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Review

Potential role of Peroxisome Proliferator Activated Receptor gamma analogues in regulation of endothelial progenitor cells in diabetes mellitus: An overview

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ABSTRACT

Endothelial progenitor cells are recognized as the potential targets for the revascularization and angiogenesis because of their ability to get themselves transformed into mature endothelial cells. Underlying pathophysiology in diabetes mellitus leads to decrease in circulatory endothelial progenitor cells, resulting in diabetic macro-vascular and micro-vascular complications. Peroxisome Proliferator Activated Receptor (PPAR) gamma analogues serves as an effective therapy for controlling blood sugar levels and preventing its complications. Reports of clinical trials and meta-analysis of clinical trial suggests the beneficial aspects of PPAR gamma therapy in increasing the number and function of circulating endothelial progenitor cells. This review highlights the pleotropic effect of PPAR gamma analogs, apart from their antidiabetic action via reduction of oxidative stress, increasing expression of eNOS, reducing level of miR 22, miR 222 levels and positive modulation of rapamycin/Protein kinase B/phosphoinoside3-kinase pathways, preventing the early apoptosis, enhanced mobility proliferation and transformation into mature endothelial cells. PPAR gamma therapy in diabetes regulates endothelial progenitor cells, reduces complications of diabetes like retinopathy, nephropathy, neuropathy, cardiomyopathy, deep vein thrombosis, and maintains the healthy vasculature.

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1. Introduction

Diabetes is a metabolic disorder characterized by abnormal protein, carbohydrate and fat metabolism resulting in persistent hyperglycemia. Uncontrolled glycaemia in diabetes results in diabetic macro-vascular and micro-vascular complications [1]. These complications arise due to the marked decrease in circulatory Endothelial Progenitor Cells (EPCs). EPCs are immature endothelial stem cells with potential to form the mature endothelial cells, thus helpful in repairing the endothelial layer (Angiogenesis), formation of new vasculature (Neoangiogenesis) [2]. Peroxisome proliferator-activated receptor gamma analogs serve as effective therapy in management for type 2 diabetes mellitus, a cornerstone for achieving euglyceamia [1,3,4]. Underlying pathophysiology in diabetes mellitus predisposes patients to develop premature cardiovascular complications because of reduced circulating endothelial progenitor cells involved in the healing of dysfunctional endothelium of the walls of blood vessels as well as cardiac linings [5]. Reduced endothelial progenitor cells result in macrovascular and microvascular complications [6]. Peroxisome proliferator activating receptor γ agonists, thiazolidinedione derivatives are used in diabetes for maintaining the optimum blood glucose level with additional effects of adipogenesis, achieving normal lipid profile [7]. Recent studies states the shred of evidence that PPAR γ analogs have the pleiotropic effect on endothelial progenitor cells, they act by increasing number as well as functioning of endothelial progenitor cells [8]. Maintenance of healthy vasculature depends on the balance between on-going endothelial repair and vascular damage, an imbalance between this homeostasis leads to endothelial dysfunctioning [9]. Endothelial progenitor cell plays an important role in maintenance of healthy vasculature, they migrate to the site and repair the damaged vascular endothelium by transforming themselves into matured endothelial cells [10]. EPCs eternize this cycle by secreting pro-angiogenic cytokines [11]. In diabetes, functioning of endothelial progenitor cells is affected, due

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to their reduced ability to proliferate, differentiate into endothelial cells. Reduced efficacy of cells to get themselves transformed into tubular structures, resulting in failure of repair of endothelium [12]. Other mechanism, which explains dsyfunctioning of endothelium and failure in its repair, are excessive accumulation of sophisticated glycated products, stimulation of protein kinase c pathway, stimulation of RAAS (renin-angiotensin aldosterone system), migration of leukocytes, reduced bioavailability of a nitric oxide and oxidative stress [13]. Dysfunctioned endothelium leads to atherosclerosis and predisposes patient to develop risk of cardiovascular diseases [14]. The endothelium plays a vital role in homeostasis, viz. they cause relaxation of various smooth muscles release of endothelial-derived relaxing factor (EDRF) i.e. nitric oxide [13]. Nitric oxide activates an guanylyl cyclase pathway leading to increase in cyclic guanosine monophosphate (cGMP) results in vasodilation, thus leading to cardiovascular protective action [15]. There are various studies which proves that PPAR gamma analogue improves circulating endothelial progenitor cells via direct anti-inflammatory effect, direct effect on lipid modification and by various other pathways [16].

