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► To cite this version:

Alexandre Vallée, Jean-Noël Vallée, Yves Lecarpentier. Metabolic reprogramming in atherosclerosis: Opposed interplay between the canonical WNT/ β -catenin pathway and PPAR γ . *Journal of Molecular and Cellular Cardiology*, 2019, 133, pp.36 - 46. 10.1016/j.yjmcc.2019.05.024 . hal-03480702

HAL Id: hal-03480702

<https://hal.science/hal-03480702>

Submitted on 20 Dec 2021

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**Metabolic reprogramming in atherosclerosis: opposed interplay between the canonical
WNT/ β -catenin pathway and PPAR γ**

Running title: Metabolic reprogramming in atherosclerosis

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Abstract

Atherosclerosis, a chronic inflammatory and age-related disease, is a complex mechanism presenting a dysregulation of vessel structures. During this process, the canonical WNT/ β -catenin pathway is increased whereas PPAR γ is downregulated. The two systems act in an opposite manner. This paper reviews the opposing interplay of these systems and their metabolic-reprogramming pathway in atherosclerosis. Activation of the WNT/ β -catenin pathway enhances the transcription of targets involved in inflammation, endothelial dysfunction, the proliferation of vascular smooth muscle cells, and vascular calcification. This complex mechanism, which is partly controlled by the WNT/ β -catenin pathway, presents several metabolic dysfunctions. This phenomenon, called aerobic glycolysis (or the Warburg effect), consists of a shift in ATP production from mitochondrial oxidative phosphorylation to aerobic glycolysis, leading to the overproduction of intracellular lactate. This mechanism is partially due to the injury of mitochondrial respiration and an increase in the glycolytic pathway. In contrast, PPAR γ agonists downregulate the WNT/ β -catenin pathway. Therefore, the development of therapeutic targets, such as PPAR γ agonists, for the treatment of atherosclerosis could be an interesting and innovative way of counteracting the canonical WNT pathway.

Keywords: WNT pathway; PPAR gamma; atherosclerosis; Warburg effect; aerobic glycolysis

Introduction

Atherosclerosis is a chronic inflammatory and age-related disease [1,2]. The origin of the atherosclerosis process is found in a dysfunction of the endothelial cells (ECs) through the secretion of several inflammatory cytokines/chemokines, leading to the recruitment of peripheral monocytes. Adherence and then aggregation of these monocytes into the subendothelial space of the arterial wall enhance the differentiation of monocytes into macrophages and then into foam cells through the modification of low-density lipoprotein [3]. This accumulation of cholesterol-engorged macrophages, known as foam cells [4], is a major factor in atheromatous plaque formation [5]. The process of atherosclerosis is a complex mechanism that presents a dysregulation of vessel structures. The process is initiated during childhood and progressively develops with age. Three layer structures make up the artery, i.e, tunica intima, media and adventitia. The intima is formed by subendothelial collagen and a single layer of endothelial cells. Endothelial cells are key factors in determining vascular pattern and the recruitment of smooth muscle cells (SMCs) during embryogenesis [6,7]. The intima is particularly important during atherosclerosis due to its physical properties. The media is composed of SMCs and elastin. The elasticity of arterial blood vessels is supported by elastin lamellae, a proteoglycan-rich extracellular matrix, SMCs and collagen fibers. The adventitia is made of a collagen-rich extracellular matrix produced by myofibroblasts [8]. The role of this structure is to prevent rupture of the vessel wall at very high pressures.

During the initial stage of atherosclerosis, the accumulation of lipids, SMC infiltration, proliferation and deposition of the extracellular matrix (ECM) occur under the intima [9]. This accumulation leads to a gradual impairment of the vessel through a dysregulation between the three concentric layers. The intima is infiltrated by SMCs and then recruits lymphocytes and macrophages to become an inflammatory site. Inflammation and immunity reactions are then exacerbated by the increased accumulation of cholesterol-rich lipoproteins. An atheromatous plaque is gradually formed and then the vessel lumen can be encroached, leading to diminished blood flow and even myocardial infarction due to coronary artery thrombosis [10–12]. During the final stage, the atheromatous plaques are characterized by an increase in macrophages, the appearance of calcification and a reduction in extracellular matrix (ECM) deposition, which renders them unstable (**Figure 1**) [10,11].

