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Pleiotropic role of PPARγ in Intracerebral Hemorrhage: An Intricate System involving Nrf2, RXR and NF-κB

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Abstract

Intracerebral hemorrhage (ICH) is a subtype of stroke involving formation of hematoma within brain parenchyma, which accounts for 8–15% of all strokes in Western societies and 20–30% among Asian populations, and has a one-year mortality rate greater than 50%. The high mortality and severe morbidity make ICH a major public health problem. Only a few evidence-based targeted treatments are used for ICH management, and interventions focus primarily on supportive care and comorbidity prevention. Even in patients who survive the ictus, extravasated blood (including plasma components) and subsequent intra-hematoma hemolytic products trigger a series of adverse events within the brain parenchyma, leading to secondary brain injury, edema and severe neurological deficits or death. Although the hematoma in humans gradually resolves within months, full restoration of neurologic function can be slow and often incomplete, leaving survivors with devastating neurological deficits.

During past years, peroxisome proliferator-activated receptor gamma (PPARγ) transcription factor and its agonists received recognition as important players in regulating not only glucose and lipid metabolism (which underlies its therapeutic effect in type 2 diabetes mellitus), and more recently, as an instrumental pleiotropic regulator of anti-inflammation, anti-oxidative regulation, and phagocyte-mediated cleanup processes. PPARγ agonists have emerged as potential therapeutic target for stroke. The use of PPARγ as a therapeutic target appears to have particularly strong compatibility toward pathogenic components of ICH. In addition to its direct genomic effect, PPARγ may interact with transcription factor, NF-κB, which may underlie many aspects of the anti-inflammatory effect of PPARγ. Furthermore, PPARγ appears to regulate expression of Nrf2, another transcription factor and master regulator of detoxification and anti-oxidative regulation. Finally, the synergistic co-stimulation of PPARγ and retinoid X receptor, RXR, may play an additional role in the therapeutic modulation of PPARγ function. In this article, we outline the main components of the role of PPARγ in ICH pathogenesis.

Intracerebral Hemorrhage Pathobiology and PPARγ

Intracerebral hemorrhage (**ICH**) accounts for 8–15% of all strokes in Western societies and 20–30% among Asian populations with a one-year mortality rate greater than 50–

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60%[1,2,3,4]. Despite advances in the field of stroke and neurocritical care, the 30-day mortality has not changed significantly over the past two decades. The therapeutic interventions that are currently available focus primarily on supportive care and comorbidity management and prevention[5,6,7]. Even in patients who survive the acute ictus (resulting in mass effect and increased intracranial pressure and primary brain injury[8,9]), the extravasated blood and, subsequently, the hemolytic products trigger a series of adverse events within brain parenchyma, causing secondary brain injury, edema and neurological deficits[4,10,11,12,13,14]. Only half of ICH-related deaths occur in the first 2 days after ICH onset[15], strongly pointing at the unique role of secondary brain injury in development of delayed mortality. It is generally accepted that the delayed aspect of ICH injury is multifactorial and, at least in part, is related to hematoma toxicity[16,17,18,19,20], the presence of noxious cellular debris and robust inflammation[11,21,22]. Hemolytic products such as hemoglobin (**Hb**) and its catabolic by-products (heme and iron), free radical formation (notably through iron involving Fenton-type mechanism), thrombin, metalloproteinases, complement (and other proteases), formation of oxy-modified lipid mediators, and excitotoxicity are generally listed as central components of the delayed damage after ICH[10,23,24,25,26,27]. Although the hematoma in humans gradually resolves within months, restoration of neurological function is slow and most often incomplete, and the neurological deficits can be devastating. Therefore, management of hematoma stability (e.g. preventing re-bleeding) during the acute phase followed by the control of timely clearance of hematoma-deposited blood components (to speed up hematoma resolution) may represent unique targets for the treatment of ICH[28,29,30].