2. Endothelial progenitor cells

Discovery of endothelial progenitor cells by Asahara et al., has laid the milestone in management of diabetes and other metabolic syndrome. EPCs are potential biomarkers to depict the cardiovascular risk. Endothelial cells are the stem cells, which have the potential to get them transformed into a mature endothelial progenitor cell responsible for both angiogenesis (the formation of blood vessels) and neoangiogenesis (the formation of new blood vessels). EPCs are differentiated from other cells with the help of epitope, specific surface receptors which helps in immunophenotyping of cells, aids in identification of cells at different stages of development [17,18]. Epitope helps in identification of a cluster of differentiations (CD) which are cell surface molecules. Presence and absence of CD differentiates the stem cells from mature cells [19,20]. During the maturation, EPC develops a variable type of CD marker expression over their surface, which is further classified into its subtype based on an intensity of maker as dim, mid and bright [21]. Asahara et al., modified the dogma of angiogenesis by isolating the endothelial progenitor cells and discovering the kinase insert domain receptor i.e. CD34, KDR(VEGRF). Many of the studies suggesting that these cells migrates toward the sites of neovasculature and stimulate angiogenesis [19–21]. EPCs can be isolated from placental wall, bone marrow and from blood as mononuclear cells [22–24]. EPCs originates from pluripotent cells of bone marrow, upon analysis of peripheral blood cells, EPCs accounts for 0.001%–0.0001% of blood cells. Exact phenotyping and functionality of EPCs is still warranted [25]. As the name of the EPCs suggests that, they have great potential of being differentiated into an endothelial cell, but not always, as they are consisted of a different type of cells. Protein present over the surface of endothelial cells acts as a marker for characterization of subtypes of EPCs [26]. Various studies were conducted which explicated 3 markers of advance operable EPCs as CD34, CD 133, KDR, FLK1 or CD 309 which were termed as VEGF (the vascular endothelial growth factor) [27], Markers of VEGFR2, CD 146 and Vwf (endothelial cells) as well as CD133 and CD 34 (hematopoietic stem cells) are expressed over the surface of EPCs [28]. The expression of markers present on the surface on EPCs totally depends on their stages of maturation. Endothelial progenitor cells and hematopoietic stem cells originates from bone marrow represented by a surface marker of cell i.e. CD133, a 120-kDa trans-membrane polypeptide, usually this expression starts decreasing during maturity in the peripheral circulation [29]. Decrease in a number of EPCs after an injury indicates that the higher number of EPCs are being converted into a mature endothelial cells [16]. CD34 are present over the surface of immature pluripotent stem cells; their actual function is still controversial few literatures suggest that they play a role of adhesion molecules. On maturity the markers appearing on the surface of EPCs are VEGFR-2, VE-cadherin, and von Willebrand factor (vWF), they begin to increase during the course of maturity of cells. Markers to describe endothelial progenitor cells have been looked into by various studies which are CD 133^{+} $VEGF2^{+}$, CD 34^{+} [30,31] Still it remains a controversy that endothelial phenotypic EPCs are not formed by $CD133^{+}$ as their as hematopoietic cell lines [10]. Ingram et al. justified with the help of various and assigned the term true circulating EPCs to CD45 [25,32]. Briefing up as the CD31, VE-cadherin, and vWF markers starts appearing on the surface of the cells, progresses the maturity of EPCs with loss of CD133 marker. Origination of different marker on the surface of EPCs are summarized in the Table 1 [32].

