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The molecular functions of protein kinase C (PKC) isoforms

Abstract

PKC isoforms perform a significant role in the arrangement of cell cycle, and cell division, proliferation/differentiation. The activitation mechanisms and expressions of related PKC isoforms are altered in certain types of diseases, particularly in cancer. Programmed cell death (Apoptosis) is biochemical and physiological phenomenon, also known as cell suicide. The comprehensive description of isoforms which includes apoptotic proseses indicate that certain PKC isoforms might act as a molecular inducers, support cell survival process under appropriate biological environment, and if necessary, carry out the death of damaged cells. Autophagy is a molecular mechanism that directs certain macro-molecules and organelles into a vesicle to be directed to the lysosomes and to combine with the lysosome to disintegrate. The ubiquitin-proteasome pathway degraded proteins with short lifetimes, while long-lifetime proteins, as well as intracellular organelles broken down by the autophagy pathway, are regenerated for use by the cell. Although the key molecular components playing a role in the autophage process are well described, there is a limited study in the literature about autophagic regulation and affection by cellular signaling pathways. In this detailed review, PKC family members, their structures and activators, the function of PKC in regulating cell cycle, the relevant mechanisms of certain PKC isoforms to apoptosis, the type of induction or inhibition of apoptosis by other molecular regulators of PKC and its interaction with signal transduction pathways and also detailed information on how autophagy is organized by PKC is available explained in a comprehensive manner.

Keywords: protein kinase C (PKC), apoptosis, autophagy, cell cycle phases

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Introduction

The PKC family

Protein kinase C; it belongs to the serine/threonine kinase enzyme family and is called PKC (EC 2.7.11.13).[1] Today, the PKC superfamily consists of 10 different isoenzymes. These isoenzymes are divided into 3 classes according to their structure, biochemical properties and domain structure. Conventional or classical PKCs (cPKC; classical PKC) (calcium dependent) consist of α, β1, β2 and classical isoenzymes. In the presence of phosphatidylserine, these isoenzymes respond to DAG in a calcium-dependent manner.

cPKCs are also targets of phorbol esters that promote tumor formation. Novel PKCs (nPKC) consist of δ, ε, η and δ isoenzymes. These isoenzymes show calcium-independent effects, but in the presence of phosphatidylserine; it responds to DAG or phorbol esters.[2,3] Atypical PKCs (aPKC) function independently of calcium; the DAG does not respond to phorbol esters. The isoenzymes of aPKCs include, λ/ι.[2,3] PKC heterogeneity raises the question, why are there many isoenzymes? and how to arrange the functional relationship in the range? The heterogeneity of individual PKC isoforms has been highly conserved in mammalian species, and their heterogeneity has been found to have specific roles in organisms. The tissue distributions of PKC isoforms also show distinct differences. The isoforms such as PKC alpha δ and ζ can be widely expressed, while the PKC δ, η, θ isoforms can be expressed in one type of tissue.[4–6]

Many PKC isoforms have different functional properties through different cellular and intercellular localizations, and each isoform has a unique sensitivity to signals. Thus, the heterogeneity of the PKC family allows the different messages from outside to be detected by the cell. PKCβ (β1 and β2) has many unique functions. There are 50 amino acid differences between the alternative splice forms of PKCβ (β1 and β2), giving unique roles to each PKCβ isoform in this difference.[7]

In general, the PKC polypeptide has a C-terminal catalytic domain and an N-terminal regulatory domain structure. These domains are separated by the flexible hinge domain. cPKCs contain four homologous domains (C1, C2, C3 and C4). These domains are separated by isoenzyme-specific variable domains (V1, V2, V3, V4, and V5). The C1 region is considered to be the membrane binding domain. C2 region; is the unit of the enzyme associated with Ca^{2+} sensitivity. The C3 region comprises the catalytic domain and the ATP-binding region. The C4 region is the region where the substrate is identified and directed to phosphorylation. The nPKCs do not contain C2 homolog domain structure, so they do not have any requirements for calcium to be activated. aPKCs also do not include the ½ homologous domain structure of C2 or C1 so that a sensitivity to Ca^{2+} and DAG is not mentioned in these isoforms.[8]

Ca^{+2}, DAG and phospholipids, which are the cofactors responsible for activation. In its absence, the kinase activity of the catalytic domain is inhibited by the regulatory domain. This inhibitory effect is effected by the sequence motif terminating as the pseudosubstrate region (PS). The amino acid sequence was maintained moderately in PS. They have this similarity in the phosphorylation sites of PKC substrates (eg they contain alanine rather than serine threonine residues).[9] Ca^{2+} and DAG signals activate specific PKC isoforms. While Ca^{+2} acts quickly, the binding of DAG to PKC is prevented by the presence of the PS stack. PS inhibits access to the binding site of PKC and delays both calcium-mediated and DAG mediated kinase activation.

