PI3Kγ in hypertension: a novel therapeutic target controlling vascular myogenic tone and target organ damage

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Received 6 February 2012; revised 25 April 2012; accepted 16 May 2012; online publish-ahead-of-print 19 May 2012

Abstract

In the past decade, several studies have characterized a number of cellular and molecular mechanisms that contribute to the regulation of the vascular myogenic response, thus affecting blood pressure regulation. Recently, phosphoinositide 3-kinase γ (PI3Kγ) has been identified as a main regulator of vascular myogenic tone and blood pressure, a result further strengthened by a highly significant genome-wide association of a single nucleotide polymorphism flanking this gene with blood pressure regulation, in a large human population. The goal of this review is to summarize the available information regarding the mechanism whereby PI3Kγ exerts blood pressure control, regulating myogenic tone at the level of L-type calcium channel in smooth muscle cells. Moreover, an overview of the pharmacological approaches available for targeting this signalling pathway shows that PI3Kγ is a suitable candidate for antihypertensive therapy, capable of lowering blood pressure. Finally, a survey of the studies dissecting the role of PI3Kγ in pathological conditions that are typically induced by hypertension in its target organs provides a more complete picture of the high potential of this novel therapeutic approach for fighting hypertension and, at the same time, its target organ damage, independently of blood pressure-lowering effects.

Keywords

Phosphoinositide 3-kinase γ • Myogenic tone • Cell signalling • Inflammation • Signal transduction

1. Introduction

Arterial hypertension is a cardiovascular risk factor and a major healthcare problem. So far, although it is well known that the vasculature, kidney, and central nervous system contribute to the development of hypertension,¹ the molecular pathophysiological mechanisms involved in the onset of higher blood pressure have not been completely clarified. However, it is generally recognized that both human hypertension and experimental models of hypertension are mainly characterized by increased peripheral vascular resistance.²–⁴ Indeed, whatever the primary challenge leading to high blood pressure levels, the establishment of a chronically hypertensive state involves functional and structural adaptation in resistance arteries.⁵ In particular, elevation of intravascular pressure causes constriction of vascular smooth muscle cells (VSMCs) in resistance arteries, and this behaviour, known as myogenic tone, is a key element for maintenance of blood pressure.⁶–⁸ Moreover, this myogenic behaviour, which has also been demonstrated to occur independently of neural control in isolated vessels, is considered to be an intrinsic function of the smooth muscle vessel wall,⁹ and can be described in general terms with three phases.⁹ The first phase, consisting of the development of myogenic tone or basal tone, is associated with a large increase in intracellular calcium via flux through the L-type voltage-gated calcium channel (LTCC). In the second phase, there is a further constriction in response to an increase in intraluminal pressure, with no additional change in intracellular concentrations of calcium, but with a calcium sensitization of the mechanical apparatus inside the cell. In the final phase, when the arterial wall is unable to maintain a constriction against mounting pressures, a forced dilatation could happen.¹⁰

In the past decade, several studies have begun to yield insights into the cellular and molecular mechanisms contributing to the regulation of the vascular myogenic response and novel intracellular pathways that regulate it positively or negatively, affecting blood pressure, have been characterized. In particular, innumerable signalling pathways involved in the initiation, maintenance, and control of myogenic tone and autoregulation have been identified, and include changes in intracellular calcium, protein kinases, and diacylglycerol, as well as modulation of ions and transient receptor potential-like channels.¹⁰ Here, we review pathophysiological functions of phosphoinositide 3-kinase (PI3K) signalling in the cardiovascular system. In particular,
we discuss the involvement of the γ-isoinform in the regulation of vascular tone and blood pressure, revealing a novel signalling pathway that is targeted to fight hypertension.