2.1. EPC and diabetic micro-vascular and macro-vascular complications

Diabetic patients with uncontrolled blood sugar levels are at marked risk of developing macro-vascular and micro-vascular complications such as diabetic cardiomyopathy, nephropathy, neuropathy, retinopathy and complication of slow wound healing [28,33]. These complications in diabetes are correlated with reduced circulating endothelial progenitor cells [34]. Increased blood sugar levels in diabetes reduces nitric oxide and decreases the number as well as functioning of endothelial progenitor cells thus leading to damaged endothelium. Endothelial acts as a barrier between the lumen and vessel wall. It also acts as an internal governor of platelet aggregation, vascular chant, fibrinolysis and coagulation, diabetes lead to the loss of the functioning of endothelium, which is termed as “endothelium dysfunction” [2]. Endothelium fails to perform its functions like vasodilation in conduit arteries, lysis of fibrin and antiaggregation similarly it causes vasoconstriction in smaller vessels by secreting endothelium derived hyperpolarizing factors like thromboxane A2 and endothelin 1 thus plays a role in vascular homeostasis [35]. Accomplished hyperglycemia and reduced NO levels leads to endothelial dysfunctioning in diabetes. Damaged endothelial cells lack self-repair and low proliferating potential, circulating endothelial progenitor cells help in repairing the damaged endothelium. EPCs migrates toward the site of dysfunctional endothelium and facilitate repair by transforming into differentiated endothelial cells thus repairing the endothelium layer [36]. In diabetes, their functioning as well as number decreases which is explained through various studies, which increases the risk of diabetic nephropathy, neuropathy, retinopathy and cardiomyopathy. Preclinical experimental data state shreds of evidence and links reduced EPCs with pathogenesis of cardiomyopathy in diabetic rats. Jeong et al., links reduced VGERF, increased fibrosis [37] and altered contraction as a pathogenesis of diabetes in the pathogenesis of diabetes with decrease in EPC [38]. Similarly, reduced EPC plays a role in diabetic nephropathy by impairing microcirculatory system, defective repair of a glomerular capsule. Patients with lower $CD4^{+}$ cells are potentially having higher excretion of urinary albumin. High blood glucose levels cause retinal cell death and markedly reduce EPCs causing retinopathy. Impaired neuronal metabolism and blood flow toward neurons in diabetes leads to diabetic neuropathy [39]. EPCs plays a significant role in this as explained by Busik et al., they injected EPCs to diabetic rats models, observed that the diabetic neuropathy's manifestations get reversed [40].

Table 1
Origination of cell markers during different phases of EPCs maturation.

Origination of cell marker during different phases of EPCs			
Markers	Bone Marrow	Circulation	
		Early EPCs	Mature EPCs
CD133+	+	+\-	−
$CD34^{+}$	+	+	+
VEGFR2+	+	++	+++
$CD31^{+}$	−	+	+
VE-cadherin	−	+	+
vWF	−	+	+

EPCs: Endothelial progenitor cells; **VEGFR**: Vascular endothelial growth factor receptor; **VE-cadherin:** vascular endothelial cadherin; **CD:** Cluster of differentiation.

3. PPAR γ analogs therapy

PPAR γ are retinoid X receptor belonging to a family of an nuclear hormone receptor (NHR) family [41]. These analogs are also known thiazolidinedione (TZDs) derivatives widely used in the therapeutic regimen of diabetic patients [42]. Troglitazone was the first drug of this class which was effective in controlling blood glucose level, it was banned from the market because of its severe hepatotoxic nature, similar was the case with rosiglitazone, which was banned from the market due to increased incidence of heart failure [43]. Pioglitazone is an agent which is used in diabetes and it has markedly controlled glycaemia as well it has an additive effect of increasing circulating endothelial progenitor cells thus exploring its pleiotropic effect in diabetes aside of diabetes pioglitazone also shows potential anticancer activity [3,44]. Pioglitazone actuate PPARγ which is an ligand-activated transcription factor, innervating cell differentiation and induces angiogenesis [45]. PPAR γ analogs modulate the insulin-responsive genes, conquer monocyte, macrophage and exhilarate adipocyte differentiation thus bring the glucose level to normal and also help in improving the progression of an atherogenic disease [46]. This analog decreases the insulin resistance and retards the progression of diabetes. PPAR gamma 1 and PPAR gamma 2 are the three mRNA coded by gene which give rise to PPAR gamma protein. PPAR gamma 2 m RNA codes for a protein that has an extra 28 amino acids at an N terminus S [47]. Human subjects have PPARG1 and PPARG2 subtypes expressed in liver, heart, skeletal muscles and subcutaneous fat tissues. PPAR γ analogs act with the help of signalized and well-coordinated cascade, dominating the gene expression thus innervating transcription factors [48]. Mechanisms by which PPAR analogue regulates the gene expression are DNA dependent process, transcription and second process is DNA independent, transrepression which involves another set of transcription factors [49]. Meta-analysis of nine randomized clinical trials (RCTs) of 4327 subjects and shows that the pioglitazone, PPARγ analogs prove to be more efficacious in diabetic patients with improved therapeutic outcomes. Another metaanalysis of 19 RCTs also showed the safety of PPARγ analogs, pioglitazone lower the risk of myocardial infarction and stroke in diabetic patients [50,51]. The adverse drug reaction profile of PPAR gamma analouges is described in the Table 2 [52].