The peroxisome proliferator-activated receptors (PPARs), including α, γ, and δ/β are encoded by separate genes and are members of a type II nuclear hormone receptor superfamily of ligand-activated nuclear transcription factors[31,32]. Three different PPARγ transcripts (PPARγ 1, 2 and 3), each a derivative of the PPARγ gene through differential promoter usage[33,34], have been identified. While PPARγ 2 is the isoform primarily expressed in adipose tissue, PPARγ 1 has a broader tissue distribution including presence in the brain[33,35]. The PPARγ regulates target gene expression by binding to conserved DNA sequences termed *peroxisome-proliferator response elements* (PPREs), as heterodimers with the retinoic acid receptor (RXR)[36,37]. PPARγ functions as a therapeutic target for the treatment of metabolic disorders, e.g., diabetes[32,38,39]. Phosphorylation of serine 112 at the N-terminus of PPARγ2 by MAP kinase and SUMOylation was suggested to regulate its transcriptional activities[40,41]. The ligands for PPARγ include oxidized fatty acids, monounsaturated- and, polyunsaturated- fatty acids such as oleic acid or linoleic acid[42], non-steroidal anti-inflammatory drugs[43], 15deoxy-$\Delta^{12,14}$-Prostaglandin J_2 (15d–PGJ2) [44], and a class of compounds, the thiazolidinediones (TZDs)[45]. The PPARγ receptor subtype was originally characterized in adipose tissue as an important regulator of the expression of various key enzymes involved in glucose and lipid metabolism to regulate efficient energy storage[32,38,39]. Through selective activation of PPARγ, the TZDs control insulin sensitivity [44,46]. Two of the TZDs, pioglitazone and rosiglitazone, are approved by the FDA for treatment of diabetes mellitus type 2 (DM2). It is important to stress that these drugs do not change blood insulin levels; rather they make cells more sensitive to its effect.

In response to stroke, it appears that PPARγ mRNA is robustly upregulated in the affected brain tissue, suggesting that the endogenous system is attempting to activate PPARγ pathway via increasing PPARγ transcript [47,48]. While immunohistochemistry confirm that PPARγ protein is increased in the ischemia-affected hemisphere, it seems that the PPARγ DNA binding and PPARγ gene-target expression in this region is not increased, unless animals are treated with PPARγ activator[48]. This may suggest that following brain injury the endogenous activators of PPARγ are not available or in deficit, and that the whole system requires exogenous agonist to activate the PPARγ pathway.

Intracerebral hemorrhage, primarily in the case of large hematomas, could lead to alteration in cerebral perfusion in proximity to the hematoma [49,50]. While, generally, no support exists for direct ischemic penumbra in ICH-affected tissue [50,51], it is likely that even modestly reduced perfusion at the hematoma site in combination with local hypermetabolism [52] (an event demonstrated in the brain in response to intracerebral injection of hemolysates), could lead to restricted cellular injury. PPARγ agonists, by controlling expression of the glucose transporter GLUT-3 [53], could improve glucose utilization and local metabolism and, as such, contribute to cytoprotection after ICH. In addition, the arcuate nucleus, an energy homeostasis and glucose metabolism control center in the brain, contains many neurons that show high expression of PPARγ [54], suggesting a potential role of PPARγ agonists in regulating metabolism by also affecting hypothalamic functions.

Later work on PPARγ noted that PPARγ plays important roles in regulating anti-oxidative processes and inflammation[55]. It is the anti-inflammatory properties of PPARγ ligands that ultimately brought additional attention to the whole class of PPARγ agents [56,57,58,59,60,61,62]. As a transcription factor with pleotropic mechanism of action, in terms of neurological conditions[59], PPARγ was suggested to play important roles in the pathogenesis of Alzheimer's disease[63,64], Parkinson's disease and neurodegenerative disorders[65,66], multiple sclerosis[67,68], ischemic stroke[47,69,70,71,72], neurotrauma and spinal cord injury[73,74,75,76], and ICH[77,78]. In studies with tissue culture and other injury models, it became clear that PPARγ is protective not only to neurons[47,72,79], astrocytes[80,81], oligodendrocytes[82], endothelia[83], but also to microglia/macrophages (**MMΦ**)[78,84,85,86]. Among many potential mechanisms of action, the beneficial effects of PPARγ agonists are proposed to be due to: (i) the suppression of pro-inflammatory mediators, in part by interference with nuclear factor kappa B (NF-κB)[87,88,89], (ii) the upregulation of anti-oxidant enzymes including CuZn-superoxide dismutase (**SOD**) and catalase[78,90], (iii) the inhibition of excitotoxicity[91,92], and (iv) the promotion of microglia/macrophage-mediated clearance of toxic cellular debris via mechanism involving upregulation of scavenger receptor CD36 expression[78,93,94,95] or (iv) modification of neutrophil phenotype[61].