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Following the termination of the Ca^{2+} signal, the induced DAG causes prolongation of the kinase activity.[10] The binding of DAG to the PKC regulator domain enhances the affinity of membrane lipids and, as a result, stabilizes the relationship of PKC with DAG. Forbol esters mimic the activation effect of DAG on PKCs, and this effect is achieved by binding to the same units in the regulator region on PKCs. Thus, it induces the same conformational changes. For the long-term administration of phorbol esters, it was shown that phorbol esters selectively downregulate PKC expression levels. In contrast, the nPKC isoforms can be directly activated by means of a non-Ca^{2+} DAG. The DAG-dependent domain binds the membrane with high affinity and activates nPKC in the absence of other target mechanisms.[11,12]

Selective oxidative modifications in the N-terminal regulatory domain induce PKC activation, while changes in the C-terminal domain lead to complete inactivation of the kinase. In the regulator domain, two pairs of zinc motifs and high concentrations of cystine residues make this region an important target area for redox regulation.[13] Oxidant administration to PKCs forms a new form which is not bound to phorbol esters, which shows catalytic activity in the absence of calcium and phospholipids. The PKC catalytic domain is inactivated by the loss of free sulfides. In this way, it makes PKCs a potential target as an anticancer agent. Some chemotherapeutic compounds inactivate PKC by oxidizing thiol groups in their catalytic domains.[13] At the same time, NO inactivates PKC by interacting with cysteine sulfydriles.[14] The regulation of PKC by tyrosine phosphorylation takes place by activation of the mitogen activated protein kinase (MAPK; mitogen activated protein kinase) pathway. With this signaling pathway, it triggers the transcriptional activity of PKC and causes changes in gene expression.[13]

PKC and cell cycle

The role of PKC in regulating cell proliferation has been extensively studied, but the function of specific PKC isoenzymes in the control of the cell cycle is still not fully elucidated. The regular transition between the cell cycle phases is carried out by the cyclin protein family. These cyclins bind to cyclin dependent kinases (Cdks; cyclin-dependent kinases) to activate them.[15] Under normal conditions, the cell cycle is not interrupted. In addition, when the cell cycle cells are exposed to any damage, the G1, S or G2 phases are temporarily paused by cyclins to repair the damage. If the damage can be repaired, the cell cycle is reactivated after repair.

Control points; generally, cyclin CDK activities include repression events. Control of Cdk activities is regulated by PKCs. In fact, PKCs show their contribution to cell cycle progression in G1 and G2 / M phases. In some cell systems, the regulation of growth is positively or negatively affected during the G1 phase, depending on the time of PKC activation.[16] Following the administration of 12-myristate 13-acetate (PMA) to human fibroblast or vascular smooth muscle cells, it was reported that DNA synthesis was inhibited and this event was triggered by growth factors, while in the G1 phase of the cell cycle it was reported to be blocked.[17] Following PMA administration in intestinal cells, a pause in the G1 phase of the cell cycle due to PKCα has been reported. In a different study, the expression of novel PKC isoform in NIH 3T3 cells was found to delay G1/S passage in the cell cycle. This phenomenon has been reported that the PKCα isoform is expressed excessively in NIH 3T3 cells in a synchronous manner with the growth stimulus, and a slower transition to the S phase of the cell cycle, but a faster transition to the G1 phase.[18–21]

In the context of this information, the role of the interaction between ROS and PKC in cell cycle regulation is still unclear. In fact, the damaging effect of ROS on DNA has been studied extensively and it has been found that ROS has no effect on its response at checkpoints. Regarding PMA, it was determined that high levels of ROS damage to growth and cause aging.[22–24] It was determined that this was achieved by pausing the cell cycle in the M phase by PKCδ activation.[22] Similarly, the ROS mediated G1-S pause was reported to occur by PKCα activation. As a result of this analysis, it was stated that this situation is important for cell migration and metastasis.[23] As a result, although there are many studies about the importance of the role of PKC in regulating the cell cycle, unfortunately, there is still no clear picture. In order to design effective pathological therapy strategies, the scenario is still ambiguous.