3.1. Pleotropic effects of PPAR γ analogues on EPC

Beneficial effects of PPAR γ for diabetes have been reported in various studies, various evidences suggest their efficacious potential in controlling the glycemia in diabetic patients along with decreased microvascular and macrovascular complications [43]. These promising results gave rise to the hypothesis that they are acting through alternative pathways aside of improving insulin sensitivity [53,54]. PPAR γ agonist has a pleiotropic effect on endothelial progenitor cells; they help in their easy mobilization from bone marrow as well as prevent their early apoptosis. Pistrosch et al. for the first time described the effect of PPAR analogs on endothelial progenitor cells in 2005 with 3 months of therapy with rosiglitazone in diabetic patients which results in the increase in a number and functional capacity of EPC including their migration and this effect was observed for a longer period of time [55–57]. Similar results were seen when subjects were on metformin and pioglitazone therapy, at the end of study it was observed that therapy resulted in an increase in number, enhanced migration and attachment of endothelial progenitor cells to fibronectin [58,59]. PPAR gamma analogues therapy help in eliminating negative effects of advanced glycation end products (AGEs) and also attenuates phosphorylation of activated Akt and eNOS by AGEs. Several mechanisms have been proposed for their mentioned effects [60,61]. Gench et al., conducted animal study and proved pioglitazone, PPAR gamma analog helps in improving the circulating endothelial progenitor cells independent of its insulin-sensitizing action and also observed that neoangiogenesis was increased by two-fold and apoptosis of EPC was decreased in pioglitazone-treated mice [8,16]. Wang et al., conducted randomized control trial in 36 diabetic patients to find out the impact of Pioglitazone on EPCs and proved the direct effect of pioglitazone on migration and colony formation of EPCs as well as prevents the early apoptosis of EPCs thus proves the pleiotropic effect [62]. Li et al. explained how PPAR gamma analogs improve endothelial dysfunction, mechanism by which these analogs improve the functioning of human umbilical vein endothelial cells (HUVECs) exposed with *Porpyromonas Gingivalis* when treated with PPAR gamma analogs. They help in improving the decreased expression of endothelial nitric oxide by *Porpyromonas Gingivalis* through management of PI3/Akt and ERK and NFkB pathways [63].

4. Proposed beneficial mechanisms of PPAR gamma analogue therapy

Various mechanisms have been proposed to explain the pleiotropic effect of the PPAR gamma analog therapy. Fig. 1 explains the proliferation, mobilization and maturational endothelial progenitor cells and how it has affected positively as well as negatively aside from an explanation of the effect of PPAR gamma impact on EPCs.

4.1. Pathway involving nitric oxide

Nitric oxide, primary mediators of endothelial smooth muscle that causes relaxation of smooth muscles and leading to vasodilation of endothelial smooth muscles [64]. Cofactors along with eNOS substrate help in phosphorylation of eNOS which lead to the production of NO; an intracellular signaling molecule, VGERF, FGFS along with TGF, VE-cadherin and various integrins help in stimulation of proliferation of endothelial progenitor cells and help in neoangiogenesis [65]. Li et al., explained PPAR γ elevates the

expression of endothelial nitric oxide synthase, by activating protein, phosphatidylinositol 3-kinase (PI3K). They downstream kinase which is the second messenger associated with membrane in human umbilical vein endothelial cells by decreasing the expression of eNOS with the help of *Porphyromonas Gingivalis* which is known to reduce the level of eNOS [63]. Refurbishment of PI3K/Akt/eNOS signaling energizing occurred after treating hypertensive rats with PPARγ analog, improves the expression eNOS. Elevated level eNOS help in the restoration of endothelial dysfunction thus maintain the healthy vasculature. In diabetes, there is an increase in reactive oxygen species, which leads to the desecration of nitric oxide and leading to endothelial dysfunction [66]. While PPAR γ analogs increase the expression as well as the activity of eNOS and maintains vasculature health [67]. Thus PPAR γ aside from glycemic control they are have potential role in regulating the growth, movement and proliferation of endothelial progenitor cells and also increases the production of eNOS.

4.2. Decreasing level of miR 221 and miR 222

miR 221 and miR 222 are also known as non-coding mRNA, they inhibit the protein synthesis at post-transcriptional level and impair the translation by degrading the targeted mRNA directly by showing their effect on 3' untranslated region [68]. miR 221 and miR 222 also impair the proliferation and differentiation of endothelial progenitor cells by decreasing the expression of the c-kit receptor [69]. Increase in EPC by PPAR γ is explained by a decrease in the level of miR221 and miR222 level by these analogs. miR221 and miR222 inhibit EPC mediated angiogenesis by directly attenuating Sirt1 and results in endothelial dysfunction. PPAR γ decreases the level of miR221 and miR222 leading to increase in the level of NOS3 mRNA levels and provides the protective mechanism in vascular health, causing enhanced angiogenesis with the PPAR γ therapy [70].