The canonical WNT/ β -catenin pathway controls numerous pathways involved in development

and tissue homeostasis. The pathway is modulated by transcriptional and post-transcriptional levels. The WNT/ β -catenin pathway is upregulated in atherosclerosis and participates in different stages of this process, from endothelial dysfunction to vascular calcification [12]. Moreover, the canonical WNT/ β -catenin pathway plays a key role in both cell fate decision and inflammation in the initiation of atherosclerosis [13–15].

In contrast, the peroxisome proliferator-activated receptor γ (PPAR γ) is downregulated in atherosclerosis [16]. PPAR γ agonists, by inhibiting inflammation and vascular smooth muscle cell (VSMC) proliferation, appear as an interesting therapeutic way of treating numerous diseases, especially cardiovascular diseases [17,18]. In several tissues, activation of the canonical WNT/ β -catenin pathway induces downregulation of PPAR γ , while PPAR γ activation inhibits expression of canonical WNT/ β -catenin signaling [19]. Indeed, PPAR γ agonists induce repression of canonical WNT/ β -catenin signaling in several pathophysiological states. We focus this review on the opposing interplay between the canonical WNT/ β -catenin pathway and PPAR γ in the metabolic-reprogramming pathway during atherosclerosis.

1. Canonical WNT/ β -catenin pathway

The term WNT refers to Wingless drosophila melanogaster and its mouse homolog, Int. WNT pathway, is involved in numerous signaling and regulating pathways, such as embryogenesis, cell proliferation, migration and polarity, apoptosis, and organogenesis [20]. However, during numerous pathological states, the WNT pathway can be dysregulated by developments such as inflammatory, metabolic and neurological disorders, tissue fibrosis and cancers [21]. Recent studies used the WNT pathway for cell therapy-bioengineering processes [22].

WNT ligands are lipoproteins that activate specific co-receptors. These WNT ligands activate the canonical WNT pathway through the action of β -catenin. WNT ligands activate Frizzled (FZD) receptor and low-density lipoprotein receptor-related protein 5 and 6 (LRP 5/6) [23]. The complex formed by extracellular WNT ligands and FZD/LRP5/6 stimulates intracellular Disheveled (DSH). This activation inactivates the destruction complex of β -catenin in the cytosol. β -catenin accumulates in the cytosol and then translocates to the nucleus. Nuclear β -catenin interacts with the T-Cell factor/lymphoid enhancer factor (TCF/LEF) to stimulate gene transcription, such as c-Myc and cyclin D1 [24].

During the “off-state” of the WNT/ β -catenin pathway, WNT ligands do not bind FZD and LRP 5/6. The β -catenin destruction complex, which is formed by AXIN, APC (adenomatous polyposis coli) and GSK-3 β (glycogen synthase kinase 3 β), phosphorylates the β -catenin. Thus, phosphorylated β -catenin is degraded into the proteasome.

Several WNT inhibitors inactivate the canonical WNT/ β -catenin pathway. Activated GSK-3 β is the major inhibitor of the WNT pathway. GSK-3 β is an intracellular serine-threonine kinase which regulates several pathways such as inflammation, neuronal polarity or other cell membrane signaling [25]. GSK-3 β inhibits β -catenin cytosolic stabilization and nuclear migration. Dickkopf (DKK) and soluble Frizzled-related proteins (SFRP) are also WNT inhibitors and bind FZD, LRP5 and LRP6 (**Figure 2**) [26].

2. PPAR γ

PPARs are ligand-activated transcription factors that bind PPRE (PPAR-response elements). In the nucleus, PPARs form a heterodimer with the retinoid X receptor (RXR) [27]. They are composed of a ligand-binding domain that interacts with a DNA-binding domain to modulate it [28]. PPARs are involved in numerous pathophysiological processes, such as cell differentiation, protein metabolism, lipid metabolism, carcinogenesis [29,30], adipocyte differentiation, insulin sensitivity and inflammation [31,32]. PPARs are subdivided into three isoforms PPAR α , PPAR γ and PPAR β/δ [33]. PPAR γ is highly expressed in adipose tissue and macrophages [16]. PPAR γ ligands can be synthetic or natural. PPAR γ ligands have hypoglycemic and hypocholesterolemic roles, such as glitazones, which have been used in the treatment of type 2 diabetes [34]. PPAR γ ligands, such as thiazolidinediones (TZDs), can also decrease inflammatory activity [34]. Natural ligands include prostaglandins and unsaturated fatty acids [35].