On this issue, recent evidence in humans emphasizes that phosphoinositide 3-kinase γ (PI3Kγ), a lipid and protein kinase that we have recently identified as being a main regulator of vascular myogenic tone, is an emerging suitable candidate for therapeutic intervention in hypertension. In particular, the International Consortium of Blood Pressure Genome-Wide Association Studies (ICBP-GWAS) found a genome-wide significant association, in ~120 000 individuals, of six new loci influencing pulse pressure (PP) and mean arterial pressure (MAP).

Among these, the single nucleotide polymorphism (SNP) rs17477177 on chromosome 7q22.3 caught our attention, because this SNP flanks the region PIK3CG encoding for PI3Kγ (the most significant association, with \( P = 2.3 \times 10^{-13} \)). This genome-wide association of a new locus flanking the PIK3CG region in PP and MAP strengthens our findings in experimental models, showing a pathophysiological link between PI3Kγ and blood pressure regulation.

In particular, the authors have studied the associations of risk scores with hypertension and blood pressure-related outcomes, including coronary heart disease, heart failure, stroke, echocardiographic measures of left ventricular structure, pulse wave velocity, renal function, and renal failure. The PP SNPs risk score was associated with prevalent hypertension, incident stroke, and coronary heart disease, while the MAP SNPs risk score was associated with hypertension, coronary heart disease, stroke, and left ventricular wall thickness, thus confirming the clinical relevance of the reported measures of blood pressure phenotype. The discovery of the genome-wide association between the SNP flanking the region PIK3CG and PP/MAP not only brings to light the human counterpart of our findings in mice, but also suggests the possibility for translating to humans the use of PI3Kγ inhibitors as novel tools to treat hypertension.

2. PI3K family: an overview

Phosphoinositide 3-kinases are a conserved family of enzymes involved in intracellular signal transduction, and are characterized by dual protein and lipid kinase activity. Members of this family differ in protein structure, expression, regulation, and substrate specificity, but all share a common catalytic function; they phosphorylate the 3-hydroxyl group of the inositol ring of three species of phosphatidylinositol (PtdIns) lipid substrates, namely, PtdIns, PtdIns-4-phosphate (PtdIns4P) and PtdIns-4,5-bisphosphate (PtdIns(4,5)P2).

Historically, PI3Ks have been divided into three classes (class I, class II and class III), based on structural and functional aspects (Table I). Class IA and IB PI3Ks are heterodimeric enzymes composed of a regulatory adapter subunit coupled to a tightly bound catalytic subunit, and they are the only PI3Ks that phosphorylate PtdIns(4,5)P2 to PtdIns(3,4,5)P3. Class IA catalytic subunits include p110α, β, and δ, whereas the class IB catalytic subunit is p110γ. PI3Kα and β are ubiquitous and abundantly expressed. The expression of PI3Kδ and γ has been considered for a long time to be restricted mainly to leucocytes; however, the expression of PI3Kγ has recently also been described in several cells of the cardiovascular system, including cardiomyocytes, vascular endothelial and smooth muscle cells, and platelets. A peculiarity of this enzyme is its capability to exert both kinase-dependent and kinase-independent actions. For Class II PI3Ks, three different monomers, producing PtdIns(3)P from PtdIns, have been identified: the ubiquitous PIK3CG and PIK3CD, and the liver-specific PIK3CD-γ. The vacular protein sorting 34 (Vps34), a ubiquitously expressed protein, is the only member of class III, and generates only PtdIns(3)P.

Upon receptor tyrosine kinase and G-protein-coupled receptor (GPCR) stimulation or Ras activation, these 3-phospho-inositides coordinate the localization and function of multiple effector proteins, which bind these lipids through specific lipid-binding domains, namely the pleckstrin homology domain, the phox homology domain, and the Fab 1, YOTB, Vac 1, and EEA1 domain. These domains, by binding phospholipids, facilitate the recruitment of downstream effectors to the plasma membrane. Protein kinase B (PKB/Akt), a serine–threonine kinase, is the archetypal enzyme activated by PI3Ks. Akt1, among the three different Akt isoforms, plays the most relevant role in cardiovascular functions. Other effectors able to bind PI(3,4,5)P3, through the pleckstrin homology domain, include glycogen synthase kinase 3, Raf, forhead box transcription factors, RhoA, phospholipase C and guanine nucleotide exchange factors for small GTPases, with a potential involvement in the cardiovascular system. Another level of regulation of PI(3,4,5)P3 is due to the opposite action of PI3Ks and distinct phosphatases, such as SHIP1 and SHIP2 (SH2-containing inositol phosphatase) as well as PTEN (phosphatase and tensin homologue), which dephosphorylate the inositol ring of this lipid at position 5 or 3, respectively.

