2002) P-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol Rev* 82: 131-185.
- [19]. Escalante B, Omata K, Sessa W, Lee SG, Falck JR et al. (1993) 20-hydroxyeicosatetraenoic acid is an endothelium-dependent vasoconstrictor in rabbit arteries. *Eur J Pharmacol* 235: 1-7.
- [20]. Escalante B, Sessa WC, Falck JR, Yadagiri P, Schwartzman ML (1989) Vasoactivity of 20-hydroxyeicosatetraenoic acid is dependent on metabolism by cyclooxygenase. *J Pharmacol Exp Ther* 248: 229-32.
- [21]. Randriamboavonjy V, Busse R, Fleming I (2003) 20-HETE-induced contraction of small coronary arteries depends on the activation of Rho-kinase. *Hypertension* 41: 801-806.
- [22]. Schwartzman ML, Falck JR, Yadagiri P, Escalante B (1989) Metabolism of 20-hydroxyeicosatetraenoic acid by cyclooxygenase: formation and identification of novel endothelium-dependent vasoconstrictor metabolites. *J Biol Chem* 264: 11658-61162.
- [23]. Zou AP, Fleming JT, Falck JR, Jacobs ER, Gebremedhin D et al. (1996) 20-HETE is an endogenous inhibitor of the large-conductance Ca(2+)-activated K+ channel in renal arterioles. *Am J Physiol* 270: R228-R237.

- [24]. Akbulut T, Regner KR, Roman RJ, Avner ED, Falck JR et al. (2009) 20-HETE activates the Raf/MEK/ERK pathway in renal epithelial cells through an EGFR- and c-Src-dependent mechanism. *Am J Physiol* 297: F662-F670.
- [25]. Ponnoth DS, Nayeem MA, Kunduri SS, Tilley SL, Zeldin DC et al. (2012) Role of ω -hydroxylase in adenosine-mediated aortic response through MAP kinase using A2A-receptor knockout mice. *Am J Physiol* 302: R400-R408.
- [26]. Sun CW, Falck JR, Harder DR, Roman RJ (1999) Role of tyrosine kinase and PKC in the vasoconstrictor response to 20-HETE in renal arterioles. *Hypertension* 33: 414-418.
- [27]. Carroll MA, Capparelli MF, Doumand AB, Cheng MK, Jiang H et al. (2001) Renal vasoactive eicosanoids: interactions between cytochrome P450 and cyclooxygenase metabolites during salt depletion. *Am J Hypertens* 14: 159A.
- [28]. Carroll MA, Garcia MP, Falck JR, McGiff JC (1992) Cyclooxygenase dependency of the renovascular actions of cytochrome P450-derived arachidonate metabolites. *J Pharmacol Exp Ther* 260: 104-109.
- [29]. Pratt PF, Falck JR, Reddy KM, Kurian JB, Campbell WB (1998) 20-HETE relaxes bovine coronary arteries through the release of prostacyclin. *Hypertension* 31: 237-241.
- [30]. Yu M, McAndrew RP, Al-Saghir R, Maier KG, Medhora M et al. (2002) Nitric oxide contributes to 20-HETE-induced relaxation of pulmonary arteries. *J Appl Physiol* 93: 1391-1399.
- [31]. Fang X, Faraci FM, Kaduce TL, Harmon S, Modrick ML et al. (2006) 20-Hydroxyeicosatetraenoic acid is a potent dilator of mouse basilar artery: role of cyclooxygenase. *Am J Physiol* 291: H2301-H2307.
- [32]. Cheng J, Wu CC, Godlinger KH, Zhang F, Falck JR et al. (2010) 20-hydroxy-5,8,11,14-eicosatetraenoic acid mediates endothelial dysfunction via I κ B kinase-dependent endothelial nitric-oxide synthase uncoupling. *J Pharmacol Exp Ther* 332: 57-65.
- [33]. Ishizuka T, Cheng J, Singh H, Vitto MD, Manthali VL et al. (2008) 20-Hydroxyeicosatetraenoic acid stimulates nuclear factor- κ B activation and the production of inflammatory cytokines in human endothelial cells. *J Pharmacol Exp Ther* 324: 103-110.
- [34]. Alonso-Galicia M, Sun CW, Falck JR, Harder DR, Roman RJ (1998) Contribution of 20-HETE to the vasodilator actions of nitric oxide in renal arteries. *Am J Physiol* 275: F370-F378.
- [35]. Wang MH, Wang J, Chang HH, Zand BA, Jiang M et al. (2003) Regulation of renal CYP4A expression and 20-HETE synthesis by nitric oxide in pregnant rats. *Am J Physiol* 285: F295-F302.
- [36]. Alonso-Galicia M, Drummond HA, Reddy KK, Falck JR, Roman RJ (1997) Inhibition of 20-HETE production contributes to the vascular responses to nitric oxide. *Hypertension* 29: 320-325.
- [37]. Anwar-mohamed A, Zordoky BN, Aboutabl ME, El-Kadi AO (2010) Alteration of cardiac cytochrome P450-mediated arachidonic acid metabolism in response to lipopolysaccharide-induced acute systemic inflammation. *Pharmacol Res* 61: 410-418.
