

Chapter 2

Phosphoinositides and Cardiovascular Diseases

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Abstract Phosphoinositides (PIs), a family of phosphorylated derivatives of the membrane lipid phosphatidylinositol, are established regulators of multiple cellular functions. An increasing amount of evidence has highlighted potential links between PI-mediated signaling pathways and the etiology of many human diseases, including cardiovascular pathologies. This chapter will provide a detailed overview of the peculiar functions of the major cardiovascular PIs in the pathogenesis of atherosclerosis, heart failure, and arrhythmias.

Introduction

Inositol phospholipids or phosphoinositides (PIs) are a family of phosphorylated derivatives of the membrane lipid phosphatidylinositol (Sasaki et al. 2007). Among these, phosphatidylinositol 4'5'-bisphosphate (PIP2) and phosphatidylinositol 3'4'5'-trisphosphate (PIP3) represent the two major plasma membrane PIs (Czech 2000). PIP2 is synthesized from the membrane phosphatidylinositol via sequential activation of two phosphoinositide kinases, PI4K and PI5K that catalyze the addition of a phosphate group on the inositol D4 and D5 positions, respectively (Lee and Rhee 1995). In the heart, PIP2 can function as a key second messenger, controlling the activity of a wide plethora of ion channels and thus contributing to heart rhythm modulation. Alternatively, PIP2 plays an important role as a substrate for the phospholipase C (PLC), which hydrolyses PIP2 leading to inositol trisphosphate (IP3) and

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diacyl-glycerol (DAG) second messenger formation. Among these, IP3 has emerged as a key modulator of cardiac excitation–contraction coupling as well as of cardiac hypertrophy. In addition, PIP2 constitutes the preferential substrate of phosphatidylinositol 3 kinases (PI3Ks) that, by adding a phosphate group on the inositol D3 position, generates the second messenger PIP3 (Cantley 2002). In the cardiovascular system, PIP3 is mainly involved in the control of cardiomyocyte apoptosis, hypertrophy, and contractility.

Deregulation of PI metabolism underlies the onset and progression of several cardiovascular pathologies, ranging from atherosclerosis to heart failure, with different PIs playing specific non-redundant roles in defined pathological contexts. This chapter will provide a detailed overview of the pathophysiological function of the major cardiovascular PIs, including PIP2, and its derivative products, IP3, and PIP3. We will first focus on their involvement in vascular diseases, such as atherosclerosis, where PIs are key regulators of multiple cell types involved in the onset and progression of the disease. Atherosclerosis-associated vascular damage can in turn trigger cardiac dysfunction, ultimately leading to heart failure, a complex multi-factorial disease, whose progression can be affected by PI level modulation. A dedicated section will describe the role of PIs in the crucial phases of heart failure evolution. Finally, we will report the impact of PI activity on heart rhythm disturbances that often occur in association with heart failure, further triggering life-threatening complications.

Atherosclerosis

Atherosclerosis is a systemic disease of the vessel wall occurring principally in large and medium-size elastic and muscular arteries, such as aorta, carotids, coronaries, and peripheral arteries. The pathology consists in an altered permeability of the endothelium that permits the accumulation of lipoproteins within the intima, resulting in endothelial cell activation and leukocyte recruitment (Ross 1995). This process leads to the formation of the atherosclerotic plaque that can be subjected to rupture, leading to thrombosis and consequent occlusion of the vessel. Among cardiovascular PIs, PIP3 represents the major regulator of the atherosclerotic process and is critically involved in the function of key cellular players such as leukocytes and platelets. An additional contribution to the atherosclerotic vascular remodeling is provided by IP3, which primarily regulates the activity of endothelial and vascular smooth muscle cells.