Among the several PI3K isoforms, class I PI3Ks are the best-characterized isoforms, whereas less is known about class II and class III, particularly in the cardiovascular system. Given the wide distribution of PI3Ks, a global inhibition would probably be deleterious to organisms. For this reason, the identification of roles and mechanisms of action of PI3K isoforms in normal physiology and disease has become a compelling mission in order to find drugs that target specific PI3K isoforms.
3. PI3K\(\gamma\) in hypertension

Since its initial description, the \(\gamma\)-isoform of PI3K has been considered to be almost exclusively expressed by leucocytes.\(^{16}\) Nevertheless, an increasing number of studies in the last decade, prompted by the fact that PI3K\(\gamma\) is the typical isoform activated by GPCRs, and the fact that GPCR signalling is historically recognized as crucial for the modulation of cardiovascular physiology, allowed recognition of a complex pattern of expression that includes the presence of PI3K\(\gamma\) in tissues other than immune cells. Another fascinating aspect that stimulated the search for roles of PI3K\(\gamma\) outside the immune system was the common relay of environmental stress signals to cells of the cardiovascular and immune systems, following a series of intriguingly similar pathways, among which calcium regulation appears to be a remarkably recurring theme.\(^{25,26}\) Thus it became increasingly clear that PI3K\(\gamma\) is widely distributed in many cells of the cardiovascular system, namely cardiomyocytes, endothelial cells, vascular smooth muscle cells, and platelets.\(^{29}\)

The availability of genetically modified mice lacking PI3K\(\gamma\) opened up the possibility for study of its function in the cardiovascular system in vivo, bringing to light a novel molecular target in cardiovascular diseases.\(^{27–32}\)

The finding that PI3K\(\gamma\) signalling was also active in smooth muscle cells prompted the study of the function of this enzyme in the delicate balance between vasorelaxation and vasoconstriction induced by the vast variety of vasoactive GPCR agonists.\(^{13,33–36}\)

Interestingly, several studies have reported a role for PI3K in smooth muscle contractility induced by the GPCR agonist angiotensin II (Ang II).\(^{31–37}\) and PI3K\(\gamma\)s have long been considered as crucial signal transduction elements downstream of Ang II receptors. However, the nature of the PI3K isoform remained elusive for a long time, until the use of antibodies that selectively block PI3K\(\gamma\) proved to be effective in inhibiting Ang II-induced production of PtdIns(3,4,5)P\(_3\) and influx of calcium in rat portal vein myocytes.\(^{34}\)

These data strongly suggested that Ang II requires PI3K\(\gamma\) to stimulate calcium channels in smooth muscle and induce the calcium influx, thereby governing the vascular contractile response, a process that is mainly controlled by LTCCs. Indeed, an anti-PI3K\(\gamma\) antibody (anti-PI3K p110\(\gamma\); Santa Cruz Biotechnology, Santa Cruz, CA, USA) blocked the Ang II-dependent activation of LTCCs in portal myocytes, thus demonstrating that this enzyme is the link between Ang II receptors and extracellular Ca\(^{2+}\) influx.\(^{34}\)

However, the idea of a crucial role for PI3K\(\gamma\) in the regulation of vascular tone came when researchers in our laboratory found that mice lacking PI3K\(\gamma\) are protected from the hypertensive effect of chronic Ang II exposure.\(^{17}\) Moreover, the absence of PI3K\(\gamma\), as well as the expression of a PI3K\(\gamma\) kinase-dead mutant, causes a significant reduction in Ang II-evoked L-type Ca\(^{2+}\) influx and contractility in whole vessels.\(^{13}\)