PKC and apoptosis

The delicate balance between survival and apoptotic signaling determines cancer cell death. In terms of therapeutic approaches, although blocking of survival signals is seen as the key point in establishing the balance of cell death, the blockade of certain survival signals does not cause cancer cells to directly enter the apoptosis process. The main factor in the induction of apoptosis can be obtained by the regulation of the apoptotic pathway, thereby creating a dominant effect on the cells. Therefore, direct activation of the cell death response is the most accurate approach in terms of cancer therapies. In the analyzes, it was found that the best PKC that triggered apoptosis was PKCδ.[25] When PKCα and δ were compared, PKCα triggered survival and proliferation signals, and the main role of PKCδ was observed to be on the increase and induction of apoptosis.[26] The contribution of PKCδ to apoptosis was analyzed by treatments of different types of cells with a wide variety of stimuli such as H_2O_2, TNF-alpha, UV, irradiation and etoposide administration, and stimulants have been reported to increase PKCδ activation in these cells.[27]

Certain PKC isoforms are involved in the maintenance of cells, while others induce cell death. 12-0-tetradecanoylphorbol-13-acetate (TPA) induces apoptosis by stimulating the release of cytochrome c by a PKC β-dependent mechanism from classical cPKCs in U-937 leukemia cells.[28,29] In gastric cancer cells, PKC isoforms are mediated by indomethacin-induced apoptosis. It has been reported that increasing the expression of exogenous PKCβ has a protective mechanism against such apoptosis formation.[30]

PKCβ can be activated through oxidative mechanisms and cause significant phosphorylation of p66shc in the mitochondria. PKCβ also acts as an oxidoreductase. This process leads to the feed-forward cycle of ROS production, leads to the opening of mitochondrial Permeability Transition Pore (mPTP), and caspase cofactors are released and consequently apoptotic cell death is triggered. Powell et al. reported that in cell cultures derived from human prostate cancer cells, apoptosis occurred spontaneously in the presence of PKCα in the cell membrane, whereas in the absence of PKCα a resistance to TPA-induced apoptosis occurred.[31] Among the novel isoforms, the isoform with the most important role in apoptosis was found to be PKCδ. For example, Lynch et al. found that the basic fibroblast growth factor induced the inhibition of apoptosis by replacing the calcium level of the immortal granulosa cells with the PKC calcium dependent pathway. PKCδ has also been found to play a role in the release of cytochrome c from mitochondria.[32] In fact, TPA induces the translocation of PKCδ from mitochondria to the cytoplasm and

this translocation has been reported to cause cytochrome c release and caspase 3 activation.[33] The examples we have mentioned so far were in vitro triggering apoptosis. Another important phenomenon is the physiological relationship between PKC and the termination of the immune response (including Ca^{2+} and PKC). For the continuation of T cell homeostasis, it was determined that the clearance of Ag medium and the elimination of activated lymphocytes by apoptosis.[34] Apoptosis in this form includes TCR-induced expression of CD95 ligand (CD95L) on the T cell surface.[35–38] It was determined that PKCζ regulates the apoptotic machine by controlling the Bax-Bcl2 ratio at the mitochondrial level. Another important task of cytochrome c-mediated caspase activation is emphasized on the control.[39] The PKCζ isoform has been reported to increase the release of mitochondrial Ca^{2+}, thereby sensitizing the cell to apoptotic processes by causing signal change.[40] The logical explanation of this inconsistency is as follows. The direct effect of PKC on apoptosis has been demonstrated by antibiotic calphostin C (a potent PKC inhibitor), which has been shown to induce apoptosis of human acute lymphoblastic leukemia (ALL; lymphoblastic leukemia) by two mechanisms of action. These mechanisms of action; It is performed by irreversible oxidative inactivation of PKC inhibition or cytosolic Ca^{2+} increase. Calphostin C induces rapid calcium mobilization from intracellular stores in ALL cell cultures and the cytotoxicity of the antibiotic is associated with the size of the Ca^{2+} signal. In fact, death signals on cells induced by calphostin-C have been reported to be suppressed by the presence of Ca^{2+} chelator BAPTA.[41,42] Mediators involved in triggering such apoptosis pathways; vincristine, ionizing radiation, Fas agonists and TNF are examples.[43] Lyn is a family member of the src, and found to play an important role in drug-induced N-SMase stimulation. In fact, it was found that activation of Ara-c Lyn was carried out by ROS production and activation of N-SMase in which Lyn was interacting. The SM-CER apoptotic pathway is controlled by powerful regulators, which regulate both the increase and suppression of CER production. Among these regulators, PKC activity has been found to play an important role. In fact, stimulation of PKC via phorbol esters or DAG inhibits CER-induced apoptosis; N-Smase stimulation induced by DNR has also been reported to suppress CER formation and apoptosis.[44]