PIP3

Inflammation represents a key element of the atherosclerotic process and involves the migration of leukocytes into the atherosclerotic lesion (Ross 1999). Once recruited to the inflammatory site, leukocytes are able to secrete inflammatory mediators, to

proteolytically cleave the extracellular matrix and to cross-talk with local vascular cells (Libby 2002). PIP3 signaling is a key participant in each of these events. PIP3 is produced by all class I PI3Ks, but the inflammatory aspect of atherosclerosis is dominated by the pool of PIP3 produced by PI3K γ , an enzyme highly expressed in the hematopoietic cell lineage (Fougerat et al. 2009). In agreement, the inhibition of the PI3K γ -PIP3-Akt signaling pathway in murine models of atherosclerosis (ApoE- or LDLR-deficient mice) significantly reduces the development of early and advanced atherosclerotic lesions (Fougerat et al. 2008). Similar findings have been reported in PI3K γ -ApoE double knock-out mice, which exhibit smaller lesions than single ApoE-knockout controls (Chang et al. 2007). The reduced inflammation present in these mice is linked to the impaired migration of PI3K γ -null neutrophils and macrophages toward different chemokine stimuli and to their defective oxidative burst (Hirsch et al. 2000; Patrucco et al. 2004). Furthermore, transgenic mice carrying a hyperactivation of the PI3K γ -PIP3 pathway are not able to correctly localize PIP3 at the leading edge of the migrating cell, thus resulting in decreased directional migration in response to selective stimuli (Costa et al. 2007). Indeed, the formation of a proper leading edge is strictly required for the directional migration of leukocytes to the site of inflammation (Ridley et al. 2003).

Critical events following exacerbated plaque inflammation and rupture are platelet aggregation and thrombus formation, the main causes of infarction and stroke. Several factors regulate these processes, including the functional state of cellular enzymes and membrane receptors. Platelet adhesion and aggregation at sites of vascular injury are dependent on the interaction between von Willebrand factor (vWF) and two major platelet adhesion receptors, glycoprotein (GP) Ib-V-IX and integrin $\alpha_{IIb}\beta_3$. Several lines of evidence have implicated PI3K-PIP3 in such signaling pathways (Yap et al. 2002; Kasirer-Friede et al. 2004; Kim et al. 2009). Indeed, PIP3 is produced in platelets upon the interaction of the GpIb-V-IX complex with vWF and is required for the activation of a cascade involving NO/cGMP/PKG, leading to p38 MAP-kinase and ERK signaling, calcium mobilization, and, in turn, to integrin $\alpha_{IIb}\beta_3$ -dependent stable adhesion and aggregation (Li et al. 2006; Stojanovic et al. 2006; Yin et al. 2008). Several evidences demonstrate that the PIP3 produced by PI3K β is essential in mediating these effects (Jackson et al. 2005). In vivo, platelet tethering is followed by stable adhesion and spreading, a process involving collagen receptors. Several studies have demonstrated a critical role for PIP3 in the organization of a signal transduction network initiated by the collagen receptor GpVI (Pasquet et al. 1999). In this context, PIP3 is essential for the stable interaction of PLC γ 2 with the plasma membrane, thereby promoting PIP2 hydrolysis (Ragab et al. 2007). Blockade of PI3K β -PIP3 signaling pathway results in an impaired activation of downstream signaling molecules, resulting in defective aggregation responses (Canobbio et al. 2009; Martin et al. 2010; Consonni et al. 2012).

IP3

Monocyte-derived macrophages play a key role in the pathogenesis of atherosclerosis since they are activated within the atheromatous lesions (Ross 1986). Macrophages are able to accumulate lipids mainly through LDL receptor- and scavenger receptor-dependent mechanisms. Binding of LDL to these receptors stimulates PI breakdown, thus inducing a rapid IP3 production and subsequent Ca^{2+} mobilization from intracellular stores (Ishikawa et al. 1989). LDL plays an important role in the process of atherogenesis, since this lipid is able to alter the function not only of macrophages but also of other cell types involved in the pathophysiology of the disease. Indeed, LDL stimulates the production of IP3 in endothelial cells (Myers et al. 1992; Hamilton et al. 1994) and in vascular smooth muscle cells (Resink et al. 1992). In addition to humoral factors, physical or mechanical stresses also contribute to vascular remodeling. Indeed, pressure by itself triggers IP3 production and intracellular calcium release in rat vascular smooth muscle cells, resulting in cell proliferation and DNA synthesis, two processes that are closely related to the smooth muscle cell expansion and plaque formation (Hishikawa et al. 1994).