3. Opposing interplay between PPAR γ and the WNT/ β -catenin pathway

In several diseases, PPAR γ expression is decreased by β -catenin signaling over-activation [36–38]. Indeed, PPAR γ is considered as a negative β -catenin target gene [39,40]. The WNT/ β -catenin pathway and PPAR γ interact through a TCF/LEF domain of β -catenin and a catenin-binding domain within PPAR γ [41,42]. Through this link, a decrease in the WNT/ β -catenin

pathway enhances the stimulation of PPAR γ [43], whereas PPAR γ over-expression decreases the β -catenin signaling [44].

Numerous studies have shown that the canonical WNT/ β -catenin pathway and PPAR γ act in an opposing manner, such as in cancers, neurodegenerative diseases and fibrosis processes [45–47].

PPAR γ agonists are considered to offer promising treatment through the action of this crosstalk [48–50]. Pioglitazone attenuates the expression of WNT/ β -catenin signaling to prevent the development of left ventricular fibrosis [51]. PPAR γ agonists stimulate synaptic plasticity by interacting with the WNT/ β -catenin/PI3K/Akt pathway [52]. Troglitazone, a PPAR γ agonist, can decrease c-Myc levels [53]. PPAR γ agonists activate Dickkopf-1 (DKK1) activity to decrease the canonical WNT/ β -catenin pathway and then inhibit fibroblast differentiation [54]. Furthermore, PPAR γ agonists activate GSK-3 β to decrease β -catenin expression [55]. In adipocytes, adiponectin increases PPAR γ expression and then downregulates LPS-induced NF- κ B expression and IL-6 production [56].

Conversely, β -catenin signaling activates the Akt pathway to decrease PPAR γ expression in adipocytes and 2T2-L1 preadipocytes [44,57]. Several inflammatory cytokines, chemokines and intracellular signaling downregulate PPAR γ expression, such as the canonical WNT/ β -catenin pathway, TNF- α , interleukin (IL)-1 and IL-13 [58,59].

Another aspect is the regulation of PPAR γ insulin sensitizing activity by the interaction with β -catenin in bone marrow. Degradation of β -catenin positively correlates with increased expression of PPAR γ -controlled markers of insulin signaling [60].

4. Canonical WNT/ β -catenin pathway and the atherosclerosis process

Inflammation (Figure 3)

Inflammation plays a key role in the mediation of the different phases of the atherosclerosis process [61]. Several cytokines participate in atherosclerosis, such as interleukin (IL-1 and IL-4), interferon-gamma (IFN- γ) and TNF- α [62]. TNF- α activation leads directly to the process of calcification and to the proliferation and migration of VSMCs [63]. IL-1 is strongly expressed by macrophages and ECs [64], and IL-1 overexpression stimulates the atherosclerosis process [61]. TNF- α acts through bone morphogenetic protein (BMP2), a canonical WNT target [65] and by activating NF- κ B [66] to facilitate multiplication of VSMCs and mineralization of the

extracellular matrix (ECM). Moreover, the overexpression of the WNT/ β -catenin pathway in VSMCs increases inflammation by activating the NF- κ B pathway and TNF- α [67].

Endothelial dysfunction (Figure 3)

Dysfunction of ECs is observed at the onset of atherosclerosis. The boundary between the circulating tissue and the underlying tissue is constituted by ECs. ECs have a major role in hemodynamic regulation through the release of several vasoactive mediators. Lesions on these ECs induce the expression of inflammatory and pro-thrombotic genes leading to the enhanced recruitment of inflammatory cells to the subendothelial space, an important characteristic of the initiation of atherosclerosis [68].

In association with EC lesions, a high level of circulating LDLs infiltrates specific zones of the arterial wall. Although LRP5 is normally expressed in monocytes, macrophages, SMCs and ECs, the overexpression of LRP5 is only observed during inflammatory processes by modified lipids [12,23]. WNT pathway activation promotes the internalization of LDL by macrophages [23]. LRP5 is overexpressed by macrophages, aggregated LDLs enhancing lipid uptake, and foam cells [69].

The subendothelial space shows aggregation and/or oxidation of LDL, which triggers inflammation in response to the overexpression of cytokines/chemokines, leading to molecular adhesion. This phenomenon is characterized by the presence of immunity cells, such as macrophages, monocytes, T cells, neutrophils and dendritic cells, which participate in the development of the atherosclerotic plaque [11]. These proatherogenic processes increase the endothelial permeability turnover and then alter the interplay between ECs and VSMCs.

