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Liliane Michalik, Walter Wahli

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Involvement of PPAR nuclear receptors in tissue injury and wound repair

Liliane Michalik and Walter Wahli

Center for Integrative Genomics, National Research Centre "Frontiers in Genetics," University of Lausanne, Lausanne, Switzerland.

Tissue damage resulting from chemical, mechanical, and biological injury, or from interrupted blood flow and reperfusion, is often life threatening. The subsequent tissue response involves an intricate series of events including inflammation, oxidative stress, immune cell recruitment, and cell survival, proliferation, migration, and differentiation. In addition, fibrotic repair characterized by myofibroblast transdifferentiation and the deposition of ECM proteins is activated. Failure to initiate, maintain, or stop this repair program has dramatic consequences, such as cell death and associated tissue necrosis or carcinogenesis. In this sense, inflammation and oxidative stress, which are beneficial defense processes, can become harmful if they do not resolve in time. This repair program is largely based on rapid and specific changes in gene expression controlled by transcription factors that sense injury. PPARs are such factors and are activated by lipid mediators produced after wounding. Here we highlight advances in our understanding of PPAR action during tissue repair and discuss the potential for these nuclear receptors as therapeutic targets for tissue injury.

An overview of tissue injury

The clinical significance of tissue injury and the need for therapeutic agents to treat organ damage have called for an improved understanding of the causes of tissue injury and subsequent healing. The complex nature of these processes creates a challenge in identifying the specific cell types and biochemical pathways involved. Moreover, tissue protection and regeneration require tight control of cell survival and death, cell growth and differentiation, and ECM remodeling and breakdown. Chemical, biological, and mechanical stress is deleterious to epithelial tissue, and even whole organs are vulnerable to damage. For example, the liver, which metabolizes nutrients and drugs absorbed from the digestive tract, is particularly susceptible to injury, since all blood leaving the intestines and stomach must pass through it before reaching the rest of the body. Organ damage also occurs in response to an inadequate supply of oxygen (hypoxia), usually caused by blood vessel constriction or obstruction (ischemia). Under normal physiological conditions, oxygenation levels and sensitivity to hypoxia differ among the various organs. Since short periods of ischemia and reperfusion (ischemia/reperfusion, or I/R) cause extensive damage, the goal of the survival response is to maintain tissue viability. As a result, the hypoxia response requires optimal revascularization for efficient recovery.

Inflammation is a major component of early healing, and its control is essential for efficient repair. The inflammatory cytokines and eicosanoids produced during the first hours after injury recruit neutrophils and macrophages to the wound. These cells amplify the early response through their production of additional inflammatory mediators. Some of these factors promote cell proliferation and migration and are thus directly involved in wound closure. Others increase pain, delay wound healing, and promote

neovascularization (angiogenesis). A full understanding of these responses will help therapeutic interventions through the identification of molecular targets. Among such targets are transcription factors that control various pathways of cellular repair. In particular, PPARs have recently received attention for their protective and healing attributes. The PPAR agonists can be synthetic molecules, such as those used to treat hypertriglyceridemia (fibrates) and insulin resistance (thiazolidinediones), or natural ligands, such as fatty acids (FAs) and their derivatives (eicosanoids). Recent work has unveiled a variety of natural lipid-derived molecules that activate PPARs, but little is known about their action *in vivo*. Here we summarize the role of PPARs in repair of multistratified and single-cell-layer epithelia, and of injured organs.

PPAR involvement in healing stratified epithelia: skin wound healing as a model

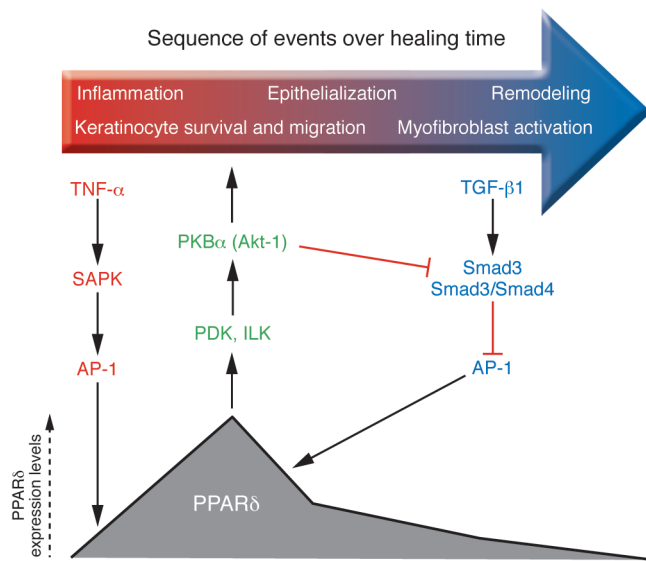
The epidermis is renewed continuously, and its integrity depends on a tightly regulated balance among cell proliferation, differentiation, and apoptosis. During its maturation, the epidermis evolves from a single layer of epithelial cells to a fully stratified and differentiated epithelium. The outermost layer of the epidermis, the stratum corneum, is the end product of keratinocyte differentiation and consists of a layer of cross-linked proteins and lipids, which functions as a barrier to transepidermal water loss and as a defense against physical damage, microbes, and xenobiotics. Several studies have examined the role of PPARs in this process.