Hypertrophy and Heart Failure

Coronary atherosclerosis is the most important primary etiologic factor in the industrialized world predisposing to ischemic heart disease and the subsequent development of heart failure (Redfield 2002). Heart failure is a complex, multifactorial disease that is characterized by the inability of the heart to pump sufficient blood to meet the metabolic needs of the body. An essential precursor of heart failure is represented by cardiac hypertrophy, which is an adaptive response of the heart to stress conditions, such as volume overload and pressure overload, resulting in an abnormal increase in cardiac mass. Although at the beginning hypertrophy has beneficial effects, resulting in normalized wall stress, chronic hypertrophy has maladaptive features and is associated with a significant increase in the risk of heart failure. In recent years, PIP3 has emerged as a critical switch of cardiac hypertrophy and heart failure development, with selected pools of PIP3 playing distinct non-redundant roles. Also, IP3 and its immediate precursor PIP2 have been shown to participate to these processes, with IP3 regulating cardiac hypertrophy in response to selected stimuli and PIP2 functioning as a key regulator of cardiomyocyte apoptosis and the subsequent transition to heart failure.

PIP3

In the healthy heart, the pool of PIP3 produced by PI3K α is a master regulator of cardiomyocyte metabolism and survival (Damilano et al. 2010). Selective cardiac overexpression of a dominant-negative PI3K α results in smaller cardiomyocytes and

reduced heart size, with normal tissue architecture and contractility (Shioi et al. 2000; Crackower et al. 2002; McMullen et al. 2003). On the other hand, selective cardiac overexpression of a constitutively active PI3K α leads to myocardial hypertrophy, without progression to cardiac dysfunction (Shioi et al. 2000). These findings phenocopy the genetic loss of myocardial PTEN, that leads to PIP3 accumulation (Crackower et al. 2002). All these results support the conclusion that PI3K α boosts myocardial growth through the activation of canonical PIP3-dependent anabolic pathways. Beyond cardiomyocyte size control, PIP3 produced by PI3K α represents a master switch of physiological but not of pathological hypertrophy. Mice expressing a dominant-negative PI3K α are resistant to left ventricular hypertrophy induced by exercise training but they develop compensatory hypertrophy following pressure overload (McMullen et al. 2003). Importantly, the pool of PIP3 produced by PI3K α is functionally relevant in conditions of myocardial damage, where it protects cardiomyocytes from cell death and dysfunction caused by various pathological noxae, including dilative cardiomyopathy, myocardial infarction, chronic adrenergic stimulation, and pressure overload (McMullen et al. 2007; Lin et al. 2010). Taken together, cardiac PI3K α -PIP3 signaling is required for the protection of cardiac function.

On the other hand, the pool of PIP3 produced by PI3K γ drives the heart toward the development of heart failure. A critical event in the natural history of heart failure is represented by immune cell recruitment to the myocardium and their subsequent activation (Frangogiannis 2008). Similar to the migration of white blood cells into the atherosclerotic plaque, PIP3 produced by PI3K γ is a crucial component of signal transduction controlling leukocyte migration to the heart (Hirsch et al. 2006). PI3K γ -PIP3 signaling pathway is also active within the cardiomyocytes (Ghigo et al. 2011). To discern the specific contribution of PI3K γ -PIP3 signaling in leukocytes and cardiomyocytes, the major cell types involved in the process of cardiac maladaptive remodelling, a model of pressure overload-induced heart failure in bone marrow-transplanted chimeric mice has been used (Damilano et al. 2011). Selective inhibition of PIP3 production within the leukocyte compartment causes a reduced leukocyte infiltration in the myocardium soon after transverse aortic constriction (TAC) that correlates with reduced fibrosis and preserved diastolic function. Conversely, selective inhibition of PIP3 production within cardiomyocytes is required to counteract TAC-induced cardiac dysfunction at later time points. This maladaptive role of cardiac PIP3 appears to be linked to its impact on β -adrenergic receptor (β -AR) signaling. Deregulation of β -AR responses is a key pathophysiological feature of heart failure (Rockman et al. 2002). Indeed, uncontrolled catecholamine stimulation of β -ARs in a failing myocardium leads both to a reduction in the number of ligand-accessible β -ARs and to a diminished response to stimulation of remaining receptors (two processes called downregulation and desensitization, respectively) (Bristow et al. 1982; Bristow 1998). Due to desensitization and downregulation, adrenergic signaling is therefore progressively impaired in the failing myocardium, which loses tonic and phasic contractile responses to catecholamine stimulation. Within this scenario, PIP3 produced by PI3K γ is an essential regulator of β -AR endocytosis (Naga Prasad et al. 2001). In particular, PI3K γ constitutes a cytoplasmic complex