In this paper, we will focus primarily on the role of PPARγ in ICH. We will discuss the interactions of PPARγ with nuclear factor erythroid 2-related factor (**Nrf2;** a master regulator of oxidative responses) and NF-κB signaling pathways pertaining to regulation of pro- and anti-inflammatory responses. We will describe a synergistic activation of PPARγ when retinoid X receptor alpha (**RXRα**) and PPARγ are co-activated to achieve optimal

cytoprotection and endogenous cleanup function - the clearance of hematoma-deposited blood components by brain MMΦ after ICH.

PPARγ and Catalase - implication in ICH pathogenesis

The TZDs (e.g. ciglitazone, pioglitazone and rosiglitazone) and cyclopentanone prostaglandins (e.g. 15d–PGJ2) are PPARγ agonists which have been proven to act as potent and safe pro-survival factors for primary neurons subjected to either excitotoxic insult, oxygen-glucose deprivation (OGD) or H2O2-induced oxidative stress. The exact mechanism behind this protective mechanism is not fully known, but one of several potential candidates is a PPARγ-mediated induction of potent anti-oxidative enzymes, such as superoxide dismutase[72,96] and catalase[72,74,97]. Catalase is a well-known gene target for PPARγ[98] and administration of PPARγ agonist, e.g. 15d–PGJ2, after ICH was demonstrated to rapidly induce catalase production in the affected brain[77,78]. This boost in production of anti-oxidative enzymes could be of particular importance for brain cells after ICH, since it was reported that hemoglobin lysis products (a protocol mimicking hematoma environment) reduce tissue levels of free-radical decomposing enzymes[99,100,101]. Catalase is a large homotetrameric protein that is highly abundant in the peroxisome (the membrane-enclosed small organelles that houses various oxidation reactions, in which toxic peroxides are generated as side products), where it serves to protect the cells from the toxic effects of H2O2 by catalyzing its decomposition into O_2 and H_2O ($2H_2O_2$ O_2 + $2H_2O$) without generating free radicals. Interestingly, catalase activity in the brain, as compared with other tissue (e.g. heart, kidney, liver or lung), is relatively low[102]. In response to PPARγ agonist, catalase expression rapidly increased in the ICH-affected brain, demonstrating two temporal peaks with differential spatial distribution. The first peak reflects, primarily, induction of catalase expression in the ICH-affected neurons (as early as 1h after ICH and sustained at higher levels for 6∼24h[77]).The second peak is mainly associated with the catalase induction in MMΦ (appeared 3∼7 days, unpublished data). The rapid catalase production by neurons may likely reflect an adaptive response aimed at improving the H_2O_2 buffering capacity of neurons and is linked to direct neuroprotection. On the other hand, the upregulation of catalase in MMΦ could facilitate effective phagocytosis-mediated cleanup functions by preventing self-injury to MMΦ. During phagocytosis MMΦ generate high levels of pro-oxidative molecules that, unless neutralized by the MMΦ, may adversely affect phagocytes themselves, as well as other perihematomal brain cells[74,78]. Although the benefits of cytoprotective approaches to reduce damage to neurons, oligodendroglia, astroglia or endothelium have been frequently discussed, the benefits of protecting the phagocytes (MMΦ) from damage at the brain injury site have been seldom addressed. In our ongoing research, subjecting primary microglia to “ICH-like” (hemolytic products plus mild OGD) injury or high (>50 μM) levels of H_2O_2 in our hands induced significant morphologic and functional damage indicating that these cells can suffer from damage similar to other brain cells. Pre-incubating the microglia with PPARγ activators improves the expression of anti-oxidative enzymes and microglia’s resistance to H_2O_2 or “ICH-like” injury[78] and could increase resistance to ICH-like damage.

PPARγ and phagocytosis-mediated hematoma resolution

The hematoma size after ICH not only predicts the magnitude of mass effect and direct physical injury, but it also reflects the volume of toxic blood breakdown products, which is the cause of “chemical” secondary damage, deposited in the brain. The larger hematomas may require more time for their resolution (blood clearance) and as such may inflict damage to the surrounding brain tissue (or to impair its repair) for a longer duration of time. Thus, it is not surprising that hematoma size is one of the strongest predictors of poor outcome [103,104]. Based on this assumption several clinical trials targeting surgical hematoma evacuation were initiated [105,106,107,108]. While the overall outcome of these studies is generally neutral, some potentially promising results were seen in patients with superficial lobar hematomas without intraventricular hemorrhage [109,110]. Also, in patients subjected to minimally invasive hematoma evacuation surgery plus rt-PA during hematoma evacuation (MISTIE trial) the procedure was associated with significant reduction in perihematomal edema[107]. These suggest that under circumstances when invasiveness of the surgical approaches are low (e.g. manipulations with superficial aspects of the brain or wash out of blood with the assistance of thrombolytic rt-PA vs. application of pressure suction), the clearance of blood from the brain could be beneficial. While surgical approaches to remove blood clots continue to be evaluated, a new concept of non-surgical approaches to assist blood cleanup through promoting the endogenous microglia/macrophages-mediated phagocytosis are being tested[18]. Normally, depending on the hematoma size, the blood clearance from the brain occurs naturally in 2–4 weeks in rodents[78,111]. Our recent studies indicated that activating PPARγ in microglia/macrophages results in upregulation of expression of CD36, a cell membrane protein, which plays an essential role in phagocytosis-mediated hematoma cleanup after ICH[12].