No gross defect is seen in epidermal maturation in mice deficient in either PPAR α or PPAR δ (also called PPAR β). Similarly, PPAR γ -null mice born after placental rescue (to prevent lethal placenta maturation defects) show no alterations in epidermal maturation. These results suggest that epidermal maturation is PPAR independent. However, PPARs can stimulate keratinocyte differentiation (1–3). All 3 PPARs are undetectable in adult mouse interfollicular epidermis, but PPAR α and PPAR γ are found upon proliferative stimuli, such as at wound edges after an injury (1). PPAR α expression is only transiently increased after injury. Interestingly, the expression of PPAR α is upregulated by antiinflammatory glucocorticoids, which increase during injury (4, 5). The inhibitory

Nonstandard abbreviations used: AP-1, activator protein-1; ARF, acute renal failure; C/EBP, CCAAT/enhancer-binding protein; FA, fatty acid; HSC, hepatic stellate cell; I/R, ischemia/reperfusion; MCP-1, monocyte chemoattractant protein-1; PKB, protein kinase B; SCC, squamous cell carcinoma; TZD, thiazolidinedione.

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**Figure 1**

Dynamic control of PPAR δ expression after skin injury. Left: TNF- α released by injured epidermal keratinocytes activates stress-associated protein kinase (SAPK) and induces AP-1 binding to the PPAR δ promoter and transcription of PPAR δ target genes. TNF- α also triggers production of endogenous PPAR δ ligands, which activate PPAR δ in keratinocytes and macrophages. Center: PPAR δ activation helps maintain a sufficient number of keratinocytes for re-epithelialization by improving apoptosis resistance through expression of integrin-linked kinase (ILK) and 3-phosphoinositide-dependent kinase (PDK), as well as via activation of the PKB/Akt-1 survival pathway. Right: The initial inflammatory signals that stimulate PPAR δ are countered by TGF- β 1/Smad3-mediated suppression of PPAR δ in the late re-epithelialization/remodeling stage. This suppression occurs via Smad3/4 complex-mediated abrogation of AP-1 activity. In addition, TGF- β 1 released by dermal wound fibroblasts increases macrophage numbers and stimulates ECM production for wound remodeling. The diverse cell types and feedback signals regulating wound repair are discussed in detail in the text.

effect of PPAR α on NF- κ B action may create a negative feedback loop, which would explain the transient PPAR α expression that allows control of early inflammation (5).

Following tissue damage, injured cells release proinflammatory cytokines. These stimulate PPAR δ expression via stress-associated protein kinase/JNK-mediated activation of the activator protein-1 (AP-1) transcription complex (6). PPAR δ , which is activated by ligands whose production is also triggered by proinflammatory cytokines, then coordinates transcriptional upregulation of *integrin-linked kinase* and *3-phosphoinositide-dependent kinase* and repression of the *phosphatase and tensin homologue 10 (PTEN)*. As a consequence, the activity of protein kinase B α (PKB α , also known as Akt-1) is increased and apoptosis cascades are repressed (7). The resulting increased resistance to cell death helps to maintain a sufficient number of viable wound keratinocytes for re-epithelialization (Figure 1). Interestingly, PPAR δ -deficient keratinocytes exhibit a migration defect and reduced expression of the gelatinolytic enzyme MMP-9. Not surprisingly, PPAR δ -null mice exhibit delayed wound closure after an injury (1).

A balanced interplay among keratinocytes, dermal fibroblasts, and macrophages is critical for efficient wound healing. This process involves secretion of TGF- β 1 by dermal wound fibroblasts, leading to the recruitment of neutrophils and macrophages. These inflammatory cells secrete TNF- α and thereby sustain PPAR δ expression and ligand production in wound keratinocytes. After levels of PPAR δ peak, its promoter activity and expression levels fall for the remainder of the healing process because of TGF- β 1/Smad3-mediated reductions in AP-1 DNA binding (1, 8) (Figure 1). Additional mechanisms that repress PPAR δ promoter activity in mouse keratinocytes involve CCAAT/enhancer-binding protein- α (C/EBP α) and C/EBP β binding to a specific C/EBP response element, and histone deacetylation via histone deacetylase-1 (9). These regulatory controls suggest that expression of PPAR δ and C/EBPs in interfollicular and hair follicle keratinocytes is mutually exclusive.

Role of PPARs in different organs after I/R injury

PPARs in kidney I/R. The kidney is vulnerable to damage by toxins, infection, immune reactions, and ischemia. Acute renal failure (ARF) affects about 5% of hospitalized patients and carries a

high mortality. Damage to renal tubules alters epithelial cells and is accompanied by the shedding of cells into the tubule lumen and the back-leakage of glomerular filtrate, further increasing epithelial apoptosis and necrosis. Surviving cells participate in regeneration of the epithelium and restoration of renal function. The prognosis for ARF is complicated by secondary injuries induced by free radicals formed during I/R, although inadequate renal cortical-medullary reperfusion may be more deleterious (10). Today, there is no treatment for this devastating clinical syndrome.

