REVIEW

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Peroxisome proliferator-activated receptor γ (PPARγ) and sepsis

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Abstract

This review describes the role of the nuclear hormone receptor PPARγ as a double-edged sword in sepsis. On the one hand, PPARγ inhibits pro-inflammatory gene expression, predominantly by scavenging transcription factors and their cofactors, thus preventing them from binding to their cognate binding sites in the promoters of target genes. The expressions of the affected genes, such as those for inducible nitric oxide synthase, TNF-α, or IL-1β, are repressed. Therefore, PPARγ is suggested to be beneficial in hyper-inflammatory diseases, such as sepsis. In animal models of sepsis, PPARγ agonist pretreatment auspiciously attenuated inflammation compared with control animals, accompanied by their improved survival rate. On the other hand, PPARγ provokes apoptosis, which in the hyper-inflammatory phase of sepsis might be helpful because the number of immune cells, such as monocytes, macrophages, and neutrophils, involved in secreting high amounts of pro-inflammatory mediators will be reduced. In contrast, during the anti-inflammatory phase, cell death of immune cells, especially of T lymphocytes, is supposed to be deleterious. Under these circumstances, a second infection cannot be adequately answered, thus causing septic shock and multi-organ dysfunction syndrome. Therefore the role of PPARγ is still ambiguous. Particularly its role in initiating apoptosis awaits further clarification to finally elucidate its impact on sepsis development.

Key words: inflammation, T cells, sepsis, apoptosis.

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SEPSIS

Sepsis is the most common cause of death in intensive care units. Although medical care has improved over the last decades, the incidence of sepsis and septic shock have increased significantly over the last 20 years [20, 35, 36]. It has been estimated that in the USA, 751,000 patients develop sepsis and septic shock every year, with an overall mortality rate of 28.6% [28]. In Europe, severe sepsis and septic shock affect three people in every 1000 and kill at least 135,000 patients each year [22].

A refined definition of sepsis was provided by Bone et al. in 1989 [6]. This definition was approved by the consensus conference of the American College of Chest Physicians and Society of Critical Care Medicine in 1991. As agreed, sepsis is characterized by a severe inflammatory response syndrome (SIRS) evoked by an infection. SIRS is defined as a general hyper-inflammatory reaction of various causes, such as infection, trauma, or burn [7]. If organ dysfunction occurs, it is designated as severe sepsis, which often results in septic shock. Because this definition was established more than 10 years ago, many new insights in sepsis pathophysiology were not considered in this sepsis criterion. However, sepsis basically is characterized by high or very low blood temperature, palpitations, cool blue extremities, and low blood pressure. An extreme fall in blood pressure, which starves the major organs, results in septic shock [2, 15].

During sepsis, the interaction of infection and immunity is very important. The origin of infection is unimportant for sepsis development. All pathogens can thus possibly induce sepsis. Immune cell-pathogen contact induces an inflammatory response by the activation of monocytes, macrophages, and neutrophils [4, 17]. These cells release tumor necrosis factor (TNF)-α and interleukin (IL)-1β, the primary pro-inflammatory

cytokines (Fig. 1), provoking local immune responses such as vascular dilatation, causing a lower blood pressure [15]. This immune response is boosted by a panel of secondary pro-inflammatory mediators, such as reactive oxygen or nitrogen species and degradation products from fatty acids. Additionally, the coagulation cascade is triggered, decreasing fibrinolysis, which causes the formation of micro-thrombi in capillaries and finally evokes multi-organ dysfunction syndrome (MODS) [39]. Following this hyper-inflammatory phase, or sometimes occurring simultaneously, soluble TNF-α receptors, IL-1-receptor antagonists, IL-4, or IL-10 are produced as anti-inflammatory molecules switching the cellular phenotype from pro- to anti-inflammatory (Fig. 1). This is often accompanied by cell death of immune-competent cells, which finally amplifies the anti-inflammatory response [24, 46].