The most excellent of these studies shows that Benzombes et al., PKCζ overexpression reduces drug-induced ROS production, Lyn activation, N-Smase stimulation, CER production, as well as inhibition of apoptosis and drug resistance.[45] In addition, PKC inhibition increases apoptosis in leukemia cells, and this increase is achieved by exposure to etoposide and TNF-α in these cells.[39] In the same study, tumor cell growth was also reported to be sensitive to etoposide in mice.[39]

TPA activates PKCδ and β by inducing cytochrome c release from mitochondria. PKC β allows the phosphorylation of p66Shcy and permits the formation of ROS. Activation of PKCα directly induces apoptosis. PKCζ induces apoptosis by triggering cytochrome c release, but also has the ability to alter Bax/Bcl2 protein status. In this way it mediates the antiapoptotic effect. Similar mechanism of action is achieved by inhibition of PKC isoforms by the use of calpostain c.[24]

PKC and autophagy

By autophagy, cytoplasmic charges occurring in a pathway related to any cellular destruction are delivered to the lysosome. Autophagy is a continuous event in the protein degredation mechanism. Especially in food deprivation, it occurs when the cells begin to self-break in self-cannibalized situations and when they begin to degrade their own compounds.[46]

Today, autophagy is one of the new areas of interest of oncologists. Following various cancer therapies in different types of cancer cells, these cells enter into autophagy.[24] At least three forms of autophagy have been identified. These; chaperone mediated micro and macro autophagy. These different types are differentiated according to their physiological functions and their way of delivering load to lysosomes.[46] Especially macro-autophagy is one of the most important regulated catabolic mechanisms. It plays a role in the degradation of long-lived proteins and organelles in eukaryotic cells. Autophagy is involved in the destruction of organelles that have lost their function in eukaryotic cells at a low level.[47]

In particular, it is involved in the upregulation of the organelle turnover and cytoplasmic turnover. This mechanism has a function in the regulation of intracellular events such as hunger, hormonal imbalance, oxidation, excessive heat, infection, external stress factors and removal of protein aggregates.[48] However, it is quite complex and how the signaling pathways regulate autophagy regulation and function. Because the signaling pathways in the autophagy are in interaction with other signal networks (crosstalk).[24] Recently, many studies have been thought to induce the induction of redox stress and, in particular, hypoxic stress within them, inducing autophagy.[49–52]

In particular, autophagy is also activated by regulation of the activities of various kinases. Phosphatases in this mechanism include phosphatase and guanosine triphosphatase.[24] Recent studies have shown that PKC-JNK interaction plays a role in hypoxia-induced autophagy. It has been reported that acute hypoxic stress induces autophagy via PKCδ.[22]

In pharmacological studies, PKCδ or siRNA-mediated PKC knockdown was reported to inhibit the autophagic response to ER stress. It has been reported that thapsigargin or tunicamycin induces PKC ve phosphorylation from mediators used in ER stress and thus activates autophagy.[24,25] Sakaki et al.[52] found that PKCδ activation against ER stress was independent of mTOR kinase signaling pathway of autophagy.[53] This result contradicts the results of Hoyer Hansen et al.[54] According to the results of this study, the autophagy response following the administration of thapsigargin is that it is caused by mTOR kinase inactivation.[55] ROS production induces JNK activation in a PKCδ-dependent manner. Activated JNK causes Bcl-2 phosphorylation, Beclin-1 is released and is thus triggered by autophagy. Fasting promotes autophagy activation through mTOR inhibition and is simultaneously triggered by ROS deposition H_2O_2. This phenomenon is especially important for autophagosome formation. The triggering process of autophagy damages Ca-ER homeostasis, leading to CaMKK-b, AMPK and TSC-1/2 activation, and the process is terminated by mTOR inhibition. Rising calcium causes PKCδ phosphorylation and the formation of the autophagic process is encouraged.[24]