A role for PPARs in reducing renal injury and dysfunction is established in animal models. PPAR α -null mice subjected to I/R injury by arterial ligation show enhanced cortical necrosis and impaired renal function (11). Conversely, induction of FA oxidation enzymes by PPAR α is thought to preserve kidney structure and function during renal I/R injury (11). In humans, nephrotoxicity is a common side effect of treatment with the antitumor agent cisplatin (12). In mice, PPAR α ligands attenuate cisplatin-induced ARF by preventing the inhibition of FA oxidation, reducing apoptosis and necrosis in the proximal tubule (13), and repressing inflammation via inhibition of NF- κ B binding activity, which attenuates neutrophil infiltration and cytokine/chemokine release (14).

Consistent with their defect in skin healing, PPAR δ -deficient mice exhibit greater kidney injury and dysfunction than wild-type counterparts after renal I/R. Conversely, wild-type mice pretreated with a PPAR δ ligand are protected from I/R damage, with a reduction in medullary necrosis, apoptosis, and inflammation. Cell culture studies show that PPAR δ ligands activate the PKB/Akt pathway, as they do in keratinocytes, and increase the spread of tubular epithelial cells. In vivo, these events may accelerate healing by suppressing tubular epithelial shedding and anoikis (15).

The PPAR γ agonists rosiglitazone and pioglitazone have protective effects against not only I/R, but also various kidney injuries including diabetic nephropathy, hypertensive nephropathy, experimental glomerulonephritis, and cyclosporine-induced renal injury (reviewed in refs. 16, 17). This protection reflects both improved glucose metabolism and insulin resistance as well as the antiinflammatory, antifibrotic, and antiapoptotic effects of PPAR γ ligands (18). The mechanisms underlying these beneficial properties are similar for synthetic agonists and the natural



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cyclopentenone prostaglandin 15d-PGJ2. The pathways involve inhibition of NF- κ B activation, together with reduced expression and/or activity of AP-1, TGF- β 1, monocyte chemoattractant protein-1 (MCP-1), ICAM-1, iNOS, fibronectin, and collagen I. The outcome of these signaling changes includes attenuated infiltration of polymorphonuclear cells into renal tissues, reducing oxidative stress and inflammation (19–23).

PPARs in lung I/R and fibrosis. Patients with end-stage pulmonary diseases are often treated with lung transplantation. Although improvements in techniques such as the preservation of vascular endothelium have significantly improved survival, I/R lung injury still occurs in over 20% of patients and remains the main cause of death during the first month after transplantation (24). Rodent models show that PPAR ligands, such as rosiglitazone and pioglitazone, can significantly attenuate I/R-induced lung injuries (17). Furthermore, treatment with the PPAR γ agonist pioglitazone before ischemia reduces I/R-induced lung damage in rats. The mechanism involves inhibition of proinflammatory cytokines (TNF- α , cytokine-induced neutrophil chemoattractant 1) and polymorphonuclear cell infiltration into the lung interstitium, resulting in reduced pulmonary edema (25). Similarly, in a murine I/R model, pretreatment with the PPAR γ agonist troglitazone prevents induction of the zinc finger transcription factor *early growth response gene-1 (Egr-1)*, a master switch for the inflammatory response in ischemic vessels. Thus, PPAR γ neutralizes the

potential for harm caused by Egr-1 target genes such as *IL-1 β* , *MCP-1*, and *macrophage inflammatory protein-2*. As a consequence of this protection, leukostasis is decreased, while oxygenation and overall survival are increased (26).

The term pulmonary fibrosis covers several life-threatening diseases for which no effective therapy exists. All have a similar pathology characterized by an immune response closely resembling a Th2-type phenotype, with proliferation and accumulation of myofibroblasts and excessive deposition of ECM proteins in the lung parenchyma. The clinical features are shortness of breath, evident diffuse pulmonary infiltrates, and varying degrees of inflammation and fibrosis (27). In humans, bleomycin treatment for cancer chemotherapy induces interstitial lung fibrosis (28). In human pulmonary fibroblast cultures, PPAR γ agonists interrupt the profibrotic effects of TGF- β (29). Similarly, mice subjected to intratracheal administration of bleomycin develop lung fibrosis, which is significantly reduced by PPAR γ agonists. As expected, this beneficial effect is attenuated by the PPAR γ antagonist bisphenol A diglycidyl ether (BADGE), suggesting that PPAR γ activity is required for protection (30).