ECs are the site of the expression of several WNT proteins and WNT receptors [70]. Proliferation of ECs is favored by the over-activation of the canonical WNT/ β -catenin pathway [71]. Activation of the canonical WNT/ β -catenin pathway is observed after stimulation of monocyte adhesion to endothelial cells (as opposed to unstimulated monocytes) [72]. Furthermore, the WNT co-receptor LRP5 is involved in the differentiation of monocytes into macrophages [69]. The migration of monocytes and macrophages is modulated by activation of the WNT/ β -catenin pathway [23,73,74]. The release of inflammatory factors, such as interleukin 18 (IL-18) during the atherosclerosis process inhibits the activity of GSK-3 β and then increases the expression of WNT target genes to initiate SMC proliferation [75,76].

VSMC proliferation (Figure 3)

Due to EC dysfunction, VSMCs proliferate and migrate toward the intima. They then induce thickening of the subendothelial space [77]. VSMC migration from the media towards the intima is considered as one of the main characteristics of the atherosclerosis process [78]. Thus, the proliferation of VSMCs also contributes to the production of cytokines/chemokines and deposition of ECM [79].

Activation of WNT/ β -catenin signaling by WNT2 and WNT3a ligands, β -catenin accumulation and inactivation of GSK-3 β , induces VSMC proliferation [80–82]. The up-regulated WNT/ β -catenin pathway enhances in-vitro pathways of arterial VSMC remodeling [83]. Inhibition of the WNT co-receptor LRP 5/6 reduces arterial VSMC proliferation [84]. The WNT target gene, cyclin D1, is overexpressed after the denudation of the carotid artery [85,86]. Dysregulation of cell adhesion mechanisms releases β -catenin from its nuclear translocation and then, through the activation of cyclin D1, activates the proliferation of VSMCs [85,86].

ECM deposition (Figure 3)

Proliferated and migrated VSMCs synthesize an abundant array of ECM elements, such as collagen and metalloproteinases, which leads to a fibrosis process encroaching on the vessel lumen [87]. One of the key drivers of ECM deposition is TGF- β signaling, which enhances the secretion of ECM proteins. In the endothelium, activated TGF- β signaling enhances the transformation of fibroblasts into α -SMA-expressing myofibroblasts [46]. Myofibroblasts are contractile non-muscle cells that present bundles of α -SMA actin filament [88]. During differentiation into protomyofibroblasts, these cells synthesize ECM and collagen proteins [89] that contain α -SMA and non-muscle myosin II, responsible for myofibroblast retraction [90]. TGF- β signaling interacts with fibronectin extra domain A (EDA) leading to differentiation of fibroblasts into myofibroblasts [89]. Moreover, TGF- β interacts with the Smad pathway in myofibroblasts by phosphorylating Smad2 and Smad3 through TGF- β receptor 1 (TGF- β R1). Thus, the formed dimer interacts with TGF- β R2 (receptor 2) to create a heterotetramer for Smad2 and 3 phosphorylation. The complex formed by Smad2/3 binds Smad4 and translocates to the nucleus and then activates a Smad binding element (SBE) responsible for the fibrosis process [91]. In parallel, TGF- β signaling activates the PI3K/Akt pathway [92] and participates in

collagen synthesis. By activating the epidermal growth factor receptor (EGFR) and thus the PI3K/Akt pathway, TGF- β signaling enhances the expression of PAI-1 (potent fibrotic matricellular plasminogen activator inhibitor). PAI-1 is responsible for the encoding of ECM elements, i.e. collagen, metalloproteinases and fibronectin. Matrix cellular elements accumulate in the endothelium through activation of PAI-1, one of the main precursors of the fibrosis process [46].

The WNT/ β -catenin pathway, through the inhibition of GSK-3 β activity, is a well-known upstream path of the PI3K/Akt pathway [46]. The WNT/ β -catenin pathway activates TGF- β expression through a β -catenin dependent Smad2 signal responsible for the differentiation of myofibroblasts [93]. Stimulation of TGF- β signaling leads to inactivation of the WNT inhibitor, DKK1 [94].