Results

The protein kinase C family consists of ten structurally related serine/threonine protein kinases.[1] The studies suggesting that PKC isozymes are activated by phorbol esters that trigger the tumor formation process have led to the idea that PKC may have a key function in triggering tumor formation and this may play a key role in anticancer therapies.[55] The presence of different activation and

tissue distribution PKC isoforms revealed the need to design different inhibitors specific to PKC isozymes. It was determined that these inhibitors have the potential to target specific specific pathways.[56] In addition, the relationship of different PKC isoenzymes with different pathological conditions was also determined. Among them; cancer, diabetes, central nervous system diseases; Alzheimer, neuronal degeneration, bipolar disorder, cardiovascular system diseases; cardiac hypertrophy, cardiac ischemia, atherosclerosis can be demonstrated.[57] To be able to use the PKC-targeted tools in the therapeutic process, a more clear understanding of the mechanism of regulation of PKC by cell cycle, apoptosis and autophagy is required. More studies are needed to clarify these mechanisms.

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Conflicts of interest

Author declares that there is no conflicts of interest.

References

1. Inoue M, Kishimoto A, Takai Y, et al. Studies on a cyclic nucleotide independent protein kinase and its proenzyme in mammalian tissues. II. Proenzyme and its activation by calcium dependent protease from rat brain. *J Biol Chem*. 1977;252:76107616.
2. Gould CM, Newton AC. The life and death of protein kinase C. *Curr Drug Targets*. 2008;9:614625.
3. Steinberg SF. Structural basis of protein kinase C isoform function. *Physiol Rev*. 2008;88:13411378.
4. Hug H, Sarre TF. Protein kinase C isoenzymes: Divergence in signal transduction?. *Biochem J*. 1993;291:329–343.
5. Mochly RD, Khaner H, Lopez J, et al. Intracellular receptors for activated protein kinase C. Identification of a binding site for the enzyme. *J Biol Chem*. 19991;266:14866–14868.
6. Schechtman D, Mochly RD. Adaptor proteins in protein kinase C-mediated signal transduction. *Oncogene*. 2001;20:6339–6347, 2001.
7. Chalfant CE, Ohno S, Konno Y, et al. A carboxy-terminal deletion mutant of protein kinase C beta II inhibits insulinstimulated 2-deoxyglucose uptake in L6 rat skeletal muscle cells. *Mol Endocrinol*. 1996;10:1273–1281.
8. Nishizuka Y. Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. *Science*. 1992;258:607–614.
9. Gschwendt M, Kittstein W, Marks F. Protein kinase C activation by phorbol esters: Do cysteine-rich regions and pseudosubstrate motifs play a role?. *Trends Biochem Sci*. 1991;16:167–169.
10. Oancea E, Meyer T. Protein kinase C as a molecular machine for decoding calcium and diacylglycerol signals. *Cell*. 1998;95: 307–318.
11. Dries DR, Gallegos LL, Newton AC. A single residue in the C1 domain sensitizes novel protein kinase C isoforms to cellular diacylglycerol production. *J Biol Chem*. 2007;282:826–830.
12. Hirai T, Chida K. Protein kinase Czeta (mechanisms PKCzeta): Activation and cellular functions. *J Biochem*. 133:1–7:2003.
13. Gopalakrishna R, Jaken S. Protein kinase C signaling and oxidative stress. *Free Radic Biol Med*. 2000;28(9):1349–1361.
14. Gopalakrishna R, Chen ZH, Gundimeda U. Nitric oxide and nitric oxide-generating agents induce a reversible inactivation of protein kinase C activity and phorbol ester binding. *J Biol Chem*. 1993;268:27180–27185.