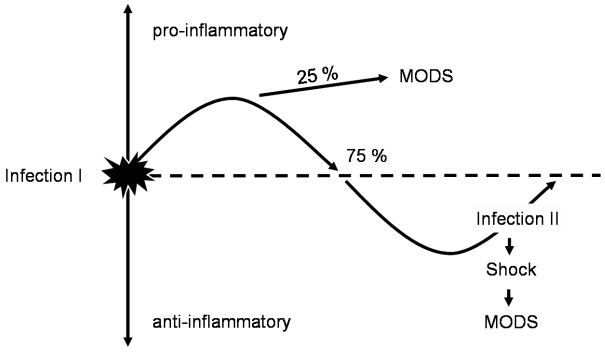

Fig. 1. Sepsis is immunologically divided into two phases. The first is characterized by a hyper-inflammatory state of the immune system, accompanied by the synthesis of large amounts of pro-inflammatory cytokines (TNF-α, IL-1β) and other mediators (ROS, NO). In 25% of all cases this may finally results in the development of MODS, often followed by the death of the patient. Often (75%) the first phase is followed by a second period, where anti-inflammatory mechanisms prevail, confining the hyper-inflammatory phase. However, a secondary infection in this phase may provoke a second formation of MODS, with its harmful consequences.

In general, an immune response should be confined after the infection has terminated. However, under certain circumstances the immune response is shut off, which provokes a shift to an anti-inflammatory and desensitized phenotype, although the infection has not been completely eliminated. Therefore, the pathogen might provoke a second infection, which now cannot be appropriately answered by an immune response. During sepsis, this stage is referred to as compensatory anti-inflammatory response syndrome (CARS) and is often accompanied by septic shock and MODS [16, 30].

Therefore, improvement of therapy strategies to treat this pathological setting is mandatory. Because it is well established that sepsis is a systemic inflammatory response, attended by an excessive synthesis of pro-inflammatory cytokines and the release of other mediators, such as nitric oxide or basic degradation products from fatty acids, finally causing septic shock and MODS, approaches which inhibit the immoderate production of pro-inflammatory messenger molecules are gaining increased interest.

PPARγ – A MODULATOR OF INFLAMMATORY GENE EXPRESSION

One more recently identified factor which is of potential interest for the therapy and, most likely, the prevention of sepsis is PPARγ. PPARγ belongs to the nuclear hormone receptor family. It was originally identified as most essential in glucose metabolism [14]. Thus, synthetic PPARγ agonists, the so-called "thiazolidinediones" (TDZs), are used in diabetes type 2 therapy as insulin sensitizers [49]. However, not only this function of PPARγ is interesting for its use in sepsis treatment, but also its anti-inflammatory properties, which have been characterized in immune cells such as B and T lymphocytes, monocytes, macrophages, dendritic cells, and granulocytes [3, 27, 34, 42, 45, 48]. PPARγ is a transcription factor which, upon ligand binding, forms a heterodimer with the retinoic acid X receptor α and then binds to peroxisome proliferator-activated receptor response elements in the promoter region of its target gene, provoking its expression or repression. Interestingly, PPARγ cannot only act via DNA binding, but also in a DNA-independent manner. This attribute is important for its anti-inflammatory role because this feature is mainly responsible for blocking pro-inflammatory gene expression.

So far, five different PPARγ-dependent mechanisms have been identified. First, PPARγ can scavenge transcriptional co-factors, such as steroid receptor co-activator-1 (SRC-1) or CREB binding protein (CBP/p300). Bound to PPARγ, these co-factors are not available for initiating gene expression (Fig. 2A). Because transcriptional co-factors are indispensable for nuclear factor (NF)-κB-dependent gene induction, NF-κB-mediated pro-inflammatory cytokine expression is retained [26, 27]. Second, PPARγ can also directly associate with transcription factors such as NF-κB, NF-AT, AP-1, or STAT. These are important transcription factors involved in pro-inflammatory gene expression. Blocking them causes a significant attenuation of pro-inflammatory gene expression (Fig. 2B) [9, 18, 37, 41, 45, 48]. Third, PPARγ can inhibit mitogen-activated protein kinase (MAPK) by a so far unknown mechanism [13]. This inhibition prevents MAPK from phosphorylating and thereby activating downstream transcription factors, which are necessary for MAPK-dependent pro-inflammatory gene expression (Fig. 2C). Additionally, PPARγ can block protein kinase C (PKC)α translocation and thereby PKCα signaling, which normally provokes activation of the NADPH oxidase system and production of reactive oxygen species, known as the respiratory burst of macrophages [23]. The underlying principle in this case is not completely clear, but due to