PPARs in digestive tract I/R. Acute mesenteric ischemia, abdominal aortic aneurysm, hemorrhagic, traumatic, or septic shock, small bowel transplantation, and severe burns cause intestinal I/R, a severe condition characterized by endothelial cell swelling, capillary plugging, and mucosal barrier dysfunction (31). In rodent

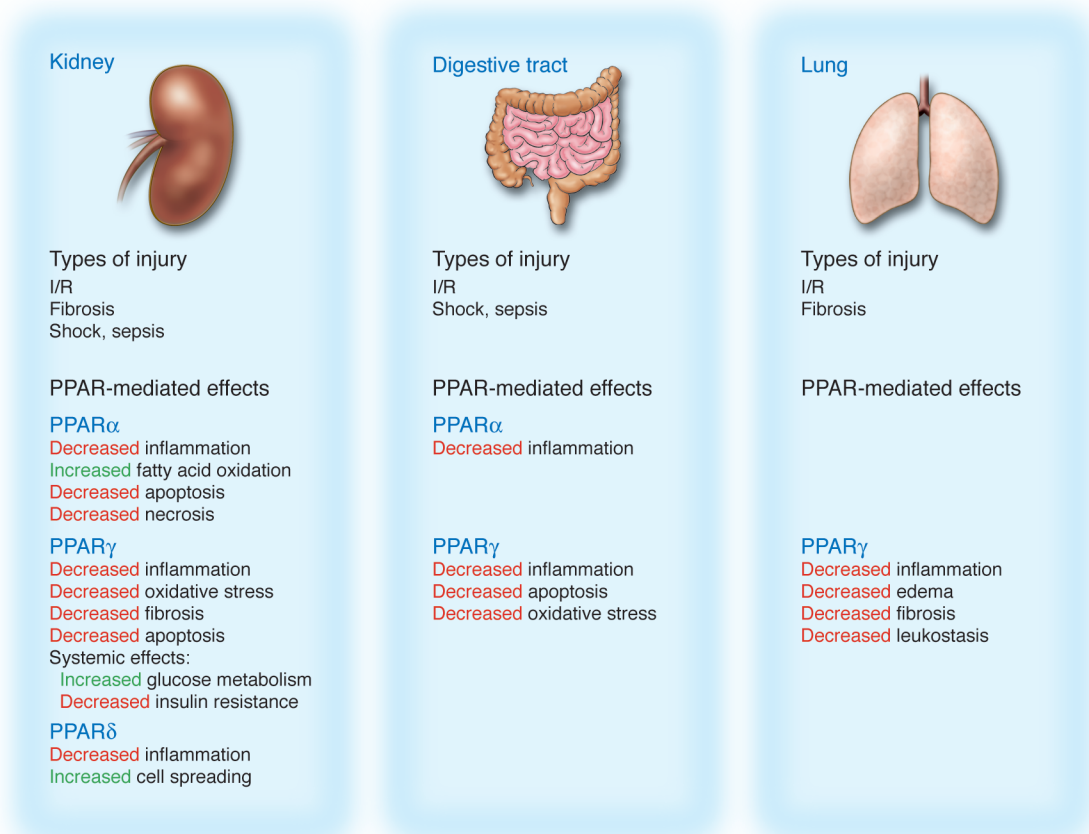


Figure 2

Epithelial repair pathways controlled by PPARs during kidney, digestive tract, and lung injury. Common to all tissue injury is a rapid increase in inflammation. PPAR activation, mediated by the binding of natural and synthetic ligands, restricts inflammation to prevent extensive tissue necrosis and chronic oxidative damage.



models of intestinal I/R injury, PPAR γ activation downregulates *TNF- α* and *ICAM-1* (probably via inhibition of NF- κ B), and pretreatment with a PPAR γ agonist before ischemia significantly reduces neutrophil infiltration (32, 33). These protective effects are attenuated by PPAR γ antagonists or reduction of PPAR γ levels in mutant PPAR γ heterozygous animals (32, 34). Similarly, activation of PPAR α attenuates I/R injury by reducing *ICAM-1* expression, peroxynitrite activity, and the production of proinflammatory cytokines (35). Additionally, enteral nutrition is beneficial when administered soon after severe gut I/R insults. For instance, the solute glutamine maintains small bowel function depending on cellular energetics and epithelial cell functions after I/R injury in rats. This effect is associated with PPAR γ induction and, logically, abrogated by a PPAR γ antagonist (36).

Evidence is also accumulating for a beneficial role of PPAR γ agonists in healing gastric mucosal damage associated with I/R in animal models (37–40). Activation of PPAR γ reduces gastric lesions and attenuates levels of lipid peroxidation, ICAM-1, TNF- α , COX-2, iNOS, and apoptosis after gastric I/R injury. As a result, PPAR γ alleviates oxidative injury and inflammation (here again the mechanism likely involves inhibition of NF- κ B). The protective and healing effects of all 3 PPAR isotypes on kidney, lung, and digestive tract epithelia after injury are summarized in Figure 2.