with G-protein coupled receptor kinase 2 (GRK-2) that, upon β -AR stimulation, mediates translocation of PI3K γ to the activated receptor (Naga Prasad et al. 2000). Herein, a local pool of PIP3 produced by PI3K γ is required for the recruitment of phosphoinositide-binding endocytic proteins, such as β -arrestin and the clathrin adaptor AP-2, which leads to the consequent organization of clathrin-coated pits orchestrating the internalization of the receptor (Laporte et al. 2000; Naga Prasad et al. 2002). In vivo studies have confirmed these mechanistic insights. Inhibition of PIP3 localized at the β -AR, through transgenic overexpression of an inactive form of PI3K γ , prevents the development of β -AR dysfunction in response to chronic catecholamine stimulation and protects from heart failure (Nienaber et al. 2003; Perrino et al. 2005; Perrino et al. 2006). Furthermore, β -AR density remains unchanged after pressure overload in mice expressing a PI3K γ defective in PIP3 production. Similarly, the administration of a PI3K γ -specific pharmacological inhibitor in wild-type mice suffering from pressure overload-induced heart failure can significantly improve both β -AR density and left ventricular contractility (Perino et al. 2011). Accordingly, the mechanical unloading of the failing human heart is associated with significant reduction in GRK2-associated PI3K γ activity initially enhanced by the disease (Perrino et al. 2007). Taken together, these findings picture a scenario where PI3K γ -PIP3 deregulation leads to maladaptive β -adrenergic perturbation during heart failure. In conclusion, these data indicate that the pool of PIP3 produced by PI3K γ occupies a central stage in the molecular pathophysiology of heart failure, which is dominated by abnormal β -adrenergic stimulation. In this context, PI3K γ escapes physiological feedback control mechanisms and orchestrates key aspects of myocardial damage and remodelling, such as β -adrenergic desensitization and downregulation, myocardial inflammation and fibrosis. Overall, these works suggest that concomitant inhibition of PI3K γ -PIP3 signaling in cardiomyocytes and leukocytes is required to promote cardiac protection.

IP3

Although IP3 receptors (IP3-Rs) are mainly located on the sarcoplasmic reticulum where they induce Ca^{2+} mobilization regulating contractility, specific pools of IP3-Rs can be located to the nucleus and exert a role in cardiac remodeling (Wu et al. 2006). The involvement of IP3-mediated Ca^{2+} signaling in cardiac hypertrophy was first described by the work of Barac et al. showing that the IP3 pathway is crucial for the development of Fas-mediated hypertrophy in a model of cultured rat neonatal ventricular myocytes (Barac et al. 2005). More recently, it has been demonstrated that a pool of IP3-Rs located within, or close to, the nucleus can specifically regulate DNA modifying enzymes involved in controlling hypertrophic growth of cardiac myocytes. In isolated rabbit myocytes, endothelin-1 stimulation, which activates plasmalemmal G-protein coupled receptors and IP3 production, elicits local nuclear envelope Ca^{2+} release via IP3-Rs. In turn, such

local Ca^{2+} release activates nuclear CamKII, which triggers HDAC5 phosphorylation and nuclear export, eventually derepressing transcription. Interestingly, this Ca^{2+} pathway cannot be activated by the global Ca^{2+} transients that cause contraction at each heartbeat, thus demonstrating that IP3-mediated signaling is highly compartmentalized in cardiomyocytes (Wu et al. 2006). The generation of heart-specific transgenic mice with both gain- and loss-of-function for IP3-R signaling has then allowed to investigate the importance of the IP3-mediated hypertrophic response in vivo, both in physiological and pathological conditions (Nakayama et al. 2010). Mice overexpressing the IP3-R2 subtype in the heart display mild baseline hypertrophy at three months of age, which is not further enhanced by two weeks of pressure-overload stimulation. By contrast, IP3-R2 overexpression significantly enhances basal hypertrophy following two weeks of isoproterenol infusion, in response to G α_q overexpression and/or to exercise stimulation. Accordingly, overexpression of an IP3 chelating protein totally abolishes cardiac hypertrophy in response to isoproterenol and angiotensin II infusion, but not pressure-overload stimulation (Nakayama et al. 2010). Altogether these studies point to a central role for IP3-mediated Ca^{2+} signaling not only in the modulation of excitation–contraction coupling (ECC), but also in the regulation of cardiac hypertrophy in response to selected stimuli.