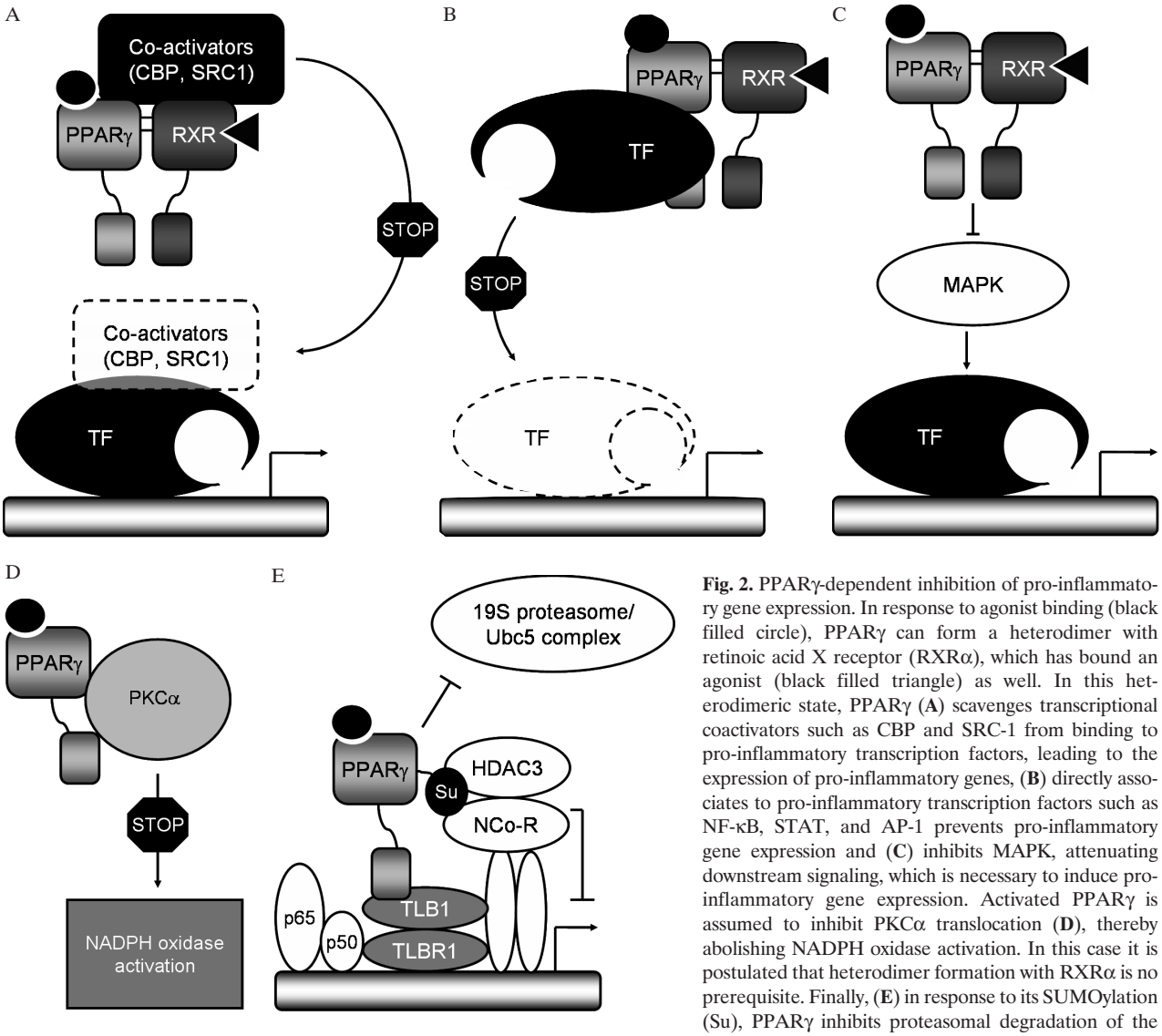

Fig. 2. PPARγ-dependent inhibition of pro-inflammatory gene expression. In response to agonist binding (black filled circle), PPARγ can form a heterodimer with retinoic acid X receptor (RXRα), which has bound an agonist (black filled triangle) as well. In this heterodimeric state, PPARγ (**A**) scavenges transcriptional coactivators such as CBP and SRC-1 from binding to pro-inflammatory transcription factors, leading to the expression of pro-inflammatory genes, (**B**) directly associates to pro-inflammatory transcription factors such as NF-κB, STAT, and AP-1 prevents pro-inflammatory gene expression and (**C**) inhibits MAPK, attenuating downstream signaling, which is necessary to induce pro-inflammatory gene expression. Activated PPARγ is assumed to inhibit PKCα translocation (**D**), thereby abolishing NADPH oxidase activation. In this case it is postulated that heterodimer formation with RXRα is no prerequisite. Finally, (**E**) in response to its SUMOylation (Su), PPARγ inhibits proteasomal degradation of the NCo-R-HDAC3-TLB1-TLBR1 complex, which in turn would allow NF-κB-(p50/p65 heterodimer)-dependent pro-inflammatory gene expression.