CD36, a type II scavenger receptor, has been shown to act as a receptor for phosphatidyl serine, thrombospondin and oxidized lipids; in addition, it mediates internalization/phagocytosis of brain apoptotic cells[112,113,114], sickled/asymmetric/dislocated red blood cells (**RBC**)[78,94,115] and apoptotic neutrophils[116,117,118]. Interestingly, expression of this phagocytosis-aiding protein is under transcriptional control of PPARγ[119], so that its expression could effectively be upregulated pharmacologically by PPARγ agonists and inhibited by selective PPARγ antagonists[120,121,122]. In agreement with this notion, administration of PPARγ activators can efficiently increase expression of CD36 by microglia and improve phagocytosis of RBC, thus promoting hematoma resolution in animal models of ICH[18,78]. This cleanup-aiding function of CD36 and PPARγ was suggested earlier based on findings that deficiency of CD36 in macrophages due to genetic deletion of PPARγ, led to delayed uptake of oxidized low-density lipoprotein (oxLDL) by macrophages and aggravated atherosclerotic lesions[119,123,124]. Thus, CD36 upregulation in MMΦ in response to PPARγ activation may ensure a more efficient interaction between MMΦ and their phagocytosis targets for a timely clearance. This line of research prompted us to launch a clinical trial with pioglitazone in ICH patients[108]. The underlying hypothesis is that pioglitazone through PPARγ activation will assist the enhancement of the endogenous cleanup process and anti-oxidative defense, as well as amelioration of pro-inflammatory responses that altogether will inhibit secondary damage caused by ICH.

PPARγ and two faces of inflammation

After ICH, phagocytosis-mediated clearance of apoptotic or damaged cells and dislocated blood components by MMΦ is believed to play a beneficial role by minimizing the exposure of the brain tissue to this toxic and pro-inflammatory milieu [125,126]. Engulfment of apoptotic cells by MMΦ was proposed to actively suppress production of pro-inflammatory mediators by the phagocyte through promoting release of anti-inflammatory mediators, such as transforming growth factors (TGF-β) and IL-10[127,128,129]. Although clearance of hematoma by MMΦ is necessary to achieve elimination of the hematoma, a source of inflammation, the deleterious molecules generated by MMΦ during phagocytosis could injure the neurovascular component of the brain (e.g. neuron, oligodendrocyte, endothelium), and also the phagocytes themselves[11,130,131]. The main deleterious components of this process include: (i) increased release of pro-inflammatory mediators (e.g. IL-1β, TNFα), (ii) activation of pro-inflammatory transcription factor NF-κB and increased expression of pro-inflammatory enzymes (e.g. iNOS, COX-2), (iii) increased synthesis and release of proteinases (e.g. MMP9), (iv) acidification of the environment, and (v) generation of free radicals. These responses are, in part, the reason why in an attempt to control inflammation after ICH, many studies focused on how to reduce microglia/macrophage activation and/or their phagocytosis function. However, as indicated above, phagocytosis is necessary for clearance of the hematoma[18,108]. Thus, it is necessary to find ways to tune-up the phagocytosis process, so that effective clearance can be generated under conditions that have minimal adverse effect to the surrounding brain tissue.