PIP2

Among major regulators of cardiac hypertrophy is the Gq signaling axis. In cardiomyocytes, heterotrimeric G proteins of the Gq family transduce signals from a variety of receptors that bind α_1 -adrenergic agonists, endothelin, purine nucleotides, or angiotensin and activate PLC, thus promoting PIP2 hydrolysis into IP3 and DAG (Dorn and Force 2005). Overexpression of the wild-type α subunit of Gq (G α_q WT) induces hypertrophy in vitro, in isolated cardiomyocytes (Adams et al. 1998). Similarly, mice with cardiac-specific overexpression of G α_q show hypertrophic cardiomyocytes (D'Angelo et al. 1997). Furthermore, in these animals, cardiac hypertrophy rapidly progresses toward heart failure when G α_q -dependent signaling is further enhanced or prolonged by concomitant expression of PLC, G α_q -coupled receptors, and stress stimuli (D'Angelo et al. 1997). Accordingly, expression of a constitutively active form of G α_q (G α_q^{Q209L}) does not cause hypertrophy, but induces cardiomyocyte apoptosis which correlates with enhanced PLC-mediated hydrolysis of PIP2 (D'Angelo et al. 1997). The simplest explanation of these findings might be that depletion of PIP2 levels leads to reduced amounts of PIP3 and, in turn, to attenuated Akt/PKB survival signaling, eventually driving cardiomyocyte apoptosis. However, G α_q^{Q209L} expressing cardiomyocytes contain elevated concentration of PIP3, suggesting that the apoptotic process is mainly linked to the loss of PIP2. Indeed, it has been suggested that PIP2 depletion alone might be sufficient to trigger apoptosis as PIP2 is able to reduce caspase activation either by a direct mechanism or by keeping

procaspases complexed with gelsolin (Azuma et al. 2000; Mejillano et al. 2001). Consistently, Gzq^{Q209L}-induced apoptosis is caspase dependent (D'Angelo et al. 1997). It is thus interesting to speculate that PIP2 depletion regulates cardiomyocyte apoptosis and subsequent heart failure.

Arrhythmias

A prominent mechanism of death in patients with heart failure is arrhythmia, where electrical activation of the heart occurs so rapidly that effective filling and pumping of blood cannot occur (Wang and Hill 2010). Cardiac rhythm disturbances or arrhythmias refer to a large and heterogeneous group of conditions characterized by abnormal electrical activity of the heart. Despite their incidence, the molecular bases of arrhythmogenesis are still incompletely understood. In the last decade, PIs have emerged as potential arrhythmogenic factors (Woodcock et al. 2009), with both membrane PIs and soluble signaling molecules potentially involved. In particular, membrane PIP2 and the soluble IP3 have been shown to impact on cardiomyocyte electrical activity, thus contributing to arrhythmogenesis, with PIP3 playing only a minor role in this pathological context.

PIP2

The arrhythmogenic activity of membrane PIP2 is linked to its ability to regulate a wide array of cardiac ion channels and exchangers, including inward rectifying K⁺ channels (K_{IR}), repolarizing K⁺ channels (K_V), and pacemaker channels.

Inwardly rectifying K⁺ (K_{IR}) channels are important regulators of resting membrane potential and cell excitability. The activity of K_{IR}, including K_{IR}2, K_{IR}3, and K_{IR}6 isoforms is critically dependent on the integrity of channel interactions with PIP2. Opening of K_{IR} requires PIP2 binding to basic and polar amino acids in cytoplasmic domains, whereas depletion of PIP2 acts to close the channel (Huang et al. 1998). K_{IR}2 family members are responsible for the current that maintains resting membrane potential, in both atrial and ventricular myocytes. Several mutations in K_{IR}2.1 channel proteins have been shown to cause the Andersen-Tawil syndrome, a condition characterized by periodic paralysis, dysmorphic features, and cardiac arrhythmias (Plaster et al. 2001; Lopes et al. 2002). Some of these mutations map to the region of K_{IR}2.1 that interacts with PIP2 and are shown to allosterically decrease channel-PIP2 interactions. The weakening of channel-PIP2 interactions, in turn, leads to inhibition of K_{IR}2.1 currents (Lopes et al. 2002) and mutant K_{IR}2.1 has been shown to be more susceptible to modulation by stimuli that decrease membrane concentrations of PIP2 (Lopes et al. 2002; Ma et al. 2007). Also, K_{IR}3 channels are strictly dependent on PIP2 for their activity. K_{IR}3 isoenzymes are muscarinic potassium