the short time necessary for its occurrence, gene regulatory mechanisms can be excluded. Thus direct PPARγ--PKCα binding might be hypothesized (Fig. 2D). Further experiments have to finally identify the basis of this observed phenomenon. However, blocking the oxidative burst further impairs immune function. Very recent data suggest a fifth possibility of how PPARγ may affect pro-inflammatory gene expression (Fig. 2E). Pascual et al. [33] provided evidence that PPARγ can trans-repress NF-κB-dependent genes by inhibiting the removal of the nuclear receptor co-repressor (NCo-R)-histone deacetylase-3 (HDAC3)-transducin beta-like protein 1 (TBL1)-TBLR1 complex by the ubiquitination machinery from the promoter. Pretreatment with the TZD rosiglitazone causes recruitment of PPARγ to the repressive complex, which prevents subsequent recruitment of the ubiquitination machinery required to clear the repressive complex from the promoter. NF-κB--dependent pro-inflammatory gene expression is thus abolished.

These possibilities of PPARγ to modulate and/or block pro-inflammatory gene expression and the synthesis of other pro-inflammatory mediators obviously support a potential role in sepsis treatment and contingent prevention.

PPARγ – AN INHIBITOR OF SEPSIS

Taking the anti-inflammatory properties of PPARγ into consideration, Collin and Thiemermann in 2003 [11] demonstrated in a rat sepsis model for the first time that the endogenous PPARγ agonist 15-deoxy-$\Delta^{12,14}$--PGJ_2 (15-$dPGJ_2$) reduced liver injury, as documented by the fall in serum transaminases. In 2004 the same group provided evidence that during hemorrhagic shock,

endogenously synthesized PPARγ agonists restricted the degree of liver injury because in the experimental rat model the PPARγ antagonist GW9662 attenuated this restriction [1, 12]. Interestingly, in contrast to the data obtained during hemorrhagic shock, no endogenous PPARγ agonist was generated during endotoxic shock. Thus, at least in the rat sepsis model, no endogenous PPARγ agonists are synthesized. From these results one may conclude that exogenously administered PPARγ agonists may compensate for this deficiency and even might be more effective in down-modulating or inhibiting the systemic inflammatory response observed during sepsis. Concerning these reports, no mechanistic aspects of PPARγ-dependent signaling pathways have been identified. Therefore, to elucidate the molecular mechanisms used by PPARγ to protect animals from sepsis, Kaplan et al. [25] demonstrated in 2005 that in the mouse sepsis model induced by subjecting the animals to peritoneal injection of lipopolysaccharide (LPS; 25 mg/kg), treatment of the mice with 1 mg/kg 15-dPGJ_2, three hours after LPS injection improved the survival rate of animals to 55% compared with 9% in vehicle--treated mice. Survival was monitored for 72 h. Analysis of the lungs of animals which did not receive 15-dPGJ_2 showed marked lung injury, as characterized by hemorrhage, infiltration of inflammatory cells, and reduction of aveolar space. Increased expressions of intercellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin were observed in the lung and small intestine. These inflammatory events were associated with reduced expression of PPARγ and with activation of the pro-inflammatory transcription factor NF-κB in the lung. 15-dPGJ_2 treatment of animals reduced adhesion molecule expression and neutrophil infiltration. These beneficial effects were associated with reduced activation of NF-κB, whereas expression and DNA binding of PPARγ where increased in the lung.

The above study supports the hypothesis that PPARγ might improve the clinical picture of sepsis by inhibiting NF-κB-dependent pro-inflammatory gene expression. However, one may speculate that the endotoxin model used is not an appropriate system to mimic septic conditions [8]. Thus, Siddiqui et al. [38] very recently provided further evidence for a PPARγ-dependent improvement of sepsis outcome. In their study they also used a rat model, but in contrast to the work of Collin and Thiemermann [11], they employed a different sepsis model. Rats where subjected to sepsis by cecal ligation and puncture. They provided evidence that persisting PPARγ expression in the liver attenuated tissue injury, reduced mortality, and decreased TNF-α expression in septic animals. To achieve this protective effect they applied the phytochemical curcumin. With this substance the protective effect was independent of the time point of administration, i.e. before or after the onset of sepsis. Pretreatment of the animals with the PPARγ antagonist GW9662 restored the septic characteristics and substantiated a PPARγ-dependent effect. In addition to the animal model, they stated that stimulation of RAW 264.7 mouse macrophages with curcumin inhibits endotoxin--induced increases in TNF-α expression. In RAW 264.7 cells, PPARγ was markedly up-regulated, further supporting its role during macrophage desensitization.