15. Heichman KA, Roberts JM. Rules to replicate by. *Cell*. 1994;79:557–562.
16. Zhou W, Takuwa N, Kumada M, et al. Protein kinase C-mediated bidirectional regulation of DNA synthesis, RB protein phosphorylation, and cyclin-dependent kinases in human vascular endothelial cells. *J Biol Chem*. 1993;268:23041–23048.
17. Bi N, Mamrack MD. PMA inhibits the growth of human fibroblasts after the induction of immediate-early genes. *Exp Cell Res*. 1994;212:105–112.
18. Livneh E, Shimon T, Bechor E, et al. Linking protein kinase C to the cell cycle: Ectopic expression of PKC eta in NIH3T3 cells alters the expression of cyclins and Cdk inhibitors and induces adipogenesis. *Oncogene*. 1996;12:1545–1555.
19. Nakagawa M, Oliva JL, Kothapalli D, et al. Phorbol ester-induced G1 phase arrest selectively mediated by protein kinase Cdeltadependent induction of p21. *J Biol Chem*. 2005;280:33926–33934.
20. Watanabe T, Ono Y, Taniyama Y, et al. Cell division arrest induced by phorbol ester in CHO cells overexpressing protein kinase C-delta subspecies. *Proc Natl Acad Sci USA*. 1992;89:10159–10163.
21. Thompson LJ, Fields AP. betaII protein kinase C is required for the G2=M phase transition of cell cycle. *J Biol Chem*. 1996; 271: 15045–15053.
22. Takahashi A, Ohtani N, Yamakoshi K, et al. Mitogenic signaling and the p16INK4a-Rb pathway cooperate to enforce irreversible cellular senescence. *Nat Cell Biol*. 2006;8:1291–1297.
23. Wu WS, Tsai RK, Chang CH, et al. Reactive oxygen species mediated sustained activation of protein kinase C alpha and extracellular signal-regulated kinase for migration of human hepatoma cell Hepg2. *Mol Cancer Res*. 2006;4:747–758.
24. Giorgi C1, Agnoletto C, Baldini C, et al. Redox control of protein kinase c: cell- and disease-specific aspects. *Antioxid Redox Signal*. 2010;13(7):1051–1085.
25. Brodie C, Blumberg PM. Regulation of cell apoptosis by protein kinase C delta. *Apoptosis*, 2003;8(1):19–27.
26. Mandil R, E Ashkenazi, M Blass, et al. Protein kinase Calpha and protein kinase Cdelta play opposite roles in the proliferation and apoptosis of glioma cells. *Cancer Res*. 2001;61:4612–4619.
27. Yuan ZM, Utsugisawa T, Ishiko T, et al. Activation of protein kinase C delta by the c-Abl tyrosine kinase in response to ionizing radiation. *Oncogene*. 1998;16(13):1643–1648.
28. Cross TG, Scheel TD, Henriquez NV, et al. Serine threonine protein kinases and apoptosis. *Exp Cell Res*. 2000;256:34–41.
29. Pandey P, Nakazawa A, Ito Y, et al. Requirement for caspase activation in monocytic differentiation of myeloid leukemia cells. *Oncogene*. 2000;19:3941–3947.
30. Zhu GH, Wong BC, Slosberg ED, et al. Overexpression of protein kinase C-beta1 isoenzyme suppresses indomethacin-induced apoptosis in gastric epithelial cells. *Gastroenterology*. 2000;118:507–514.
31. Powell CT, Brittis NJ, Stec D, et al. Persistent membrane translocation of protein kinase C alpha during 12-0-tetradecanoylphorbol-13-acetateinduced apoptosis of LNCaP human prostate cancer cells. *Cell Growth Differ*. 1996;7:419–428.
32. Lynch K, Fernandez G, Pappalardo A, et al. Basic fibroblast growth factor inhibits apoptosis of spontaneously immortalized granulosa cells

by regulating intracellular free calcium levels through a protein kinase Cdelta-dependent pathway. *Endocrinology*. 2000;141: 4209–4217.