The anti-inflammatory role of PPARγ in ICH appears to be significant. Many studies using PPARγ activators showed a robust reduction in expression of pro-inflammatory mediators (TNF-α, IL-1β, iNOS, MMP9) in MMΦ with concurrently increased expression of anti-inflammatory cytokines (TGF-β and IL-10)[59,78,89,132,133]. In rat primary microglia in culture, PPARγ agonists not only increased microglia-mediated phagocytosis of RBC, but also reduced the production of H_2O_2 during the process of engulfment[78]. Treatment with PPARγ agonist is associated with increased production of anti-oxidative defense system enzymes such as catalase and superoxide dismutase that may explain reduced pro-oxidative responses in cells with activated PPARγ[72,74,77,78]. It appears that prevention of oxidative stress is obligatory in allowing microglia to show optimal cleanup capacity. We have demonstrated that exogenous application of catalase to primary microglia in culture can enhance internalization of RBC by these cells, suggesting that a self-protective mechanism (anti-oxidative defense) from the excessive oxidative stress is critical to ensure MMΦ survival and efficient clean-up function. Interestingly, one of key important gene targets of PPARγ is CD36. As mentioned above, PPARγ-induced CD36 expression may play an important role in stimulating phagocytotic efficacy of microglia[78]. While the process of phagocytosis is overall beneficial from the point of removal of toxic and pro-inflammatory cellular debris, it is well-recognized that microglia-mediated scavenging activities are associated with generation of massive amount of pro-oxidants[134] which could adversely affect surrounding brain cells. As such, it is intriguing to note the same transcription factor (PPARγ) not only up-regulates genes associated with enhanced phagocytosis (e.g. CD36), but also simultaneously up-regulates anti-oxidative genes (e.g.

catalase) that permit more effective neutralization of oxidative stress associated with more robust scavenging activities. Interestingly, this cooperative generation of CD36 and anti-oxidative enzyme exists not only for PPARγ. In our ongoing research (unpublished results), we have determined that Nrf2, a transcription factor considered a master regulator of cellular anti-oxidative defense, is also capable of inducing CD36 expression in microglia. These findings strongly suggest that for optimal function of CD36 in hematoma resolution (and likely cleanup after ischemic stroke), the anti-oxidative defense system needs to be enhanced to eliminate the deleterious consequences (oxidative damage) associated with CD36-mediated phagocytosis/endocytosis.

Lastly, it should be mentioned that PPARγ is proposed to act as a signaling molecule downstream from the IL-4 receptor; a pathway that has a key role in an alternative activation of MMΦ [135,136,137], which results in formation of a “healing” trophic phenotype of MMΦ. In our ongoing research, we have established that IL-4 is generated locally in the brain and via IL-4 receptor activates STAT6 and PPARγ signaling leading to reduction of pro-inflammatory and induction of anti-inflammatory phenotype of microglia after stroke.

Taken together, PPARγ may benefit the inflammation in ICH by directly down-regulating the production of pro-inflammatory mediators and up-regulating anti-inflammatory mediators. This is in addition to its role in hematoma clearance, the process that leads to removal of the toxic and pro-inflammatory debris from the intraparenchymal tissue.

PPARγ activation and interaction of PPARγ and RXR

PPARγ and RXR, both are ligand-dependent pleiotropic transcription factors belonging to the nuclear hormone receptor family. Upon dimerization, PPARγ-RXR as “partners” regulate target gene expression by binding to conserved DNA sequences, PPRE[38]. There are three RXR isotypes, RXRα (NR2B1), RXRβ (NR2B2), and RXRγ (NR2B3), which have considerable tissue-specific differences in their expression[138] and are present in various cells of brain tissue[139]. The PPARγ-RXR heterodimer complex can be activated either by PPARγ ligands (e.g. TZD or 15d–PGJ2) and/or by RXR ligands (e.g. 9-*cis* retinoic acid) [140]; however, the occupancy of both (PPARγ plus RXR) ligand binding domains simultaneously could provide maximal receptor activity[32,141,142,143]. It is necessary to acknowledge that when comparing PPARγ activation in response to RXR- vs. PPARγ-activating ligand, RXR may dimerize with and activate other nuclear receptors (e.g. retinoic acid receptor, RAR; liver X receptor, LXR; pregnane X receptor, PXR; or farnesoid X receptor, FXR). As such, RXR agonists could have broader biological activity than PPARγ. However, it is often proposed that some key effects including anti-inflammatory effects of RXR agonists appear to be executed largely through a PPARγ pathway[144]. In our lab, we have demonstrated that the co-treatment of primary cortical cultured neurons with the combination of 15d–PGJ2 and 9-*cis* retinoic acid protected the cells from OGD-induced damage more robustly than each of the ligands alone. Also, primary rat microglia in response to combined PPARγ activator (e.g. pioglitazone) and RXR activator (e.g. Bexarotene), appear to demonstrate a significantly higher phagocytosis efficacy toward erythrocytes, as compared to each of the ligands alone (ongoing studies), further supporting the existence of synergy between PPARγ and RXR activators in various biological

processes. These beneficial interactions of PPARγ and RXR ligands is consistent with an earlier report that 15d–PGJ2 plus 9-*cis* retinoic acid was superior in reducing behavioral dysfunction in a mouse model of experimental encephalomyelitis (EAE)[145]. Interestingly, it was recently demonstrated that retinoic acid at higher concentration can elicit different, even contrasting effect (to that seen with lower concentration) by activating PPARβδ/RXR heterodimers[146].