PPARs in liver injury (cirrhosis and fibrosis). Chronic liver disease remains an important cause of mortality and morbidity. Recurring or chronic injury and inflammation trigger tissue remodeling pathways that can lead to severe fibrosis and end-stage cirrhosis. Unfortunately, no effective treatment exists for these injuries except liver transplantation (41). The causes of liver fibrosis and cirrhosis include genetic abnormalities, toxic, alcoholic, and autoimmune-mediated damage, nonalcoholic steato-hepatitis associated with the metabolic syndrome, and viral hepatitis forms B and C. Liver fibrosis involves proliferation of myofibroblasts derived from hepatic stellate cells (HSCs, also called Ito cells or lipocytes). In the damaged areas, the transition of normally quiescent HSCs to proliferative myofibroblasts, through the action of cytokines and oxidative stress, increases ECM deposition. In the fibrotic and cirrhotic liver, matrix degradation by MMPs occurs but is restricted by tissue inhibitors of metalloproteinases (TIMPs). Encouraging results from experimental models suggest that fibrosis could be attenuated by enhancing apoptosis of stellate cells or blocking their transdifferentiation, as well as by manipulating the TIMP-MMP balance to facilitate matrix degradation and improve liver architecture (42).

PPAR γ agonists suppress the growth and fibrotic activity of HSCs by the downregulation of proteins such as α 1(I) collagen, fibronectin, α -SMAs, and MCP-1, which is consistent with reduced PPAR γ levels in transdifferentiated HSCs (43–46). Experimental overexpression of PPAR γ in myofibroblasts reverses their phenotype to quiescent cells, restores their ability to store retinyl esters, and represses activation markers such as α 1(I) procollagen and TGF- β 1 by suppressing AP-1 and nuclear factor-1 activities (47, 48). Interestingly, an analogy has been proposed between preadipocyte-adipocyte differentiation and HSC transdifferentiation. The high level of expression of adipogenic transcription factors in quiescent HSCs rapidly declines during their transdifferentiation to myofibroblastic HSCs. Similarly, treating these cells with an adipocyte differentiation “cocktail” or ectopic expression of SREBP-1c or PPAR γ reverts them to quiescent HSCs (49). The COX-2 inhibitor SC-236 attenuates liver inflammation and fibrosis through PPAR γ activation and downregulation of α -SMA expression and

MMP-2 and -9 activities, as well as by the induction of Kupffer cells and HSC apoptosis (50). In addition, ligands of the farnesoid X receptor stimulate expression of PPAR γ in HSCs and maintain its enhanced levels after injury, thereby promoting the antifibrotic action of PPAR γ agonists (51). In addition to their action on HSCs, PPAR γ ligands also reduce ductal proliferation and fibrosis after bile duct ligation in rats, showing that PPAR γ attenuates fibrosis through not only direct action on matrix-producing cells, but also modulation of the epithelial-mesenchymal interactions in chronic obstructive cholestasis (52).

The function of PPAR δ in fibrogenesis is less well studied, but PPAR δ expression is strongly induced after HSC activation. In a model of carbon tetrachloride-induced acute liver damage, PPAR δ activation induces HSC proliferation during early fibrogenesis and enhances expression of fibrotic markers (53). Thus, PPAR γ and PPAR δ appear to have antagonistic effects that require further investigation using PPAR γ - and PPAR δ -deficient mice. The possibility of manipulating the balance of PPAR γ and PPAR δ pharmacologically signifies a promising development for the attenuation of liver fibrosis. Future studies should improve our understanding of pathways regulating HSC survival, death, and clearance, leading to potential therapies to induce HSC apoptosis (41).

PPAR α ligands also have antifibrotic effects in the rat thioacetamide model of liver cirrhosis, probably via their antioxidant action associated with enhanced catalase expression and activity (54). Interestingly, in a mouse model of I/R, PPAR α regulates hepatic neutrophil accumulation and reduces iNOS expression after hepatocellular injury. This finding is important because activation of PPAR α in hepatocytes protects against oxidant injury, indicating that parenchymal cells might impact the inflammatory response (55). Finally, the function of PPAR α in liver regeneration after partial hepatectomy remains unclear. PPAR α is not necessary for compensatory hyperplasia induced by partial hepatectomy, yet PPAR α -dependent regulation of genes associated with cell cycle progression, cytokine signaling, and metabolic changes appears to be involved (56–59).

PPARs in ischemic brain injury and neurodegenerative disease. Brain injury resulting from insufficient blood (oxygen) supply can be transient (from syncope or ischemic attack) or permanent (from infarct or irreversible stroke). The latter is a major cause of disability and death in developed countries, and because of limited therapeutic strategies there is increasing interest in prophylactic pharmacological treatment (60). It was first observed that the fibrate gemfibrozil reduces stroke incidence in men with low HDL cholesterol and low LDL cholesterol who suffer from coronary heart disease (61). In mice this outcome is associated with improved endothelial relaxation, reduced brain oxidative stress, and decreased VCAM-1 and ICAM-1 expression and is thus independent of lipid metabolism (62). Similarly, the PPAR α and PPAR γ agonist resveratrol, a polyphenol found in grapes, protects the murine brain from stroke, in a PPAR α -dependent manner (63). Thus, PPAR α agonists may prevent or reduce the severity of ischemic stroke in humans. In rat hippocampal neurons, the PPAR α agonist Wy-14,463 induces peroxisomal proliferation that attenuates β -amyloid peptide-dependent neurotoxicity and decreases intraneuronal oxidative stress (64). In addition, PPAR γ ligands have neuroprotective effects in experimental models of ischemic injury, Alzheimer disease, multiple sclerosis, and autoimmune encephalomyelitis. The benefits result from suppressing inflammation (65–68). In addition, in a mouse model of amyotrophic lateral sclerosis for which neuro-