In line with this report, we found that LPS/interferon (IFN)-γ treatment of RAW 264.7 macrophages provoked DNA binding and transcriptional activation of PPARγ starting from 2 h onwards with a maximum at 15 h after LPS/IFN-γ stimulation [44]. Based on this finding, we proposed that a pro-inflammatory activation regimen provokes the endogenous production of a PPARγ agonist or activator which in turn signals in an autocrine and/or paracrine manner to activate PPARγ. The activated transcription factor is then able to switch the cellular phenotype from pro- to anti-inflammatory. This can be achieved by scavenging cofactors and transcription factors or inhibiting signaling pathways that release pro-inflammatory mediators in a DNA-unbound state or by blocking transcription of relevant genes encoding proteins such as NADPH oxidase components by direct DNA binding. As shown in the rat model of sepsis, endogenous PPARγ ligands are not produced during endotoxic shock. Thus compensatory therapy with PPARγ agonists such as TZDs might be beneficial in the hyper-inflammatory phase of sepsis. However, besides these anti-inflammatory properties of PPARγ, PPARγ can also induce cell death.

PPARγ-DEPENDENT APOPTOSIS – A TRIGGER OF SEPSIS?

Activation of PPARγ in response to its agonists, e.g. TZDs or arachidonic acid metabolites, may initiate apoptosis. Different pathways for this pro-apoptotic role of PPARγ have been identified. In pre-monocytic THP-1 cells, the TZD pioglitazone induces apoptosis via caspase-3 and -9 activation, which was prevented by the PPARγ antagonist GW9662, supporting PPARγ--dependent apoptosis [5]. In line with this report, Chen et al. [10] observed PPARγ-mediated apoptosis in response to the TZDs rosiglitazone, troglitazone, and ciglitazone in HL-60 cells. In their experiments, apoptosis was caspase-3 dependent. A role of PPARγ was verified using its antagonists GW9662 and BADGE, blocking caspase-3 and PARP cleavage. These data corroborated the work of Yamakawa-Karakida et al. [47], showing apoptosis in HL-60 cells in response to the PPARγ agonists 15-dPGJ_2 and troglitazone via caspase-3 activation. In addition, they found that PPARγ-dependent apoptosis in HL-60 cells is mediated by downregulating c-myc expression via blocking Tcf-4 activity, a transcription factor known to induce c-myc. PPARγ--mediated apoptosis in lymphocytes has been observed as well. Padilla et al. [32] provided evidence that PPARγ is expressed in primary B cells and B cell lymphomas. Stimulation of these cells with PPARγ agonists provoke apoptosis [31]. However, no PPARγ antagonist or PPARγ dominant negative mutants were used in this

study to prove the involvement of PPARγ. Therefore a PPARγ-independent mechanism cannot be completely excluded. This is different in T cells. There, PPARγ expression has been described by several groups. PPARγ is marginally expressed in resting T cells, but significantly induced in response to T cell activation. In T cells derived from peripheral blood of sepsis patients, PPARγ is significantly upregulated as well. These data support the assumption that PPARγ activation in T cells may cause cell death and concomitant T cell depletion in sepsis. Based on these PPARγ expression results, it is not surprising that T cells from sepsis patients were highly sensitive to PPARγ-dependent apoptosis. In these experiments, specificity of a PPARγ-dependent mechanism was confirmed using the PPARα agonist WY14643, which did not alter cell viability. In addition, the PPARγ antagonist SR-202 inhibited TZD-induced cell death in T cells, further supporting a PPARγ-dependent mechanism [40, 42]. These data suggested one pathway how T cells might be depleted during sepsis, which has been observed by several groups [19, 21, 29, 43]. T cell depletion might be one reason for the development of CARS and a concomitant possible second infection with its deleterious consequences.

CONCLUSION

Based on recent findings, the assumption that activation of PPARγ might be helpful in treating sepsis is strongly supported. Its anti-inflammatory property can terminate the first pro-inflammatory phase of sepsis (Fig. 3), thus not allowing a systemic inflammatory reaction to occur. However, in the second phase of sepsis, with its anti-inflammatory and probably desensitized characteristics, any loss of immune cells might be deleterious if a second infection develops or the first infection recurs (Fig. 3). Therefore, a possible impact of activated PPARγ should be considered as a contingent side effect of PPARγ agonist treatment. Further studies are required to finally elucidate the role of PPARγ-dependent apoptosis in the development of sepsis.