4.3. Oxidative stress

Pioglitazone Suppresses the NAD(P)H oxidase p22(phox) as well as Rac1 which responsible for a generation of reactive oxygen species (ROS), thus they reduce the production ROS which negatively modulates the migration proliferation and differentiation of endothelial progenitor cells [34]. Oxidative stress alters the function of endothelial progenitor cells. In diabetes, higher glucose level (hyperglycemia) increases the oxidative stress. PPAR gamma analogs independent of their antidiabetic effect reduces the production of ROS and improves the functional capacity of endothelial progenitor cells [71]. Oxidized low-density lipoprotein, has a central role in the pathogenesis of atherosclerosis. Oxidative stress along with ROS oxides LDL leading to pathophysiology of various vascular diseases in the same ROS react with NO and form reactive species which impairs the functioning of EPC negatively, causing early apoptosis of endothelial progenitor cells [72]. Oxidation of LDL involves conversion of unsaturated fatty acids of an LDL molecule into lipid peroxides, which results in formation of active aldehyde. PPAR gamma analogue suppresses NADPH oxidase, p22 (phox) and Rac1 leading to reduction of the ROS. Ultimately, reducing the oxidative stress and lowering down the ROS and inhibiting the pathway as explained above. Nakamura et al., conducted animal study in stroke-prone spontaneously hypertensive rats (SHRSP) to investigate the effect of pioglitazone in hypertensive cardiovascular injury and found that pioglitazone act by inhibiting the NAD(P)H oxidase p22 (phox) and Rac1, reduce the production of ROS and proved that pioglitazone improves the functioning of EPCs, showed protective effect in preventing hypertensive cardiovascular injury. Healthy subjects have higher levels of enzymes such as magnesium super oxide dismutase and glutathione peroxide, which serves as antioxidants for scavenging ROS. In diabetes these enzymes get saturated due to excessive production of ROS, so pioglitazone serves a beneficial effect as it decreases the production of reactive molecules, increases the survival of EPC and prevents the damage caused by superoxide to DNA of EPC [42].

4.4. Pathway involving Mammalian target of rapamycin/protein kinaseB/phosphoinoside3-kinase

Mammalian target of rapamycin (mTOR)/protein kinase B (Akt)/phosphoinositide 3-kinase (P13k) plays a crucial role in long term survival and increases number as well as function of endothelial progenitor cells [73]. Central role in transduction pathway is played by Phosphatidylinositol3,4,5-triphosphate (PIP3), lipid secondary messenger. Phosphorylation of mTOR is governed by Akt playing a central role in cell growth with the aid of protein synthesis [74]. NO pathway of signaling is governed by P13K/Akt pathway, which in return is associated with angiogenesis. Vascular endothelial growth factors (VEGF) are angiogenic factors, which helps in stimulation of neoangiogenesis; VEGF also helps in production of nitric oxide (NO). Impaired mTORAkt/P13k reduces EPC leading to dysfunctional endothelium. PPAR gamma therapy is believed to increase the number as well as function of circulating EPC through positive modulation of these pathways [75].

5. Conclusion

PPAR gamma analogs are not only helpful in controlling blood sugar levels; maintain healthy vascular independent of antidiabetic action, and increases number as well as functioning of endothelial progenitor cells. Various studies have proved their pleiotropic effect. Using these analogs in diabetes lowers the risk of diabetic complications, because of their pleiotropic action. They can also be used for various cardiovascular and cerebrovascular disorders due to their pleiotropic nature. PPAR gamma analogues enhance the mobilization proliferation and transformation of endothelial cells. PPAR gamma analogs, serves as a wonder therapy for controlling blood sugar level, reducing the risk of diabetic complication like retinopathy, neuropathy, nephropathy and other macro-vascular complications. Further randomized control trials are needed to be

Table 2
Benefits of PPARgamma analogs with their clinical benefits as well as their reported adverse effects of analogs of PPAR gamma.