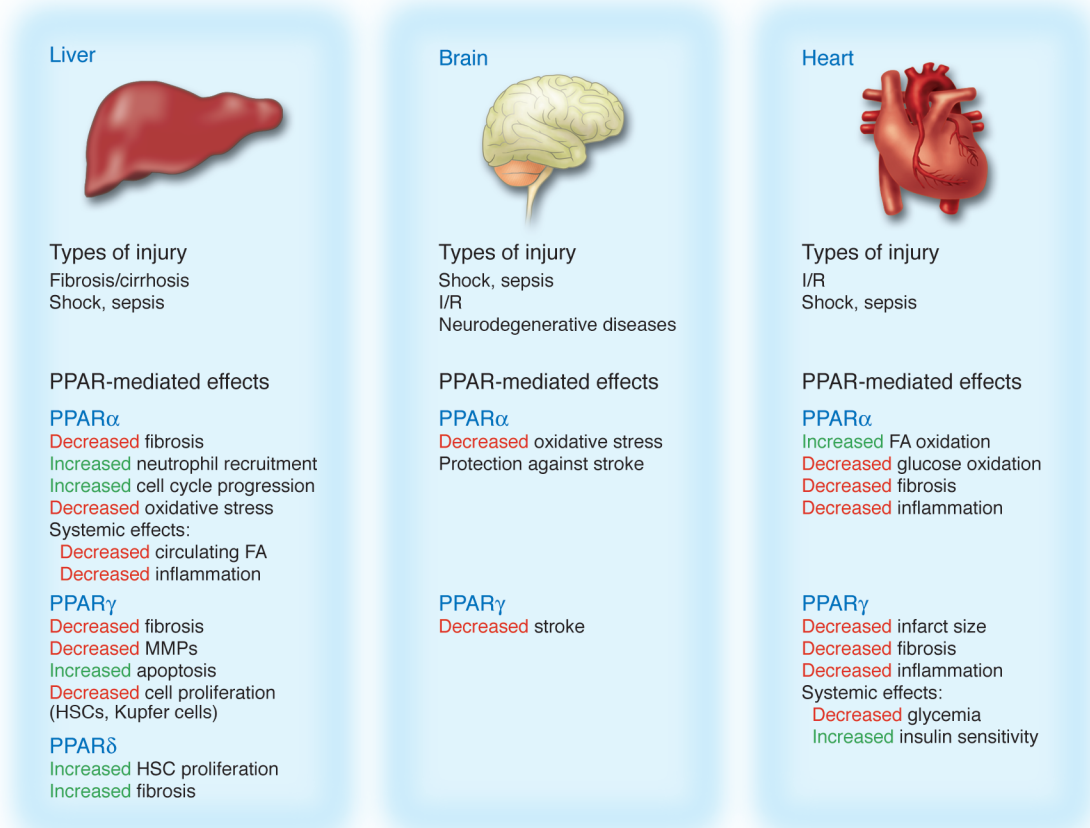


Figure 3 Role of PPARs in repair of liver, brain, and heart damage. Various systemic states such as shock or sepsis can lead to organ injury and failure. These injuries, as well as tissue-specific insults such as cirrhosis, fibrosis, and I/R injury, can be partially alleviated or prevented through the actions of PPARs.

inflammation may contribute to motor neuron death, the PPAR γ ligand pioglitazone improves muscle strength and body weight, delays disease onset, and increases lifespan (69).

PPARs in cardiac I/R. Myocardial I/R is a clinically relevant problem associated with reestablishment of blood flow by coronary bypass surgery, thrombolysis, and angioplasty, and with the need to minimize myocardial damage after heart infarct. Heart tissue normally uses FAs as the major energy source. However, hypoxia or pressure overload in the heart results in a substrate switch from FAs to glucose, caused by downregulation of PPAR α (70). It is thought that partial inhibition of FA oxidation improves the functional recovery of the heart during reperfusion (71). In support of this idea, experimental overexpression of PPAR α in the heart impairs cardiac recovery after ischemia (72). Thus, pharmacological treatments that stimulate glucose oxidation and repress FA oxidation appear to be beneficial for cardiac recovery (73). Along this line of thought, it has been proposed that downregulation of PPAR γ coactivator-1 and PPAR α may shift myocytes toward a more glycolytic metabolism (74). However, beneficial effects of PPAR α agonists on I/R damage have been reported as well (75–77). Experimentally, this contradiction could be resolved by determination of whether PPAR α agonists improve myocardial function via metabolic and antiinflammatory actions, and

whether cardiac overexpression of PPAR α has deleterious effects on the heart when circulating FA levels are high. Nevertheless, these observations suggest that cardiac PPAR α antagonism could be a therapy for treating I/R damage (72).