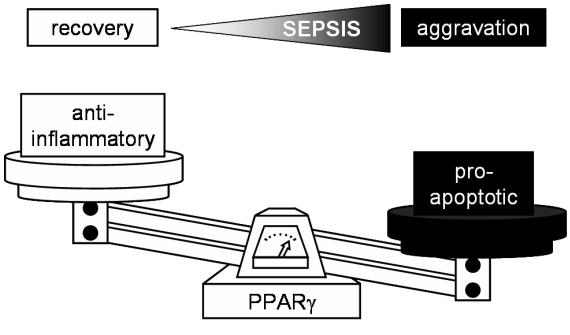

Fig. 3. The role of PPARγ in sepsis is ambiguous. Its anti-inflammatory impact seems to be beneficial in sepsis treatment, aiding at least in part in the patients recovery. In contrast, its possible pro-apoptotic role appears to be more deleterious, aggravating the patient's state of health.

REFERENCES

1. Abdelrahman M., Collin M. and Thiemermann C. (2004): The peroxisome proliferator-activated receptor-gamma ligand 15-deoxyDelta12,14 prostaglandin J2 reduces the organ injury in hemorrhagic shock. Shock, **22**, 555–561.
2. Annane D., Bellissant E. and Cavaillon J. M. (2005): Septic shock. Lancet, **365**, 63–78.
3. Appel S., Mirakaj V., Bringmann A., Weck M. M., Grunebach F. and Brossart P. (2005): PPAR-gamma agonists inhibit toll-like receptor-mediated activation of dendritic cells via the MAP kinase and NF-kappaB pathways. Blood, **106**, 3888–3894.
4. Beutler B. and Rietschel E. T. (2003): Innate immune sensing and its roots: the story of endotoxin. Nat. Rev. Immunol., **3**, 169–176.
5. Bodles A. M., Varma V. Yao-Borengasser A., Phanavanh B., Peterson C. A., McGehee R. E. Jr., Rasouli N., Wabitsch M. and Kern P. A. (2006): Pioglitazone induces apoptosis of macrophages in human adipose tissue. J. Lipid Res., **47**, 2080–2088.
6. Bone R.C., Fisher C. J. Jr., Clemmer T. P., Slotman G. J., Metz C. A. and Balk R. A. (1989): Sepsis syndrome: a valid clinical entity. Methylprednisolone Severe Sepsis Study Group. Crit. Care Med., **17**, 389–393.
7. Brun-Buisson C. (2000): The epidemiology of the systemic inflammatory response. Intensive Care Med., **26** (suppl. 1), S64–S74.
8. Buras J. A., Holzmann B. and Sitkovsky M. (2005): Animal models of sepsis: setting the stage. Nat. Rev. Drug Disc., **4**, 854–865.
9. Chen F., Wang M., O'Connor J. P., He M., Tripathi T. and Harrison L. E. (2003): Phosphorylation of PPARgamma via active ERK1/2 leads to its physical association with p65 and inhibition of NF-kappabeta. J. Cell. Biochem., **90**, 732–744.
10. Chen Y. C., Shen S. C. and Tsai S. H. (2005): Prostaglandin D(2) and J(2) induce apoptosis in human leukemia cells via activation of the caspase 3 cascade and production of reactive oxygen species. Biochim. Biophys. Acta, **1743**, 291–304.
11. Collin M. and Thiemermann C. (2003): The PPAR-gamma ligand 15-deoxy(delta12,14) prostaglandin J2 reduces the liver injury in endotoxic shock. Eur. J. Pharmacol., **476**, 257–258.
12. Collin M., Abdelrahman M. and Thiemermann C. (2004): Endogenous ligands of PPAR-gamma reduce the liver injury in haemorrhagic shock. Eur. J. Pharmacol., **486**, 233–235.
13. Desreumaux P., Dubuquoy L., Nutten S., Peuchmaur M., Englaro W., Schoonjans K., Derijard B., Desvergne B., Wahli W., Chambon P., Leibowitz M. D., Colombel J. F. and Auwerx J. (2001): Attenuation of colon inflammation through activators of the retinoid X receptor (RXR)/peroxisome proliferator-activated receptor gamma (PPARgamma) heterodimer. A basis for new therapeutic strategies. J. Exp. Med., **193**, 827–838.
14. Desvergne B., Michalik L. and Wahli W. (2006): Transcriptional regulation of metabolism. Physiol. Rev., **86**, 465–514.
15. Dhillon S. S., Mahadevan K., Bandi V., Zheng Z., Smith C. W. and Rumbaut R. E. (2005): Neutrophils, nitric oxide, and microvascular permeability in severe sepsis. Chest, **128**, 1706–1712.