channels (K_{ACh}), functioning in atrial and pacemaker myocytes. K_{ACh} belongs to the G protein regulated inward rectifying K^+ channel family (GIRK), which are modulated via activation of the heterotrimeric G protein, G_i , causing release of $G\beta\gamma$ subunits (Hommer et al. 2003). Blockade of PIP2 binding to channels impairs the stimulatory effects of $G\beta\gamma$ on channel activity and such effects can be reversed by restoring PIP2 (Sui et al. 1998). K_{IR3} currents play a key role in atrial tachycardia-induced electric remodeling and in the pathogenesis of atrial fibrillation in dogs (Cha et al. 2006). However, there is currently no evidence that PIP2 plays a role in this pathogenetic mechanism. Similarly, whether PIP2-mediated regulation of K_{IR6} channels can lead to cardiac dysfunction or arrhythmogenesis is currently unknown (Haider et al. 2007).

Besides its impact on K_{IR} channel function, PIP2 affects the activity of repolarizing K^+ channels (K_V), thus contributing to the termination of the cardiac action potential. Among K_V channels, $K_{V11.1}$ (also known as HERG) is responsible for the rapid phase of repolarization, while $K_{V7.1}$ (KCNQ1/KCNE1) mainly regulates the slow repolarization. Both $K_{V11.1}$ and $K_{V7.1}$ have six trans-membrane spanning regions that form an ion pore, together with a long C-terminal tail and a relatively short cytosolic N-terminal tail and are regulated by PIP2, although its interaction has not been studied as extensively as for K_{IR} channels (Li et al. 2005b; Bian and McDonald 2007). Changes in the concentration of intracellular PIP2 have been found to alter both the current amplitude and the voltage-dependent gating of heterologously expressed HERG channels (Bian et al. 2001): PIP2 significantly increases the current amplitude, accelerates the voltage-dependent activation, and slows the voltage-dependent inactivation of the channel. As a result of these biophysical regulations, elevation of membrane PIP2 concentration triggers more effective currents, while PIP2 depletion has an opposite effect (Bian et al. 2001). Similarly, in rabbit ventricular myocytes, native HERG currents are reduced by 15–20 % upon application of epinephrine, a stimulus known to trigger G_{12} -mediated activation of PLC, and subsequent depletion of membrane PIP2 (Bian et al. 2004).

HERG function is also modulated by β -adrenergic receptor activation and the cAMP/Protein kinase A (PKA) axis. PKA phosphorylates the channel in its polybasic region responsible for PIP2 binding and causes its opening (Bian and McDonald 2007). Weakening of PIP2-HERG channel interaction is potentially involved in the induction of an inherited form of arrhythmia, the long-QT (LQT) syndrome, a genetic disease characterized by prolonged cardiac repolarization, cardiac arrhythmias, and a high risk of sudden death (Li et al. 1998). Several of the known LQT mutations are characterized by either alterations or deletions of the polybasic PIP2 interacting site (Schwartz et al. 2001). However, the detailed mechanism linking aberrant PIP2-HERG interaction to cardiac arrhythmias or acquired heart diseases is still incomplete and needs further investigation.