Viard et al., shortly before, showed that in nervous system cells the PI3K-induced calcium entry occurs through the phosphorylation of the Ca\(_{\beta} \beta_2\) subunit of the LTCC on an Akt consensus site, which promotes its translocation to the plasma membrane.\(^{37}\) Notably, researchers in our laboratory found in resistance arteries that the molecular link between PI3K\(\gamma\) and LTCCs was the kinase PKB/Akt, because the expression of a dominant negative PKB/Akt mutant in vessels drastically reduces Ang II-evoked vasoconstriction.\(^{13}\)

More recently, we have revealed, for the first time, that inhibition of kinase-dependent PI3K\(\gamma\) signalling, as well as of its downstream signalling, Akt, is able markedly to impair the vascular myogenic tone, in an experimental setting for isolated vessels where the myogenic response to perfusion pressure represents the main component of vascular tone, in the absence of any neurohormonal influence.\(^{15}\) On this issue, it is tempting to regard PI3K\(\gamma\)/Akt signalling as one of the main pathways recruited by pressure-induced mechanical stress and strictly required for establishment of myogenic tone in response to increases in intraluminal pressure in resistance arteries.

Furthermore, our novel data on PI3K\(\gamma\) have added a further piece of knowledge on how this signalling pathway regulates myogenic tone in resistance arteries, by finely tuning LTCC activity.

As stated above, a main role in myogenic vascular contraction is played by calcium influx through LTCCs. Signalling through Akt is of key importance for the structural organization and functionality of the LTCC complex at the plasma membrane. In particular, regulation of LTCC activity has been demonstrated to be directly related to the Akt-mediated phosphorylation of the accessory/chaperone subunit Ca\(_{\alpha} \beta_2\).\(^{37,38}\) which in turn, protects the pore-forming Ca\(_{\alpha} \alpha_1\)C subunit from the proteolytic degradation system.\(^{34}\) This complex regulation results in a greater density of Ca\(_{\alpha} \alpha_1\)C in the plasma membrane and a consequent increase in the open probability of LTCCs. The recent finding that inhibition of PI3K\(\gamma\) signalling finely modulates LTCCs by impairing both Ca\(_{\alpha} \beta_2\) phosphorylation and Ca\(_{\alpha} \alpha_1\)C translocation in the plasma membrane of smooth muscle cells,\(^{12}\) explains how PI3K\(\gamma\) is capable of exerting a major role in the establishment of vascular myogenic tone.

It is also worth emphasizing that we documented that PI3K\(\gamma\) signalling is crucial not only for Ang II-induced L-type Ca\(^{2+}\) influx but also for oxidative stress,\(^{13}\) thus strengthening the reported common link between myogenic tone and oxidative stress.\(^{39}\) This evidence also suggests that the possible role of PI3K\(\gamma\) in regulating the vascular inflammatory response induced by high blood pressure requires further exploration.

With regard to how PI3K\(\gamma\) is activated, it is well known that the \(\gamma\)-isoform is activated by the \(\beta\) subunit of the GPCR. Indeed, stimulation of the Ang II type 1 receptor (AT1R) by Ang II in vascular myocytes has been demonstrated to activate PI3K\(\gamma\), which, in turn, regulates LTCCs.\(^{37,38}\)

In contrast, more enigmatic is how the perfusion pressure per se, devoid of neurohormonal signals, can activate a \(\beta\)\(\gamma\)-dependent enzyme, such as PI3K\(\gamma\). Interestingly, it has been recently reviewed how cellular mechanotransduction of pressure could be mediated by membrane receptors and associated second messengers.\(^{40}\) On this issue, it has been shown that the AT1R could be required for mechanosensitivity, even in the absence of its ligand, Ang II. The capability of these receptors to adopt an active conformation, when recruited by a mechanical stimulus, allows G protein coupling and consequent \(\beta\)\(\gamma\) activity.\(^{40}\) Thus, it is tempting to speculate that these mechanisms through AT1R/\(\beta\)\(\gamma\) could activate PI3K\(\gamma\) signalling, allowing a fine modulation of myogenic response through regulation of LTCC subunits, in both a ligand-dependent and a ligand--independent manner (Figure 1).