Vascular calcification (Figure 3)

Vascular calcification is a major factor in cardiovascular morbidity and mortality. The overexpression of WNT ligands promotes the WNT target gene BMP2. BMP2 is induced by ECs that are oxidized by LDL and TNF- α [95]. BMP2 activation promotes vascular calcification by acting through the osteogenic transcription factor Msh Homeobox 2 (MSX2), which induces WNT3a and WNT7a activation and DKK1 downregulation [96].

Moreover, the chondrogenic differentiation of pericytes is observed at sites of calcification in the intima and media of arteries. This suggests a relationship between pericytes and vascular cell calcification, indicating that pericytes play a role in the different stages of vascular diseases [97]. The WNT pathway increases osteogenic and chondrogenic differentiation and decreases adipogenic differentiation of pericytes [98]. Thus, over-activation of the canonical WNT pathway can stimulate progenitor cell differentiation in the vascular wall, leading to cartilage deposition and bone in vessels [97]. Indeed, the WNT/ β -catenin pathway plays a major role in the remodeling and formation of bone [99].

5. Metabolic reprogramming: the Warburg effect

The Warburg effect, also called aerobic glycolysis, was discovered in 1930 by Otto Warburg [100]. It was initially observed in cancer cells, which were found to have a high glycolytic rate

compared with normal cells, even in a normoxic environment. This phenomenon involves a shift in ATP production from mitochondrial oxidative phosphorylation to aerobic glycolysis, leading to an overproduction of intracellular lactate. This mechanism is partially due to injury of mitochondrial respiration and an increase in the glycolytic pathway [101]. A heightening of glycolytic activity is typically indicative of a metabolic response to oxygen privation. However, in cancer cells, this occurs in the presence or absence of oxygen and then leads to the accumulation of lactic acid. Metabolites produced through this phenomenon also participate, far beyond ATP production, in the regulation of cell proliferation, apoptosis, autophagy and extracellular matrix production [101]. Thus, through activation of several glycolytic enzymes and related metabolic markers, the Warburg effect induces numerous processes such as fibrosis [46], cancers [45], neurodegenerative disease [47] and atherosclerosis [102].

Per unit of glucose, aerobic glycolysis is an inefficient means of generating adenosine triphosphate (ATP) compared to the amount obtained by mitochondrial chain respiration [103]. Nevertheless, the rate of glucose metabolism by aerobic glycolysis is higher such that the lactate production from glucose occurs 10 to 100 times faster than the complete oxidation of glucose in mitochondria [104]. Cells with a higher rate, but lower yield, of ATP production could gain a selective advantage when competing for shared and limited energy resources [105]. Moreover, when ATP demand increases by altering the demand of ATP-dependent membrane, aerobic glycolysis is rapidly stimulated [106].

Biosynthetic aspects of the Warburg effect

The Warburg Effect has been considered as an adaptation mechanism to support the biosynthetic requirements of uncontrolled proliferation. Aerobic glycolysis generates amount of metabolites involved in the regulation of cellular functions, such as proliferation, extracellular matrix production, autophagy and apoptosis [107]. The increase in glucose consumption is used as a carbon source for anabolic processes needed to support cell proliferation [108]. This excess carbon is used for the *de novo* generation of proteins, lipids and nucleotides. Thus, this excess is diverted into numerous branching pathways that emanate from glycolysis. Proliferating cells have a rate-limiting demand for ATP and a greater need of reducing equivalents in the form of nicotinamide adenine dinucleotide phosphate (NADPH). The increase in glucose uptake allows for greater synthesis of these reducing equivalents in the oxidative branch of pentose phosphatase

pathway, which are then used in reductive biosynthesis, most notably in *de novo* lipid synthesis [103,109].

Moreover, the regeneration of NAD⁺ from NADH in the pyruvate to lactate step completes the aerobic glycolysis signaling. NADH, produced by glyceraldehyde phosphate dehydrogenase (GAPDH), is consumed to generate NAD⁺ to keep glycolysis active.

Mechanisms involved in the Warburg effect (Figure 4)

Glycolysis is induced by the WNT/ β -catenin pathway activation via direct stimulation of WNT target genes (as pyruvate dehydrogenase kinase 1 (PDK1) and mono-carboxylate transporter 1 (MCT-1)) and via the stabilization of the hypoxia-inducible factor 1 alpha (HIF-1 α) [110–112].