33. Reyland ME. Protein kinase Cdelta and apoptosis. *Biochem Soc Trans*. 2007;35:1001–1004.
34. Russell JH. Activation-induced death of mature T cells in the regulation of immune responses. *Curr Opin Immunol*. 1995;7:382–388.
35. Brunner F. Dependence of endothelin-1 secretion on Ca2þ. *Biochem Pharmacol*. 1995;49:1785–1791.
36. Ashkenazi A, Dixit VM. Death receptors: signaling and modulation. *Science*. 1998;281:1305–1308.
37. Villalba M, Kasibhatla S, Genestier L, et al. Protein kinase ctheta cooperates with calcineurin to induce Fas ligand expression during activation- induced T cell death. *J Immunol*. 1999;163:5813–5819.
38. Berra E, Diaz MMT, Dominguez I, et al. Protein kinase C zeta isoform is critical for mitogenic signal transduction. *Cell*. 1993; 74(3):555–563.
39. Filomenko R, Poirson BF, Billerey C, et al. Atypical protein kinase C zeta as a target for chemosensitization of tumor cells. *Cancer Res*. 2002;62(6):1815–1821.
40. Pinton P, Giorgi C, Siviero R, et al. Calcium and apoptosis: ER-mitochondria Ca2+ transfer in the control of apoptosis. *Oncogene.* 2008;27:6407–6418.
41. Zhu DM, Fang WH, Narla RK, et al. A requirement for protein kinase C inhibition for calcium triggered apoptosis in acute lymphoblastic leukemia cells. *Clin Cancer Res*. 1999;5:355–360.
42. Bezombes C, Plo I, MansatV, et al. Oxidative stress-induced activation of Lyn recruits sphingomyelinase and is requisite for its stimulation by Ara-C. *FASEB J*. 2001;15:1583–1585.
43. Levade T, Jaffrezou JP. Signaling sphingomyelinases:Which, where, how and why?. *Biochim Biophys Acta*. 1999;1438:1–17.
44. Mansat V, Laurent G, Levade T, e al. The protein kinase C activators phorbol esters and phosphatidylserine inhibit neutral sphingomyelinase activation,ceramide generation, and apoptosis triggered bydaunorubicin. *Cancer Res*. 1997;57:5300–534.
45. Bezombes C, de Thonel A, Apostolou A, et al. Overexpression of protein kinase C zeta confers protection against antileukemic drugs by inhibiting the redox-dependent sphingomyelinase activation. *Mol Pharmacol*. 2002;62:1446–1455.
46. Cuervo AM. Autophagy: In sickness and in health. *Trends Cell Biol*. 2004;14:70–77.
47. Kanazawa T, Taneike I, Akaishi R, et al. Amino acids and insulin control autophagic proteolysis through different signaling pathways in relation to mTOR in isolated rat hepatocytes. *J Biol Chem*. 2004;279:8452–8459.
48. Meijer AJ, Codogno P. Regulation and role of autophagy in mammalian cells. *Int J Biochem Cell Biol*. 2004;36: 2445–2462.
49. Pastor MD, Garcia–YI, Fradejas N, et al. mTOR=S6 kinase pathway contributes to astrocyte survival during ischemia. *J Biol Chem*. 2009;284:22067–22078.
50. Tracy K, Macleod KF. Regulation of mitochondrial integrity, autophagy and cell survival by BNIP3. Autophagy. 2007;3:616–619.
51. Zhang H, Bosch MM, Shimoda LA, et al. Mitochondrial autophagy is an HIF-1-dependent adaptive metabolic response to hypoxia. *J Biol Chem*. 2008;283:10892–10903.
52. Sakaki K, Kaufman RJ. Regulation of ER stress-induced macroautophagy by protein kinase C. *Autophagy*. 2008;4:841–843.
53. Sakaki K, Wu J, Kaufman RJ. Protein kinase Ctheta is required for autophagy in response to stress in the endoplasmic reticulum. *J Biol Chem*. 2008;283:15370–15380.
54. Hoyer HM, Bastholm L, Szyniarowski P, et al. Control of macroautophagy by calcium, calmodulin-dependent kinase kinase-beta, and Bcl-2. *Mol Cell*. 2007;25(2):193–205.
55. Corina E. Antal, Andrew M. Hudson, et al. John brognard cancer-associated protein kinase c mutations reveal kinase's role as tumor suppressor. *Cell*. 2015;160(3);489–502.
56. Shen GX. Selective protein kinase C inhibitors and their applications. *Curr Drug Targets Cardiovasc Haematol Disord*. 2003;3(4):301–307.
57. Fields AP, Gustafson WC. Protein kinase C in disease: cancer. *Methods in molecular biology (Clifton, N.J.)*. 2003;233:519–537.