We believe that now a further piece of knowledge has been added on the signalling pathways activated when the mechanical stress caused by pressure itself is perceived by the vessel.

4. PI3K\(\gamma\) in pressure-induced target organ damage

Given the wide expression of PI3K\(\gamma\) in the cardiovascular system and the fact that the heart is subjected to the continuous challenge of high
Interestingly, while both PI3K<sub>g</sub> enzyme, namely the kinase dependent and the kinase independent, can recruit PI3K<sub>g</sub> to the plasma membrane and consequent increased LTCC open probability. Perfusion pressure per se can induce the GPCR to adopt an active conformation, when recruited by a mechanical stimulus, allowing G protein coupling and consequent βγ activation that activates PI3K<sub>g</sub> signalling to regulate of LTCC subunits. Abbreviations: α1C and β2 are LTCC subunits; AngII, angiotensin II; βγ, Gβγ; Go, Golgi complex; GPCR, G-protein coupled receptor; M, mitochondria; PIP<sub>2</sub>, phosphatidylinositol bisphosphate; PIP<sub>3</sub>, phosphatidylinositol trisphosphate; rER, rough endoplasmic reticulum.

Figure 1 PI3K<sub>g</sub> signalling in smooth muscle cells. Agonist-induced stimulation of the GPCR in vascular smooth muscle cells activates PI3K<sub>g</sub> that, in turn, regulates, through Akt-dependent phosphorylation of LTCC subunit Ca<sub>aβ2a</sub>, translocation of the pore-forming Ca<sub>aα1C</sub> subunit in the plasma membrane and consequent increased LTCC open probability. Perfusion pressure per se can induce the GPCR to adopt an active conformation, when recruited by a mechanical stimulus, allowing G protein coupling and consequent βγ activation that activates PI3K<sub>g</sub> signalling to regulate of LTCC subunits. Abbreviations: α1C and β2 are LTCC subunits; AngII, angiotensin II; βγ, Gβγ; Go, Golgi complex; GPCR, G-protein coupled receptor; M, mitochondria; PIP<sub>2</sub>, phosphatidylinositol bisphosphate; PIP<sub>3</sub>, phosphatidylinositol trisphosphate; rER, rough endoplasmic reticulum.

blood pressure, here we will review a large body of literature that has, in the past decade, explored the role of PI3K<sub>g</sub> in cardiac remodelling and heart failure, in the light of the increasing knowledge concerning the involvement of this signalling in control of blood pressure.

When PI3K<sub>g</sub>-null mice were generated, the first evidence that came to light was that targeted inactivation of this enzyme enhances in vivo and in vitro contractility of cardiomyocytes in basal conditions, indicating that PI3K<sub>g</sub> is as a negative regulator of cardiac muscle contractility.27 On the contrary, this cardiac phenotype, counterintuitive as regarding the antihypertensive effect of blocking this signalling, further emphasizes the major role of vascular PI3K<sub>g</sub> signalling in blood pressure control.

However, when a pressure overload was imposed on the left ventricle, PI3K<sub>g</sub> activity was found to be increased in the heart.28 This finding paved the way for exploration of this signalling in cardiac remodelling and heart failure. It is important to note that, as indicated in a number of studies, GPCR signalling, which is linked to PI3K<sub>g</sub> activation, plays a crucial role in the compensatory hypertrophic response to mechanical overload. On this issue, the hypertrophic response observed in mice chronically treated with β-adrenergic agonists, accompanied by fibrosis and heart tissue damage, is less pronounced when PI3K<sub>g</sub> is absent.29 As a consequence, it could be envisaged that inhibition of the function of PI3K<sub>g</sub> might prevent cardiac hypertrophy and failure in response to hypertension.