HIF-1 α stabilization is sustained in a hypoxia-independent manner through the activation of WNT/ β -catenin target genes (c-Myc and cyclin D1), the PI3K/Akt pathway and β -catenin-induced c-Myc [113].

HIF-1 α is a heterodimeric nuclear transcription factor which is composed by two subunits: HIF-1 α and HIF-1 β . HIF-1 α stabilization results in its nuclear translocation, dimerization with HIF-1 β , and the transcription of genes encoding glycolysis enzymes [114]. Aberrant HIF signaling involves a metabolic reprogramming by increasing glycolysis and then decreasing the entry of glucose-derived carbons into the [Krebs](#) cycle leading to reduce the mitochondrial oxidative phosphorylation metabolism [115].

HIFs also promotes glutamine metabolism. HIF-1 α stabilization increases glycolysis by the stimulation of glucose transporters (Glut) mediating increased glucose uptake and the stimulation of glycolytic enzymes including HK2, PKM2, LDH-A, and PDK1 [116,117]. Thus, HIF-1 α leads to promote lactate production by increasing LDH-A activity and decreasing the conversion of pyruvate into acetyl-CoA through the upregulation of PDK1 and then the decrease of PDH activity [118]. PI3K/Akt signaling is stimulated by cytosolic accumulation of β -catenin [119]. Activation of PI3K/Akt pathway induces HIF-1 α stabilization to increase the rate of glucose metabolism [120].

After glucose entered the cell, the final step of glycolysis is the conversion of the phosphoenolpyruvate (PEP) and ADP into pyruvate and ATP, a reaction catalyzed by the enzyme pyruvate kinase M2 (PKM2). PKM2 presents low affinity with PEP [121]. Under high glucose concentration, PKM2 is acetylated and translocated to the nucleus through the action of the

peptidyl-prolyl isomerase 1 (Pin1) [122], reducing its activity and targeting PKM2 towards a lysosome-dependent degradation [123]. Nuclear PKM2 binds nuclear β -catenin and then induces c-Myc-mediated expression of glycolytic enzymes in a positive feedback loop, thus strengthening aerobic glycolysis [124].

The shunting of glucose carbons far from the [Krebs](#) cycle results in glutamine metabolism reprogramming. c-Myc stimulates glutaminolysis and drives glutamine uptake into the cytosol and the mitochondria [125]. c-Myc-activated HIF shifts from oxidative decarboxylation to reductive carboxylation of glutamine to generate citrate and acetyl-CoA for lipid synthesis [126–128]. c-Myc-induced glutamine enhances aspartate and nucleotide synthesis [125]. Then, a minor part of the pyruvate is converted into acetyl-CoA which enters the [Krebs](#) cycle and then become citrate for promoting protein and lipid synthesis. Through this complex mechanism, the Warburg effect supports a metabolic environment that allows for the rapid biosynthesis to support growth and proliferation [129].

6. Interaction between WNT/ β -catenin pathway and the Warburg effect

A partial explanation of the contrast observed between proliferating and quiescent metabolism may be the level of glucose uptake controlled by the growth factor signal transduction [130]. Activation of the WNT pathway largely suppresses the pyruvate oxidation in the [Krebs](#) cycle [131]. In parallel, the PI3K/Akt pathway rewires the glucose metabolism to enhance protein synthesis [103], leading to inhibition of the oxidative metabolism and protection against ROS stress by activation of HIF-1 α [132]. The WNT pathway synergizes with the PI3K/Akt pathway to enhance cell proliferation [133]. PDK-1 (pyruvate dehydrogenase kinase 1), HK-2 (hexokinase 2) and MCT-1 (monocarboxylate transporter 1) are considered as important WNT targets, and activation of the LDH-A (lactate dehydrogenase A) gene diverts glycolytic pyruvate away from the [Krebs](#) cycle through the conversion of pyruvate into lactate [133].

7. Warburg effect in atherosclerosis

Several metabolic dysregulations have been observed in the atherosclerotic process [134]. The phenomenon of aerobic glycolysis is increased in atheromatous plaques of ApoE $-/-$ mice [135]

and in rabbit atherosclerosis arteries [136]. Few recent studies have indicated that the process of the Warburg effect is involved in the proliferation of VSMCs, inflammation and dysregulation of ECs (**Figure 3**) [102].