Benefits of PPAR Agonists	Clinical benefits	Adverse effects
Improves insulin sensitivity	Improves insulin sensitivity	Bladder cancer
Improves NO level	Reduction of myocardial stroke atherosclerosis and Inflammation	Heart failure
Angiotensin II and ET1		Bone fracture
Dec. inflammation		
Dec. Aneurysm		
Dec. Pul arterial HTN		
Dec. Atherosclerosis		

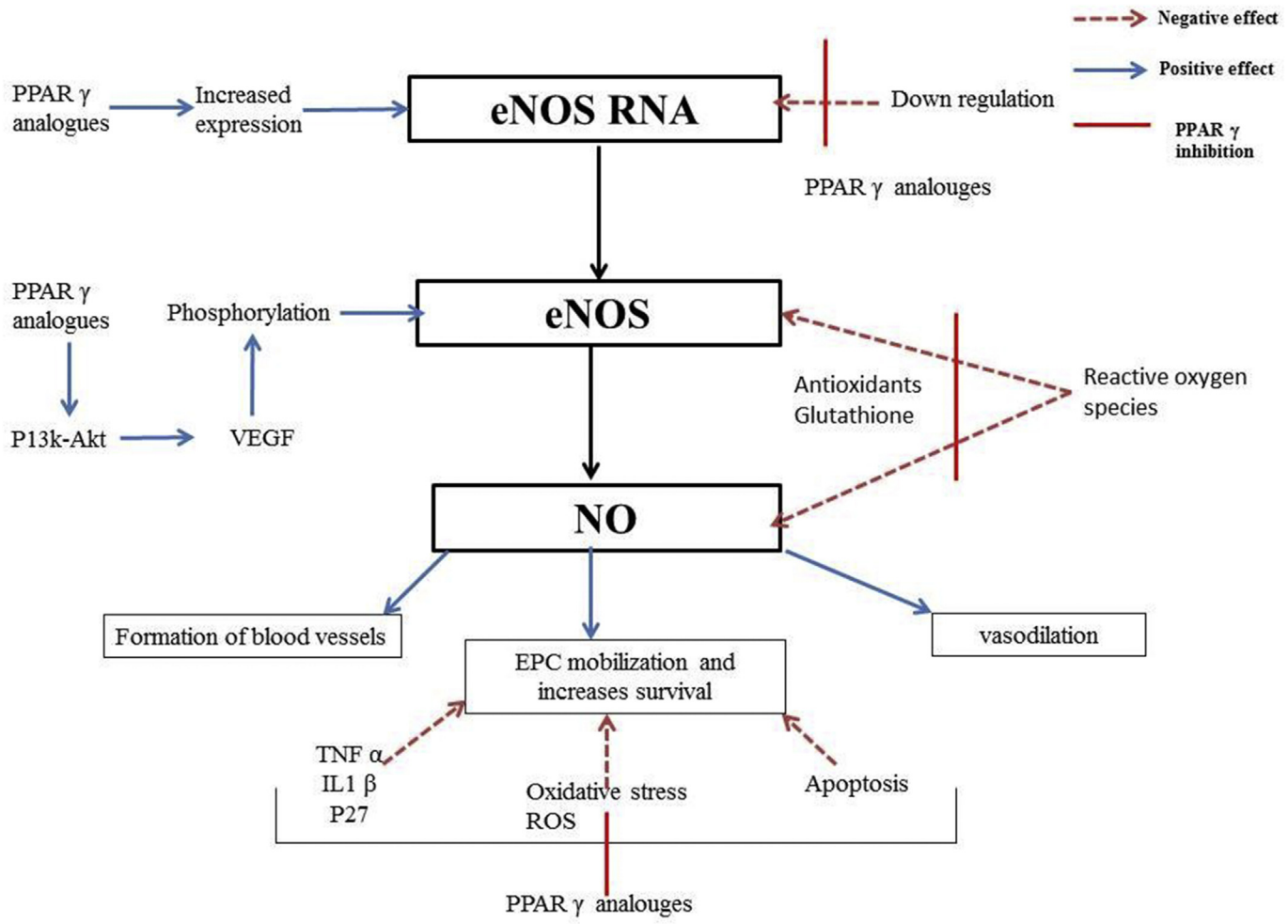

Fig. 1. Proposed molecular mechanism of action of PPAR γ analogs on the growth, mobilization and prevention of early apoptosis of EPCs. EPC: Endothelial progenitor cell; NO: Nitric oxide; eNOS: Endothelial nitric oxide synthase; VEGF: Vascular endothelial growth factor; mRNA: Messenger ribonucleic acid; TNF: Tumor necrosis factor alpha; IL-1: Interleukin1.

designed to elucidate the potential effect of these analogs to design the effective therapeutic intervention.

Consent of publication

Not Applicable.

Conflicts of interest

Authors declare no conflict of interest.

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