Interaction of PPARγ and Nrf2 and NF-κB

NF-κB is a transcription factor that regulates expression of many pro-inflammatory enzymes, cytokines, chemokines, proteases and adhesion molecules, contributing to amplification of the secondary inflammation response and neuronal damage after ICH[11,147,148,149,150]. The functional NF-κB exists as a dimer, which in neurons is composed primarily of the (NF-κB1) p50 and (RelA) p65 subunits. Other NF-κB members of the NF-κB/Rel family, include RelB, c-Rel, and p52 (NF-κB2)[151]. Numerous studies have confirmed that PPARγ may bind to the NF-κB subunits, p50 and p65, directly resulting in NF-κB inactivation[77,87,152]. PPARγ may also indirectly inhibit NF-κB by (1) competing for common transcription co-activators such as SRC-1[153] and p300/CBP (CREB-binding protein)[154,155]; (2) up-regulating the inhibitor kappa B (IκB), protein that prevents NF-κB nuclear translocation which is a prerequisite for NF-κB activation[88,156]; and (3) indirectly inhibiting NF-κB by activating transcription factor Nrf2, which reduces generation of pro-oxidative molecules which are required for NF-κB activation. Ultimately, inhibition of NF-κB by PPARγ agonists were reported to reduce generation of pro-inflammatory mediators/responses[56,57] and consequently the secondary brain damage associated with these pro-inflammatory responses[72,73,77,78].

Nrf2 is a ubiquitous pleiotropic transcription factor and a master genomic homeostatic regulator of intracellular stress[157,158,159]. Combining with Mif family proteins, Nrf2 forms heterodimeric complexes to transactivate the antioxidant response elements **(ARE**) within the regulatory region of many cytoprotective target genes [e.g. catalase, heme oxygenase-1 (HO-1), superoxide dismutase (SOD), glutathione-S-transferase (GST), thioredoxin and NAD(P)H dehydrogenase quinone 1 (NQO1)) [160] and also other proteins with important roles in neutralization of oxidative stress and detoxification of hemolytic products (e.g., haptoglobin, hemopexin, ferritin and hemooxygenase-1)[30,161]. In most cells, Nrf2 is present at low concentrations due to continuous Nrf2 degradation through the proteasome pathway. Nrf2 contributes to neuroprotection and amelioration of brain damage after cerebral ischemia[162,163], neurotrauma[164,165], neurodegenerative diseases[166,167,168] and ICH[30,161,169] primarily through reducing oxidative stress, inflammation, and generation of detoxifying molecules capable of neutralizing many noxious products generated in response to injury. The interaction between PPARγ and Nrf2 may involve multiple mechanisms. First, PPRE and ARE co-exist in the same genes, such as CD36[170] and catalase[171,172]; second, a reciprocal transcriptional regulation exists between Nrf2 and PPARγ genes, Nrf2 gene contains putative PPREs[173], and conversely, PPARγ gene appears to contain the ARE[174,175]; third, an interaction between PPARγ and Nrf2 may be through NF-κB inhibition. Since NF-κB activation highly depends upon the presence of oxidative stress, then the effect of Nrf2 in ameliorating oxidative stress was

proposed to inhibit NF-κB[176]. As different mechanisms are used by Nrf2 and PPARγ in inhibiting NF-κB, it is likely that the simultaneous activation of both Nrf2 and PPARγ may have a synergistic effect. Due to the interactions among PPARγ, Nrf2 and NF-κB, it has been suggested that co-activation of PPARγ and Nrf2 may improve outcomes of several neurological disorders[177].