Warburg effect and inflammation

The process of atherosclerosis is largely associated with inflammation [137]. Recent studies have shown a relationship between inflammation and metabolic dysfunction in atherosclerosis [138]. The aerobic glycolysis drives the M1-like pro-inflammatory macrophage phenotype leading to the stimulation of inflammation and then atherosclerosis [139]. Several key integrators of inflammation, such as IL-1 α are induced by aerobic glycolysis [140]. These integrators promote lipid plaque formation and their destabilization in ApoE $-/-$ mice [141]. Moreover, HIF-1 α activation during aerobic glycolysis promotes the differentiation of TH17 cells to aggravate the inflammatory process [142]. In atherosclerosis, the increase of glycolytic enzymes is associated with activation of circulating monocytes [143].

Warburg effect and the dysfunction of endothelial cells (ECs)

EC dysfunction enhances the accumulation of lipids and thus the formation of atherosclerotic plaques [144]. The rate of aerobic glycolysis is high in normal ECs whereas the level of miR-143 is very low. A recent study has shown that during the atherosclerotic process, the level of miR-143 and mRNA levels of key enzymes (HK2, LDHA, PKM2) of aerobic glycolysis are increased [145]. The increase of miR-143 is associated with the dysfunction of ECs.

Warburg effect and the promotion of VSMC proliferation

Several studies have shown that increased glycolytic metabolism with a bioenergetics shift occurs during VSMC proliferation and migration [146,147]. The metabolism of aerobic glucose directly affects the proliferation of VSMCs [148] and increases the PDGF-BB (platelet derived growth factor brain barrier)-induced VSMC proliferation [149]. The PKK-1 (phosphofructokinase 1) could have a major role in this determination of glucose flux through the aerobic glycolysis process. VSMC proliferation is associated with an increase in energy demand [150]. This observation may be associated with ATP production by aerobic glycolysis. Upregulation of LDH-A during aerobic glycolysis stimulates the proliferation and migration of VSMCs [151]. This

upregulation is associated with an increase of lactate and ATP production.

8. PPAR γ agonists: potential therapeutic implications

PPAR γ and Warburg effect

Few studies have examined the role of PPAR γ in the regulation of the glycolytic pathway [45,152,153]. However, it has been found that the PPAR γ shift, through a Ski oncogene, takes place through a glycolysis oxidative metabolic metabolism [154]. Administration of GW1929, a PPAR γ agonist, increases the expression of PPAR γ target genes involved in lipid oxidation in adipose tissue [155]. CD36 and FATP-1, two PPAR γ target genes, enhance palmitate oxidation into mitochondria [156].

PPAR γ and atherosclerosis

Numerous studies have shown the beneficial effect of PPAR γ agonists in the treatment of atherosclerosis by reducing inflammation, regulating endothelial function and improving the thrombosis process [157–159].

PPAR γ regulates the process of change in the immune system by modifying macrophage polarization toward an anti- or pro-inflammatory (M2 or M1) phenotype [160]. PPAR γ agonists inhibit M1 phenotype and decrease the expression of inflammatory cytokines, such as TNF- α , IL-1 and IL-6 [161]. In contrast, the differentiation of M2 macrophages (with anti-inflammatory properties) results in increased expression of PPAR γ [162]. The mechanism of macrophage polarization can be regulated by PPAR γ agonists, underlying their anti-inflammatory and anti-atherosclerosis activities [16]. Moreover, PPAR γ regulates the inflammatory involvement of the immunogenicity of dendritic cells observed in atherosclerosis [163,164], but this mechanism is not yet fully understood [16]. TZDs can suppress thromboxane synthase and receptor expression in both macrophages and VSMCs [165,166]. Thromboxane, an arachidonic acid metabolite, plays a major role in the atherosclerosis process by acting on VSMC proliferation and the aggregation of platelets. PPAR γ overexpression decreases VSMC proliferation [167,168] by arresting the VSMC re-entry cell cycle [169] and diminishes VSMC migration by reducing the mitogen-activated protein kinase (MAPK) pathway [32]. PPAR γ activation reduces inflammation by

inhibiting NF-kappaB activity [161]. Lobeglitazone and pioglitazone reduce NF-kappaB activity and then decrease VSMC proliferation [17].