- [38]. Theken KN, Deng Y, Kannon MA, Miller TM, Poloyac SM et al. (2011) Activation of the acute inflammatory response alters cytochrome P450 expression and eicosanoid metabolism. *Drug Metab Dispos* 39: 22-29.
- [39]. Imig JD, Simpkins AN, Renic M, Harder DR (2011) Cytochrome P450 eicosanoids and cerebral vascular function. *Expert Rev Mol Med* 13: e7.
- [40]. Williams JM, Murphy S, Burke M, Roman RJ (2010) 20-hydroxyeicosatetraenoic acid: a new target for the treatment of hypertension. *J Cardiovasc Pharmacol* 56: 336-344.
- [41]. Wu CC, Schwartzman ML (2011) The role of 20-HETE in androgen-mediated hypertension. *Prostaglandins Other Lipid Mediat* 96: 45-53.
- [42]. Seubert JM, Zeldin DC, Nithipatikom K, Gross GJ (2007) Role of epoxyeicosatrienoic acids in protecting the myocardium following ischemia/reperfusion injury. *Prostaglandins Other Lipid Mediat* 82: 50-59.
- [43]. Cuez T, Korkmaz B, Buharalioglu CK, Sahan-Firat S, Falck J et al. (2010) A synthetic analogue of 20-HETE, 5,14-HEDGE, reverses endotoxin-induced hypotension via increased 20-HETE levels associated with decreased iNOS protein expression and vasodilator prostanoid production in rats. *Basic Clin Pharmacol* 106: 378-388.
- [44]. Tunctan B, Korkmaz B, Buharalioglu CK, Firat SS, Anjaiah S et al. (2008) A 20-HETE agonist, N-[20-hydroxyeicosa-5(Z),14(Z)-dienoyl]glycine, opposes the fall in blood pressure and vascular reactivity in endotoxin-treated rats. *Shock* 30: 329-335.
- [45]. Tunctan B, Korkmaz B, Cuez T, Sari AN, Kacan M et al. (2011) Contribution of iNOS, COX-2 and CYP4A1 to the protective effect of a synthetic analog of 20-HETE, 5,14-HEDGE, against endotoxin-induced hypotension and mortality in experimental model of septic shock in rats and mice. *Inflam Res* 60: S55.
- [46]. Tunctan B, Korkmaz B, Sari, AN, Kacan M, Gilik U et al. (2012) A synthetic analog of 20-HETE, 5,14-HEDGE, reverses endotoxin-induced hypotension and mortality via increased expression and activities of CYP4A1 and CYP2C23 in a rodent model of septic shock: contribution of MEK1/ERK1/2/IKK β pathway and soluble epoxide hydrolase. *Sepsis* 4: 158-159.
- [47]. Goodman AI, Choudhury M, da Silva JL, Schwartzman ML, Abraham NG (1997) Overexpression of the heme oxygenase gene in renal cell carcinoma. *Proc Soc Exp Biol Med* 214: 54-61.
- [48]. Chen P, Guo M, Wygle D, Edwards PA, Falck JR et al. (2005) Inhibitors of cytochrome P450 4A suppress angiogenic responses. *Am J Pathol* 166: 615-624.
- [49]. Guo M, Roman RJ, Falck JR, Edwards PA, Scicli AG (2005) Human U251 glioma cell proliferation is suppressed by HET0016 [N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine], a selective inhibitor of CYP4A. *J Pharmacol Exp Ther* 315: 526-533.
- [50]. Guo M, Roman RJ, Fenstermacher JD, Brown SL, Falck JR et al. (2006) 9L gliosarcoma cell proliferation and tumor growth in rats are suppressed by N-hydroxy-N'-(4-butyl-2-methylphenol) formamidine (HET0016), a selective inhibitor of CYP4A. *J Pharmacol Exp Ther* 317: 97-108.
- [51]. Guo AM, Sheng J, Scicli GM, Arbab AS, Lehman NL et al. (2008) Expression of CYP4A1 in U251 human glioma cell induces hyperproliferative phenotype in vitro and rapidly growing tumors in vivo. *J Pharmacol Exp Ther* 327: 10-19.
- [52]. Alexanian A, Rufanova VA, Miller B, Flasch A, Roman RJ et al. (2012) Down-regulation of 20-HETE synthesis and signaling inhibits renal adenocarcinoma cell proliferation and tumor growth. *Anticancer Res* 29: 3819-3824.
- [53]. Alexanian A, Miller B, Roman RJ, Sorokin A (2012) 20-HETE-producing enzymes are up-regulated in human cancers. *Cancer Genomics Proteomics* 9: 163-169.
- [54]. Yu W, Chen L, Yang YQ, Falck JR, Guo AM et al. (2011) Cytochrome P450 ω -hydroxylase promotes angiogenesis and metastasis by upregulation of VEGF and MMP-9 in non-small cell lung cancer. *Cancer Chemother Pharmacol* 68: 619-629.
- [55]. Yu W, Chai H, Li Y, Zhao H, Xie X et al. (2012) Increased expression of CYP4Z1 promotes tumor angiogenesis and growth in human breast cancer. *Toxicol Appl Pharmacol* 264: 73-83.
- [56]. Nithipatikom K, Isbell MA, See WA, Campbell WB (2006) Elevated 12- and 20-hydroxyeicosatetraenoic acid in urine of patients with prostatic diseases. *Cancer Lett* 233: 219-225.