In healthy, diabetic, or obese animals (76, 78–82), PPAR γ agonists reduce myocardial infarct size. These effects are associated with increased glucose uptake and improved insulin sensitivity. In addition, PPAR γ agonists reduce postischemic myocardial apoptosis (83). However, the role of PPAR γ in heart failure is debated, particularly with regard to patients with type 2 diabetes mellitus. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study concluded that pioglitazone may improve cardiovascular outcome (84), while a retrospective cohort study suggested that thiazolidinediones (TZDs) may increase the risk of heart failure. Since type 2 diabetes patients are at increased risk of heart failure, those with underlying myocardial disease may be especially vulnerable to the effects of TZDs (85). Exacerbation of heart failure is documented in animal studies. TZDs are associated with increased post-myocardial infarction mortality in rats (86), and increased susceptibility to ventricular fibrillation during myocardial I/R in pigs (87). Finally, PPAR α or PPAR γ stimulation prevents or attenuates cardiac fibrosis by reducing endothelin-1, collagen type I, and MMP-1 production,



and by improving myocardial inflammation in anoxia/reoxygenation and pressure-overloaded hearts (88–91).

These experimental studies suggest that PPARs exert beneficial effects in reducing infarct size, myocardial reperfusion injury, and hypertrophic signaling and inflammatory responses. However, clinical applications have revealed some undesirable side effects, suggesting that TZDs should be used with caution in diabetic patients predisposed to heart failure (92). Obviously, there are uncertainties that require additional research (93). The protective effects of PPARs on liver, brain, and heart injury are summarized in Figure 3.

PPARs in shock and sepsis

Sepsis and shock are intrinsically complex, causing failure of multiple organs, including the gastrointestinal tract, kidneys, pancreas, heart, and brain. Since these conditions are a major cause of death in intensive care units, they are high-priority targets for new therapies. Mortality levels increase with the number of failed organs, reaching over 80% when dysfunction occurs in 4 or more organs (94). Preclinical studies have investigated the protective effects of activated PPARs against multiple-organ failure resulting from septicemic and hemorrhagic shocks. Several studies provide evidence for an amelioration through pharmacological treatment with 15d-PGJ2 of endotoxic shock induced in rodents by bacterial products such as LPS, and wall fragments of Gram-positive and Gram-negative bacteria (reviewed in refs. 95, 96). The 15d-PGJ2 likely counteracts the inflammatory response by activating PPAR γ , repressing NF- κ B, and enhancing the heat shock response (97). Evidence for direct involvement of PPAR γ in organ protection is provided by a reduction of the beneficial action of 15d-PGJ2 in the presence of the PPAR γ antagonist GW9662 (95). Similarly, pretreatment with the PPAR α agonist fenofibrate protects the endothelia in rabbit *E. coli* endotoxin-induced shock (98). Severe hemorrhage and subsequent resuscitation also causes multiorgan injury. A study in rats suggested that treatment with 15d-PGJ2 before hemorrhagic shock attenuates liver injury and kidney dysfunction, an effect that is reduced by GW9662 (99). Although none of these sepsis or shock models is ideal, they can improve our knowledge of disease mechanisms and help us identify patient populations that would most benefit from therapeutic trials (100).

PPARs in cancer

Wound healing after injury is a high-priority survival response. In this situation, epithelial cells change their intercellular contacts, modify their matrix, proliferate, and migrate over the wound. In addition, new blood vessels form rapidly. Interestingly, each of these healing behaviors is similarly involved in tumorigenesis and metastasis. As mentioned earlier, epithelia are highly susceptible to, and are efficient healers of, injury, which correlates with the observation that 95% of all cancer deaths are from epithelial tumors. This suggests that the repair mechanisms activated in response to injury may promote cancer if uncontrolled. Indeed, some tumors, especially those prone to metastasis, activate wound-healing genes (101). Although the PPARs may be involved in tumor-associated pathways, their regulation of wound-healing genes within specific tumor types remains largely unexplored (102).

Tumor development involves changes in noncancerous cells and tissues of the transformed mass, including activation of stromal cells, inflammation, and angiogenesis. As a result, these changes are popular targets for cancer therapy design. For example, as angio-