16. Docke W. D., Randow F., Syrbe U., Krausch D., Asadullah K., Reinke P., Volk H. D. and Kox W. (1997): Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. Nat. Med., **3**, 678–681.
17. Fujihara M., Muroi M., Tanamoto K., Suzuki T., Azuma H. and Ikeda H. (2003): Molecular mechanisms of macrophage activation and deactivation by lipopolysaccharide: roles of the receptor complex. Pharmacol. Ther., **100**, 171–194.
18. Gupta R. A., Polk D. B., Krishna U., Israel D. A., Yan F., DuBois R. N. and Peek R. M. Jr. (2001): Activation of peroxisome proliferator-activated receptor gamma suppresses nuclear factor kappa B-mediated apoptosis induced by *Helicobacter pylori* in gastric epithelial cells. J. Biol. Chem., **276**, 31059–31066.
19. Hotchkiss R. S., Swanson P. E., Cobb J. P., Jacobson A., Buchmann J. G. and Karl I. E. (1997): Apoptois in lymphoid and parenchymal cells during sepsis: findings in normal T- and B-cell deficient mice. Crit. Care Med., **25**, 1298–1307.
20. Hotchkiss R. S. and Karl I. E. (2003): The pathophysiology and treatment of sepsis. N. Engl. J. Med., **348**, 138–150.
21. Hotchkiss R. S., Coopersmith C. M. and Karl I. E. (2005): Prevention of lymphocyte apoptosis - a potential treatment. Clin. Infect. Dis., **41** (suppl. 7), S465–S469.
22. Hunter P. (2006): Sepsis under siege: a new understanding of sepsis might lead to the development of therapies to treat septic shock. EMBO Rep., **7**, 667–669.
23. Johann A. M., von Knethen A., Lindemann D. and Brune B. (2006): Recognition of apoptotic cells by macrophages activates the peroxisome proliferator-activated receptor--gamma and attenuates the oxidative burst. Cell Death Differ., **13**, 1533–1540.
24. Joshi V. D., Kalvakolanu D. V. and Cross A. S. (2003): Simultaneous activation of apoptosis and inflammation in pathogenesis of septic shock: a hypothesis. FEBS Lett., **555**, 180–184.
25. Kaplan J. M., Cook J. A., Hake P. W., O'Connor M., Burroughs T. J. and Zingarelli B. (2005): 15-Deoxy--delta(12,14)-prostaglandin J(2) (15D-PGJ(2)), a peroxisome proliferator activated receptor gamma ligand, reduces tissue leukosequestration and mortality in endotoxic shock. Shock, **24**, 59–65.
26. Kodera Y., Takeyama K., Murayama A., Suzawa M., Masuhiro Y. and Kato S. (2000): Ligand type-specific interactions of peroxisome proliferator-activated receptor gamma with transcriptional coactivators. J. Biol. Chem., **275**, 33201–33204.
27. Li M., Pascual G. and Glass C. K. (2000): Peroxisome proliferator-activated receptor gamma-dependent repression of the inducible nitric oxide synthase gene. Mol. Cell. Biol., **20**, 4699–4707.
28. Martin G. S., Mannino D. M., Eaton S. and Moss M. (2003): The epidemiology of sepsis in the United States from 1979 through 2000. N. Engl. J. Med., **348**, 1546–1554.
29. Oberholzer C., Oberholzer A., Clare-Salzler M. Moldawer L. L. (2001): Apoptosis in sepsis: a new target for therapeutic exploration. FASEB J., **15**, 879–892.
30. Osuchowski M. F., Welch K., Siddiqui J. and Remick D. G. (2006): Circulating Cytokine/Inhibitor Profiles Reshape the Understanding of the SIRS/CARS Continuum in Sepsis and Predict Mortality. J. Immunol., **177**, 1967–1974.
31. Padilla J., Kaur K., Cao H. J., Smith T. J. and Phipps R. P. (2000): Peroxisome proliferator activator receptor-gamma agonists and 15-deoxy-Delta(12,14)-PGJ(2) induce apoptosis in normal and malignant B-lineage cells. J. Immunol., **165**, 6941–948.
32. Padilla J., Leung E. and Phipps R. P. (2002): Human B lymphocytes and B lymphomas express PPAR-gamma and are killed by PPAR-gamma agonists. Clin. Immunol., **103**, 22–33.