Neurotoxicity following PPARγ activation

Unlike synthetic thiazolidinediones (TZDs; e.g. pioglitazone and rosiglitazone) that have considerable levels of specificity toward PPARγ, prostaglandin D2 derivatives (primarily with cyclopentanone structure), including 15d–PGJ2, which is proposed to act as endogenous PPARγ ligands demonstrate rather limited selectivity toward PPARγ with some of its biological activities including activation of Nrf2[168] or inhibition of NF-κB[87]. There is existing evidence on the dose-dependent neurotoxicity of the 15d–PGJ2 in cerebellar granule cells, primary cortical neurons and spinal cord motor neurons[178,179] which originally were believed to be linked to PPARγ. The mechanism that underlies the neurotoxic effect of 15d–PGJ2 is chiefly linked to higher doses of the compound. In addition, it is primarily associated with induction of apoptosis and not likely associated with the activation of PPARγ[180,181]. On the other hand, the clinically relevant, more selective PPARγ agonist such as rosiglitazone, was linked to peripheral edema, increase in body weight, and cardiomyopathies and heart failure[182]. Again the relationship between these side effects and PPARγ is somewhat controversial, as another TZD PPARγ agonist, pioglitazone, may show beneficial effects. The PROACTIVE (**PRO**spective pioglit**A**zone **C**linical **T**rial **I**n macro**V**ascular **E**vents; NCT00174993) randomized, double-blinded, placebo-controlled study looked at the impact of pioglitazone on total mortality and macrovascular morbidity in 5,238 patients with DM2 and macrovascular disease. This secondary prevention study showed safety and a macrovascular benefit with pioglitazone in terms of major adverse cardiovascular events including all-cause mortality, MI, and stroke[183,184]. Finally, it should be mentioned that the above side effects of rosiglitazone are described in patients taking TZDs long-term for DM2. It is likely that PPARγ agonist treatment for ICH will be short-term, potentially avoiding these side effects, although this needs careful testing.

Clinical trials of PPARγ agonists in ICH

Pre-clinical work has shown that PPARγ agonists are capable of promoting endogenous hematoma clearance, decreasing neuronal damage, and improving functional recovery in rodent model of ICH[77,78]. In addition, PPARγ agonists in vitro reduced the production of pro-inflammatory mediators and free radicals produced during phagocytosis[78]. Based on these studies, a clinical trial to evaluate the Safety of Pioglitazone for Hematoma Resolution in ICH has been launched (SHRINC)[108]. This is a prospective, randomized, blinded, placebo-controlled, dose-escalation safety trial in which patients with spontaneous intracerebral hemorrhage are randomly allocated to placebo or treatment. Pioglitazone, one of the PPARγ agonists that are approved by the Food and Drug Administration (FDA) for glycemic control in type II diabetes mellitus, was provided to the patients with escalating dosages. There was an evaluation period of 3∼6 months and the continual reassessment

method for dose finding is used to determine the maximum tolerated dose of pioglitazone. Hematoma and edema resolution is evaluated with serial magnetic resonance imaging (MRI) at specified time points. The Phase 2 study with a planned sample size of 84 patients has preliminarily demonstrated safety regarding mortality[108], and is now in the next planning stages (ClinicalTrials.gov **Identifier:** NCT00827892).

Since hematoma absorption is an extremely important objective after ICH, the SHRINC study should provide important information regarding the safety and clinical outcome regarding PPARγ agonists in the endogenous hematoma absorption. Besides primary ICH, secondary brain hemorrhage following brain trauma and brain surgery, subarachnoid hemorrhage (**SAH**), and hemorrhagic transformation of the ischemic stroke treated with rtPA may also be managed through this endogenous blood reabsorption (clearance) mechanism. Therefore, we are expecting that PPARγ, as a promising therapeutic target, could open a new field for managing hematoma clearance through a non-surgical mechanism.