genesis is necessary for wound healing and tissue repair, inhibition of angiogenesis represents a promising feature of anticancer therapy. Indeed, PPAR γ agonists have received much attention in this field (reviewed in ref. 103). Surprisingly, although they upregulate VEGF in cultured cells, PPAR γ agonists such as 15d-PGJ2, pioglitazone, rosiglitazone, ciglitazone, and BRL49653 are potent angiogenesis inhibitors. These data are obtained from in vitro and in vivo models (104–108). Several direct and indirect actions of PPAR γ ligands are reported in these studies, such as decreased VEGF-C and angiogenic chemokine production by tumor cells, inhibition of urokinase plasminogen activator, reduction of VEGF receptors 1 (Flt-1) and 2 (fetal liver kinase-1/KDR), increased plasminogen activator inhibitor type 1, and inhibition of tube formation (reviewed in ref. 103). In addition, PPAR γ agonists downregulate leptin gene expression and block leptin-induced endothelial cell migration by inhibiting Akt and iNOS (109, 110). Unfortunately, PPAR γ involvement is not yet validated by gene deletion or antagonists. Finally, PPAR γ upregulates expression of several fibrinogen/angiopoietin-related proteins (111–113). Although the function of these proteins in angiogenesis is unclear, they share structural homologies with angiopoietins, a family of proteins with roles in vascular development. Much less is known about the effects of PPAR α and PPAR δ . The PPAR α agonist fenofibrate inhibits capillary tube formation in vitro and angiogenesis in vivo. The mechanism involves disorganization of the actin cytoskeleton with decreased bFGF-induced Akt activity and COX-2 gene expression (114). Fenofibrate also inhibits constrictive remodeling after angioplasty through repression of inflammation and neovascularization (115). Like PPAR γ , PPAR α controls expression of a protein known as fasting-induced adipose factor/angiopoietin-like protein (FIAF) (111). A study of 35 individuals found that microvessel density among PPAR δ -immunoreactive squamous cell carcinomas (SCCs) was higher than that of nonreactive SCCs (116), consistent with an association between VEGF and PPAR δ in head and neck SCCs (117). PPAR δ may also be involved in vascular development via modulation of the angiogenesis-associated PKB α /Akt-1 pathway (7, 118). Together, these results suggest that the PPAR α and PPAR γ agonists already used in clinics may be harnessed for angiogenic diseases.

Conclusions

PPARs are major regulators of lipid, glucose, and amino acid metabolism. Here we have presented some of their less well known functions in tissue protection and repair. A majority of the studies reviewed herein are descriptive, and even the use of specific ligands does not necessarily distinguish between PPAR isotypes or between PPAR-dependent and -independent mechanisms. However, collectively, the studies have improved our understanding of the role of PPARs in healing. Their actions are simultaneously systemic and cellular. Systemic effects are antiinflammatory, antioxidant, and metabolic, such as the normalization of circulating lipids and insulin resistance. During the early postinjury inflammatory phase, lipoxygenases and cyclooxygenases stimulate production of PPAR ligands. Indeed, perhaps the most striking action of PPARs is the control of inflammation, an event first observed 10 years ago (119). Inhibition of the NF- κ B pathway appears to be central to this process.

Although protective against infections, the inflammatory milieu is a hostile environment for resident host cells at the injury site. This insult is abrogated by the antiapoptotic role of PPAR δ . These PPAR δ effects are best described in skin repair, where PKB α /Akt-1



activity is central. Fibroblasts in inflamed wound areas further support healing. These cells transdifferentiate to activated myofibroblasts with elevated α -SMA expression and contractility to constrict the exposed wound surface. They secrete growth factors, inflammatory cytokines, and ECM components that provide a scaffold for migration of epithelial cells (120). Chronic injury, repetitive injury-repair cycles, or failure to shut off the healing signals leads to fibrosis, during which there are antagonistic actions of PPAR γ and PPAR δ . PPAR γ sustains fibroblast quiescence and promotes the reversal of myofibroblasts to quiescent cells, while PPAR δ expression is high in differentiated myofibroblasts (although its functions are unclear). After skin injury, the interaction of PPAR and TGF- β 1 pathways is indispensable for spatiotemporal control of the repair program, suggesting a role for PPARs in fibrosis. Studies to determine how PPAR pathways communicate with TGF- β 1, angiotensin II, leptin, and endothelin pathways may inspire novel therapeutic strategies for tissue fibrosis (121–124).

A recurrent observation in wound-healing studies is the protective effect of PPAR ligands. Today, the precise nature and function of natural lipid activators of PPARs in repair are unclear. This knowledge should assist the development of truly selective drugs to augment or antagonize PPAR action according to the desired cellular response. In terms of PPAR biology and pharmacology, the acute conditions described herein are quite distinct from the chronic metabolic disorders for which PPAR agonist use is already established. A collective effort is required to translate promising

basic-science data on PPAR-mediated tissue repair into clinical application for acute injuries. As discussed above, short-term preconditioning strategies with PPAR agonists can be protective in animal models. Thus, PPARs appear to have potential as new strategies for injury prevention or preconditioning, and as targets for syndromes with high morbidity and mortality rates. Finally, tissue repair activates ECM remodeling, cell proliferation, migration, and angiogenesis pathways essential for not only normal tissue development but also cancer invasion and metastasis (101, 125). Identifying the distinct signals that trigger or block gene expression during the wound response will improve our understanding of tissue repair, fibrosis, organogenesis, and oncogenesis.

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Address correspondence to: Walter Wahli or Liliane Michalik, Center for Integrative Genomics, University of Lausanne, Le Genopode, CH-1015 Lausanne, Switzerland. Phone: 41-21-692-41-10; Fax: 41-21-692-41-15; E-mail: walter.wahli@unil.ch (W. Wahli). Phone: 41-21-692-41-47; Fax: 41-21-692-41-15; E-mail: liliane.michalik@unil.ch (L. Michalik).

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