Conclusion

The canonical WNT/ β -catenin pathway plays a key role in several pathophysiological mechanisms that are involved in cardiovascular diseases, such as inflammation, calcification, fibrosis and lipid infiltration. The dysregulation of this pathway in ECs results in damage to the arterial wall through a cascade of interactions between its molecular targets. Enhancing our knowledge of this pathway leads to a better understanding of the complex network of the different molecular components involved in the reprogramming of the metabolic pathway observed during the atherosclerosis process. This metabolic mechanism, known as the Warburg effect, appears to be a central element in the atherosclerosis process. Numerous studies have shown that the WNT/ β -catenin pathway and PPAR γ act in an opposing manner. Therefore, the development of therapeutic targets, such as PPAR γ agonists, for the treatment of atherosclerosis could be an interesting and innovative way to counteract the influence of the canonical WNT pathway.

Abbreviations

Acetyl-coA: Acetyl-coenzyme A; APC: Adenomatous polyposis coli; EC: endothelial cell; ECM: Extracellular-matrix; FZD: Frizzled; Glut: Glucose transporter; GSK-3 β : Glycogen synthase kinase-3 β ; HIF-1 α : Hypoxia induce factor 1 alpha; LDH: Lactate dehydrogenase; LRP 5/6: Low-density lipoprotein receptor-related protein 5/6; MCT-1: Monocarboxylate lactate transporter-1; NF- κ B: nuclear factor kappaB; PDH: Pyruvate dehydrogenase complex; PDK: Pyruvate dehydrogenase kinase; PKM2: Pyruvate kinase M2; PPAR γ : Peroxisome proliferator-activated receptor gamma; PI3K-Akt: Phosphatidylinositol 3-kinase-protein kinase B; TCF/LEF: T-cell factor/lymphoid enhancer factor; TNF- α : tumor necrosis factor alpha; TZD: Thiazolidinedione, VSMC: vascular smooth muscle cell.

Author contributions

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication

Conflict of Interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Acknowledgments

The authors thank Mr. Brian Keogh, PhD, for the proofreading of the manuscript.

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Figure 1: Atherosclerosis process in blood vessel

Endothelial cells present impaired conversion in vascular smooth cells (VSMCs), inflammatory processes, differentiation in monocytes and fibroblasts, and foam cell formation.

Figure 2: Schematic representation of the canonical WNT pathway ('activated' state and 'inactivated' state)

Figure 3: Central role of the canonical WNT/beta-catenin pathway in atherosclerosis

Abbreviations: EC: endothelial cell; ECM: extra matrix cellular; Glut: Glucose transporter; LDH: Lactate dehydrogenase; PDH: Pyruvate dehydrogenase complex; PDK: Pyruvate dehydrogenase kinase; PKM2: Pyruvate kinase M2; VSMC, vascular smooth cell

Figure 4: Mechanisms involved in the Warburg effect.

WNT target gene transcription is activated by cytosolic accumulation and then nuclear β -catenin (PDK, c-Myc, cyclin D1, MCT-1). MCT-1 favors lactate expulsion out of the cell. WNT/ β -catenin pathway activates tyrosine kinase receptors (TKRs) activity. Stimulation of HIF-1 α activity, by PI3K/Akt and β -catenin, activates the expression of the glycolytic enzymes (GLUT, HK, PKM2, LDH-A). Aerobic glycolysis is observed with the increase of lactate production and the decrease of mitochondrial respiration. HIF-1 α induced PDK phosphorylates PDH, which resulting in cytosolic pyruvate being shunted into lactate by inducing LDH-A activation. PDK inhibits the PDH complex into the mitochondria, thus pyruvate cannot be fully converted into acetyl-CoA and enter the [Krebs](#) cycle. c-Myc and cyclin D1 also stimulates LDH-A activity which converts cytosolic pyruvate into lactate. Activated PKM2 translocates to the nucleus to

996 bind β -catenin and then to induce the expression of c-Myc. Glucose metabolism over-activation
997 leads to nucleotide synthesis; glutaminolysis to lipid and amino-acid synthesis and lactate release.
998 Abbreviations: Acetyl-coA: Acetyl-coenzyme A; Glut: Glucose transporter; HIF-1 α : Hypoxia
999 induce factor 1 alpha; LDH: Lactate dehydrogenase; MCT-1: Monocarboxylate lactate
1000 transporter-1; PI3K-Akt: Phosphatidylinositol 3-kinase-protein kinase B; PDH: Pyruvate
1001 dehydrogenase complex; PDK: Pyruvate dehydrogenase kinase; PKM2: Pyruvate kinase M2.