In order to characterize the role of PI3K<sub>g</sub> in the heart further, knock-in mice expressing a kinase-dead PI3K<sub>g</sub> (PI3K<sub>g</sub>KD) were generated, allowing disclosure of the contribution of both faces of this enzyme, namely the kinase dependent and the kinase independent. Interestingly, while both PI3K<sub>g</sub>-null and kinase-dead mice exhibited an overlapping impairment of the immune response, the kinase-dead mutant mice did not show enhanced myocardial contractility and were protected from cardiac damage induced by pressure overload, which is the converse of what was observed in PI3K<sub>g</sub>-null mice.30 In particular, PI3K<sub>g</sub>-deficient mice subjected to a short period of haemodynamic overload showed massive cardiac necrosis, which was completely absent in PI3K<sub>g</sub>KD mice.30 Investigation of cardiac intracellular signalling led to understanding of the different impact of the absence or the enzymatic inactivation of PI3K<sub>g</sub>, in response to pressure overload. Indeed, while PKB/Akt and, in general, mitogen-activated protein kinase activation, was not up-regulated in both mutant strains in response to pressure overload, a different cAMP homeostasis was observed.30 A previous study had already reported that PI3K<sub>g</sub> modulates baseline cAMP levels in isolated cardiomyocytes.27 The generation of PI3K<sub>g</sub>KD mice led to the finding that regulation of cAMP levels are independent of the kinase activity of PI3K<sub>g</sub>, because the elevation of cAMP levels in PI3K<sub>g</sub>-null hearts was dramatically higher both in basal conditions and in response to pressure overload.30

These results highlighted a dual role of PI3K<sub>g</sub>. On the one hand, it controls mitogen-activated protein kinase and Akt signalling through its kinase activation and possibly by inducing fibrosis and hypertrophy, respectively. On the other hand, PI3K<sub>g</sub> regulates protein interactions in a kinase-independent way, and in particular is an essential component of a complex controlling phosphodiesterase-mediated cAMP hydrolysis, inducing cAMP level reduction, and eventually modulating cardiac contractility in a negative manner.

More recent studies have further characterized the actions accomplished by PI3K<sub>g</sub> in the heart, clarifying that it participates in the response to adrenergic stimulation of the heart by engaging cAMP.
and phosphoinositide second messenger signalling cascades, by sustaining β-adrenergic receptor internalization through its catalytic function, and by controlling phosphodiesterase 3B activity via a kinase-independent mechanism. In particular, it has been shown that PI3Kγ anchors protein kinase A, which, in turn, activates phosphodiesterase 3B to enhance cAMP degradation and phosphorylates PI3Kγ to inhibit PI3P production, thus providing a local feedback control.\(^1\)

Finally, to better define the translational potential of PI3Kγ inhibition in preclinical models of pressure-induced heart failure and to clarify the cell types involved, we analysed PI3Kγ KD mice and bone-marrow chimeras with bone-marrow-derived cells and hearts of different genotypes subjected to long-term pressure overload.\(^3\) With the use of PI3Kγ KD bone-marrow chimeras, we have demonstrated that inhibition of PI3Kγ in both bone-marrow-derived and cardiac cells is required for protection from cardiac dysfunction, indicating that PI3Kγ exerts combined effects in different cell types during the cardiac response to pressure overload and transition towards heart failure.\(^3\)

5. Therapeutic applications of PI3Kγ selective inhibitors: novel antihypertensive?

The discovery of a central role for PI3Kγ in diseases caused by dysfunctional immune responses, whose conventional treatment only sometimes gives a fairly good control of disease progression and might have important adverse effects, has led to the development of selective pharmacological inhibitors of this molecular target. These diseases include autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis, allergic disorders, respiratory diseases, such as asthma and chronic obstructive pulmonary disease, and also cardiovascular pathologies whose onset and/or progression is driven by an inflammatory insult, such as myocardial infarction and atherosclerosis.