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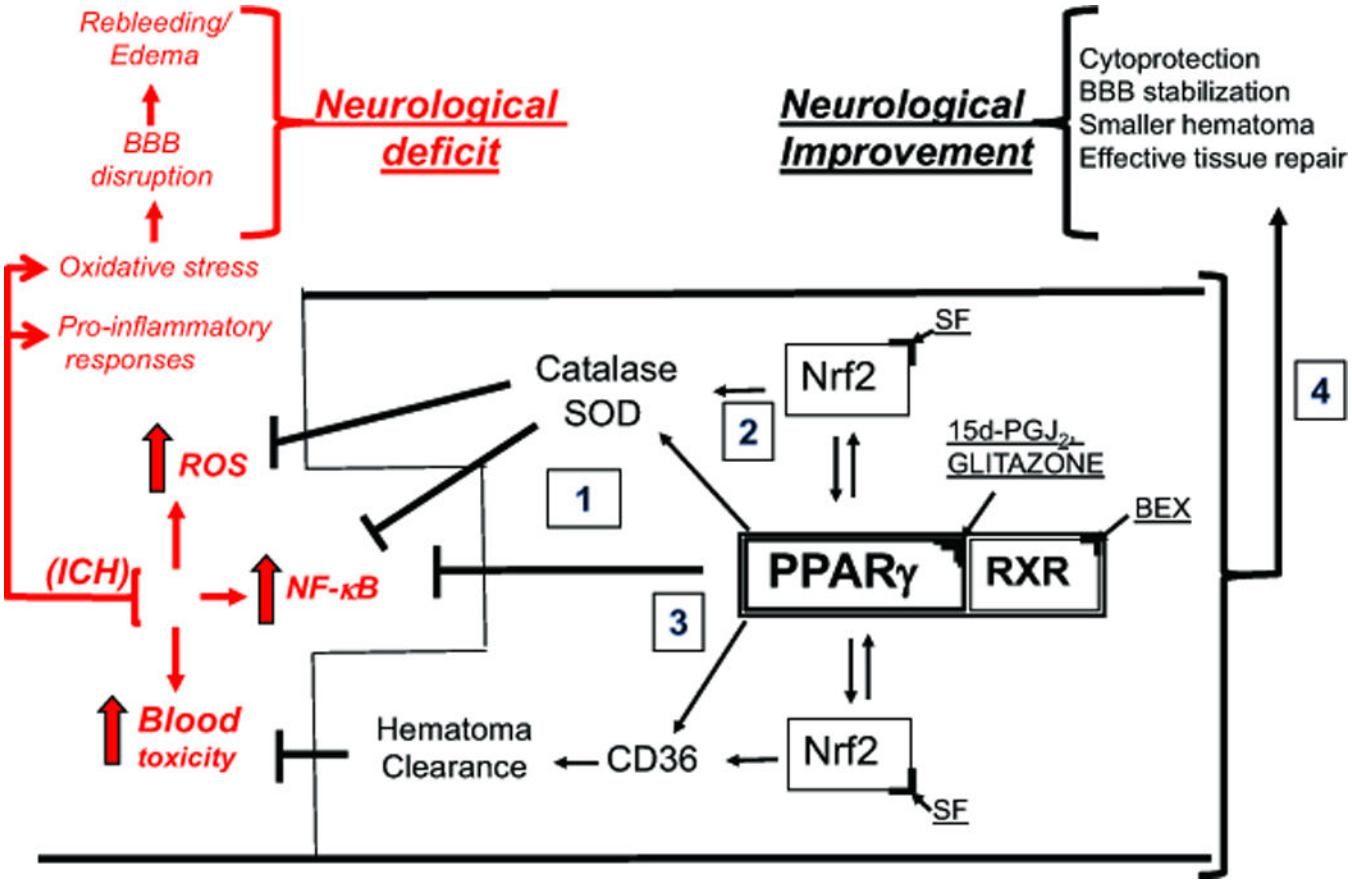

Figure 1.

PPARγ as therapeutic targets for ICH. In response to ICH, the local generation of reactive oxygen species (ROS), accumulation of toxic blood components (e.g. hemolytic products) in brain parenchyma, and activation of pro-inflammatory transcription factor NF-κB (causing generation of pro-inflammatory cytokines and enzymes) leads to brain injury, often referred to as secondary brain damage, which manifest itself with blood brain barrier (BBB) disruption, rebleeding, edema and ultimately neurological deficit or death. Activation of PPARγ with, e.g., 15d–PGJ2 or thiazolidinediones (known as glitazones) leads to: upregulation of the anti-oxidative enzymes, catalase and superoxide dismutase (SOD); scavenger receptor (e.g. CD36 on macrophages/microglia MMΦ) for RBC and hematoma clearance. Both PPARγ and Nrf2 (which can be activated with sulforaphane, SF) regulate transcription of these genes. PPARγ suppresses NF-κB to limit the pro-inflammatory response. Also, activation of RXR, an obligatory heterodimeric partner for PPARγ activity (e.g. with 9-cis-retinoic acid or Bexarotene, BEX), could augment the effect of PPARγ ligand acting alone. Thus, PPARγ activation may benefit the acute ICH and post-ICH recovery by: (1) down-regulating the production of pro-inflammatory mediators, (2) up-regulating the anti-oxidative enzymes production, (3) promoting endogenous hematoma clearance thus eliminating the source of inflammation and allowing for more effective repair, and (4) direct and indirect cytoprotection.