On the contrary, the involvement of PIP2-mediated regulation of KCNQ1/KCNE1 in arrhythmogenesis has been extensively studied. In the heart, KCNQ1 assembles with KCNE1 to form a channel complex constituting the slow component of the delayed rectifier current (Sanguinetti et al. 1996). Intracellular PIP2

regulates KCNQ1/KCNE1 channel activity via stabilization of the open state of the channel, leading to increased current amplitude, slowed deactivation kinetics, and a shift in the activation curve toward negative potentials (Loussouarn et al. 2003; Li et al. 2005b). The PIP2-binding sequence is part of an endogenous inhibitory region on KCNQ1, and PIP2 association prevents this inhibition (Oliver et al. 2004). Mutations in this channel have been linked to diverse forms of arrhythmia, including atrial fibrillation and inherited arrhythmias, such as long QT and short QT syndromes (Chen et al. 2003; Bellocq et al. 2004). Some of these mutants are in residues likely to be important for PIP2 interactions. For instance, R555C and R539W mutations, which have been associated to the LQT syndrome, have the same consequences on the channel biophysical properties as a decrease in PIP2 concentrations (Park et al. 2005). In particular, the mutant channels display reduced affinity for PIP2 compared to the wild-type protein and an alteration in PIP2 binding in mutants R555C and R539W fully explains the channel dysfunction. In patch clamp studies, addition of excess PIP2 reverses the lowered activity of the mutant channels and returns channel activity to normal. This confirms the importance of PIP2 binding for the optimal functioning of the channel and raises the possibility that changes in PIP2 availability could initiate arrhythmia (Park et al. 2005). A recent work suggests that PIP2 sensitivity of KCNQ1 can be controlled by the auxiliary subunit, KCNE1 (Li et al. 2011). KCNE1 increases the PIP2 sensitivity of the channel by several orders of magnitude. Mutations of the key residues in KCNE1 that are determinants of PIP2 sensitivity, R67C, R67H, K70M, and K70N, are associated with LQT syndrome. These mutations reduce the channel current and PIP2 sensitivity. Interestingly, application of supernormal levels of exogenous PIP2 is able to rescue wild-type channel function. Thus, decreased sensitivity to PIP2 is at the base of this inherited rhythm dysfunction.

PIP2 also regulates the pacemaker current by controlling the hyperpolarization-activated cyclic nucleotide-gated channels (HCN). PIP2 shifts the voltage of the pacemaker channels toward depolarized potentials and thus increases the spontaneous firing rate. Although these channels have been suggested to be important in the development of atrial fibrillation, there is currently no evidence that this involves PIP2 (Zolles et al. 2006).

Altogether these results unveil a central role for PIP2 in the control of cardiomyocyte electrophysiology and suggest that PIP2-mediated arrhythmogenesis is mainly due to defective regulation of the K_{IR2} , HERG, and KCNQ1/KCNE1 channels.

IP3

In the heart, IP3 binding to IP3-Rs on the sarcoplasmic reticulum (SR) generates Ca^{2+} fluxes that amplify the Ca^{2+} signal occurring during the excitation–contraction coupling (ECC) (Marks 2000). During ECC, action potential-induced membrane depolarization leads to the opening of voltage-gated Ca^{2+} channels on the plasma

membrane, resulting in Ca^{2+} influx. In turn, entering Ca^{2+} activates the ryanodine receptors (RyRs) which lead to massive Ca^{2+} release from the SR, via a mechanism initiating contraction, known as Ca^{2+} -induced Ca^{2+} -release (CICR) (Bers 2002). Given their low expression levels in cardiomyocytes compared to the more abundant RyRs, IP3-Rs do not contribute to the modulation of global intracellular Ca^{2+} levels, rather they control spatially restricted Ca^{2+} pools within specific subcellular microdomains. The predominant IP3-R isoform in cardiomyocytes, IP3-R2, co-localizes with RyR and locally increases Ca^{2+} levels sensitizing RyR to CICR and enhancing ECC efficiency (Mackenzie et al. 2002). In agreement, direct stimulation of IP3-Rs has positive inotropic effects in both atrial and ventricular myocytes (Proven et al. 2006).