In the last 10 years, several small molecules targeting PI3Kγ have been developed by different companies (Table 2) and rapidly explored in experimental models of immune disease.\(^4\)–\(^5\) Furthermore, we have recently demonstrated a beneficial role of PI3Kγ inhibition in cardiomyopathy caused by pressure overload, in which challenges for cardiac and inflammatory cells are strictly intertwined.\(^3\)

Our results identified a role for PI3Kγ in the regulation of myogenic tone\(^1\) and the hypertensive response to Ang II,\(^3\) which led us to explore the effectiveness of inhibition of this signalling in hypertension.\(^1\) The use of two independent small molecules inhibiting PI3Kγ, namely AS605240, which is already commercially available, and the novel molecule developed in our laboratory, GE21 (patent pending), allowed us to disclose, for the first time, an unprecedented antihypertensive effect of the inhibition of kinase-dependent signalling of PI3Kγ,\(^1\) which until then had gained increasing attention only as a promising pharmacological target for the treatment of inflammation and for protection against maladaptive cardiac remodelling. We further disclosed that the antihypertensive effect of PI3Kγ inhibitors is realized by reducing total peripheral resistance, obtained by countering the development of myogenic tone in response to pressure and thus relaxing resistance arteries.\(^1\)

On the whole, the data obtained with drugs that selectively inhibit the PI3Kγ isofrom and the recent genetic evidence in humans that associates PI3Kγ with blood pressure regulation strongly support the premise that inhibition of this pathway could be considered further as a novel tool to fight hypertension and its deleterious damage in target organs.

6. Perspectives

In the light of the recently discovered haemodynamic effect of PI3Kγ inhibition, at least two aspects of potential clinical use should be considered.

First, an interesting issue emerges when considering that PI3Kγ signalling has a well-known role in inflammation, and that inflammation represents a consistent pathophysiological trait of hypertension-induced organ damage.\(^1\) Thus, the use of PI3Kγ inhibitors could be a combined strategy, with beneficial effects for both haemodynamics and inflammation-related organ damage. This seems especially intriguing because the use of classical non-steroidal anti-inflammatory drugs is frequently reported to dampen the blood pressure-lowering actions of various antihypertensive medications,\(^4\) in contrast to that observed with PI3Kγ inhibitors. Therefore, it would be important in the future to define the effect of PI3Kγ inhibition better in the inflammatory response accompanying hypertension, in order to validate the use of these inhibitors as a double strategy to fight both hypertension and hypertension-related inflammation and/or concomitant inflammatory diseases.

The second aspect to be borne in mind is that recent studies identify PI3Kγ as a new target in atherosclerosis, because it modulates multiple stages of plaque formation, such as fatty streak constitution, cellular composition, and final fibrous cap establishment. In particular, it has been shown that pharmacological inhibition of PI3Kγ alleviates atherosclerotic plaque development in two murine models of atherosclerosis, an effect ascribable to loss of PI3Kγ function in immune cells.\(^6\) Thus, PI3Kγ inhibition will allow the treatment of hypertension, which represents one of the main risk factors for atherosclerosis, while reducing inflammation in the plaque, offering a unique therapeutic strategy, in comparison to the currently available antihypertensive armamentarium.

<p>| Table 2 PI3Kγ selective inhibitors: therapeutic applications in experimental models of diseases |</p>
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Acknowledgements

We would like to thank Dr. Angelo Maffei for critical reading of the manuscript and Dr. Antonio Damato for technical support.

Conflict of interest: none declared.

Funding

This work was supported by Italian Ministry of Health ‘Ricerca corrente’, ‘Cinquepermille’, ‘Ricerca finalizzata 2007’, by ‘Sapienza’ University ‘Ateneo Federato 2008’, and by ‘ Fondazione Roma’ to G.L.

References