33. Pascual G., Fong A. L., Ogawa S., Gamliel A., Li A. C., Perissi V., Rose D. W., Willson T. M., Rosenfeld M. G. and Glass C. K. (2005): A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. Nature, **437**, 759–763.
34. Ricote M., Li A. C., Willson T. M., Kelly C. J. and Glass C. K. (1998): The peroxisome proliferator-activated receptor--gamma is a negative regulator of macrophage activation. Nature, **391,** 79–82.
35. Riedemann N. C., Guo R. F. and Ward P. A. (2003): The enigma of sepsis. J. Clin. Invest., **112**, 460–467.
36. Riedemann N. C., Guo R. F. and Ward P. A. (2003): Novel strategies for the treatment of sepsis. Nat. Med., **9**, 517–524.
37. Shipley J. M. and Waxman D. J. (2003): Down-regulation of STAT5b transcriptional activity by ligand-activated peroxisome proliferator-activated receptor (PPAR) alpha and PPARgamma. Mol. Pharmacol., **64**, 355–364.
38. Siddiqui A. M., Cui X., Wu R., Dong W., Zhou M., Hu M., Simms H. H. and Wang P. (2006): The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-gamma. Crit. Care Med., **34**, 1874–1882.
39. Singh S. and Evans T. W. (2006): Organ dysfunction during sepsis. Intensive Care Med., **32**, 349–360.
40. Soller M., Tautenhahn A., Brune B., Zacharowski K., John S., Link H. and von Knethen A. (2006): Peroxisome proliferator-activated receptor gamma contributes to T lymphocyte apoptosis during sepsis. J. Leukoc. Biol., **79**, 235–243.
41. Subbaramaiah K., Lin D. T., Hart J. C. and Dannenberg A. J. (2001): Peroxisome proliferator-activated receptor gamma ligands suppress the transcriptional activation of cyclooxygenase-2. Evidence for involvement of activator protein-1 and CREB-binding protein/p300. J. Biol. Chem., **276**, 12440–12448.
42. Tautenhahn A., Brune B. and von Knethen A. (2003): Activation-induced PPARgamma expression sensitizes primary human T cells toward apoptosis. J. Leukoc. Biol., **73**, 665–672.
43. Tinsley K. W., Chen S. L., Buchman T. G., Hui J. J., Karl I. E. and Hotchkiss R. S. (2000): Caspases-2, -3, -6, and -9, but not caspase-1, are activated in sepsis-induced thymocyte apoptosis. Shock, **13**, 1–7.
44. von Knethen A. and Brune B. (2001): Delayed activation of PPARgamma by LPS and IFN-gamma attenuates the oxidative burst in macrophages. FASEB J., **15**, 535–544.
45. Wang P., Anderson P. O., Chen S., Paulsson K. M., Sjogren H. O. and Li S. (2001): Inhibition of the transcription factors AP-1 and NF-kappaB in CD4 T cells by peroxisome proliferator-activated receptor gamma ligands. Int. Immunopharmacol., **1**, 803–812.
46. Wesche-Soldato D. E., Lomas-Neira J. L., Perl M., Jones L., Chung C. S. and Ayala A. (2005): The role and regulation of apoptosis in sepsis. J. Endotoxin Res., **11**, 375–382.
47. Yamakawa-Karakida N., Sugita K., Inukai T., Goi K., Nakamura M., Uno K., Sato H., Kagami K., Barker N. and Nakazawa S. (2002): Ligand activation of peroxisome proliferator-activated receptor gamma induces apoptosis of

leukemia cells by down-regulating the c-myc gene expression via blockade of the Tcf-4 activity. Cell Death Differ., **9**, 513–526.

48. Yang X. Y., Wang L. H., Chen T., Hodge D. R., Resau J. H., DaSilva L. and Farrar W. L. (2000): Activation of human T lymphocytes is inhibited by peroxisome proliferator-activated receptor gamma (PPARgamma) agonists. PPARgamma co-association with transcription factor NFAT. J. Biol. Chem., **275**, 4541–4544.
49. Yki-Jarvinen H. (2004): Thiazolidinediones. N. Engl. J. Med., **351**, 1106–1118.