Atrial myocytes express IP3-R2 at higher levels than ventricular myocytes and several reports have underlined the importance of IP3/IP3-R2 signaling in atrial ECC (Mackenzie et al. 2002). For instance, in mouse atrial myocytes, selective activation of IP3-R2 causes an increase in basal levels of Ca^{2+} , an enhancement of action potential-induced Ca^{2+} transients and of fractional SR Ca^{2+} release (Li et al. 2005a). IP3-Rs-mediated Ca^{2+} signaling can interfere with the highly orchestrated Ca^{2+} responses mediated by the RyR, thereby predisposing to arrhythmia. IP3-R2 stimulation of atrial cells induces spontaneous arrhythmogenic Ca^{2+} release events, a potential source of ectopic beats (Li et al. 2005a). Similarly, in cat atrial myocytes IP3 causes spontaneous Ca^{2+} transients, Ca^{2+} waves as well as Ca^{2+} alternans, all disturbances in Ca^{2+} signaling related to cardiac arrhythmias (Zima and Blatter 2004). In rat, IP3-R activation increases the amplitude of electrically induced Ca^{2+} transients and triggers premature extra Ca^{2+} transients (Mackenzie et al. 2002). Spontaneous Ca^{2+} release events are fully abrogated in IP3-R2-deficient atrial myocytes (Li et al. 2005a) thus suggesting a crucial role for IP3/IP3-R signaling in the initiation and perpetuation of atrial fibrillation (AF), the most common form of cardiac arrhythmia (Li et al. 2005a).

IP3-R2 is also present in ventricular myocytes, although its expression is 3.5-fold lower than in atrial myocytes (Domeier et al. 2008). However, the contribution of IP3 signaling to ECC and arrhythmogenesis in these cells is still controversial and appears to be species specific. For example, IP3-R-dependent Ca^{2+} signaling produces positive inotropic effects and evokes spontaneous pro-arrhythmic Ca^{2+} signals in rat (Proven et al. 2006). In contrast, IP3-R-mediated arrhythmogenic events are detected neither in rabbit (Domeier et al. 2008) nor in cat ventricular myocytes (Zima and Blatter 2004). Therefore, it appears that atrial rather than ventricular arrhythmia can be associated with perturbations in IP3 signaling. In this respect, it has been suggested that ventricular arrhythmias, apparently associated with IP3, derive primarily from the conductive tissue where highest levels of IP3-Rs are found (Woodcock et al. 2009).

PIP3

Different from the case of IP3 and PIP2, evidence linking PIP3 signaling to cardiac arrhythmias are few. Two reports demonstrate that enhanced PI3K α -PIP3 signaling can lead to atrial fibrillation and heart failure-associated ventricular arrhythmia (Pretorius et al. 2009; Yang et al. 2012). Cardiac-specific expression of a dominant-negative mutant of PI3K α in the DCM-Tg model of dilated cardiomyopathy leads to atrial fibrillation. Interestingly, in atrial appendages from patients with atrial fibrillation, PI3K activity is lower than in tissues from patients in sinus rhythm. However, no evidence is reported that arrhythmia is mediated by low PIP3 levels (Pretorius et al. 2009). Consistent with a positive role for the PI3K α -PIP3 axis in the protection against arrhythmia, enhanced PIP3 signaling due to PI3K α overexpression has been shown to mitigate the arrhythmogenic electrical remodeling associated to pathological hypertrophy and heart failure. Increased activation of PI3K α leads to a transcriptional upregulation of the repolarizing K⁺ channel (Yang et al. 2012). Whether other PIP3 pools produced by distinct PI3K isoforms are necessary for cardiac rhythm control is not known and further studies are required to better define whether PIP3 directly controls channel activity.

Conclusion

In the cardiovascular system PIs do not represent merely structural components of cell membranes; rather they function as substrates for enzymes that generate second messengers modulating fundamental processes, such as cardiac hypertrophy and contractility. Besides, PIs can function as direct regulators of signaling proteins, such as cardiac ion channels, eventually contributing to cell excitability and heart rhythm modulation. Aberrant PI metabolism is known to contribute to diverse human cardiovascular pathologies, including atherosclerosis, heart failure, and arrhythmia and molecules involved in PI signaling pathways are thus considered attractive drug targets for therapy. However, in view of the pleiotropic cellular processes controlled by each PI, it can be predicted that pharmacological modulation of PI signaling is likely to incur into undesired, important side effects. For clinical interventions to be effective, there is urgent need to elucidate the mechanisms by which PI effectors that bind to the same lipid, but that mediate different processes, are independently regulated. The understanding of the spatio-temporal compartmentalization of each PI and of their related signaling in specific pathophysiological settings is crucial to achieve this goal. Such knowledge could potentially pave the way of successful PI manipulation for human therapy.

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