



Multiple subcellular localizations and functions of protein kinase C δ in liver cancer

Kohji Yamada, Kiyotsugu Yoshida

ORCID number: Kohji Yamada 0000-0001-9493-5269; Kiyotsugu Yoshida 0000-0003-3108-7383.

Author contributions: All authors contributed equally to the conception and design of the study, literature review, analysis, drafting, critical revision and editing, and approval of the final version.

Conflict-of-interest statement: Authors declare no conflict of interest for this article.

Supported by the Japan Society for the Promotion of Science, KAKENHI Grant, No. 19H03519, 16K18434, and 18K15253 to Yamada K, No. 17H03584, 18K19484, and 20H03519 to Yoshida K; AMED under Grant No. A326TS to Yamada K; The Jikei University Graduate Research Fund to Yamada K; and the Science Research Promotion Fund to Yoshida K.

Country/Territory of origin: Japan

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific

Kohji Yamada, Kiyotsugu Yoshida, Department of Biochemistry, The Jikei University School of Medicine, Tokyo 105-8461, Japan

Corresponding author: Kiyotsugu Yoshida, MD, PhD, Professor, Department of Biochemistry, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan. kyoshida@jikei.ac.jp

Abstract

Protein kinase C δ (PKC δ) is a member of the PKC family, and its implications have been reported in various biological and cancerous processes, including cell proliferation, cell death, tumor suppression, and tumor progression. In liver cancer cells, accumulating reports show the bi-functional regulation of PKC δ in cell death and survival. PKC δ function is defined by various factors, such as phosphorylation, catalytic domain cleavage, and subcellular localization. PKC δ has multiple intracellular distribution patterns, ranging from the cytosol to the nucleus. We recently found a unique extracellular localization of PKC δ in liver cancer and its growth factor-like function in liver cancer cells. In this review, we first discuss the structural features of PKC δ and then focus on the functional diversity of PKC δ based on its subcellular localization, such as the nucleus, cell surface, and extracellular space. These findings improve our knowledge of PKC δ involvement in the progression of liver cancer.

Key Words: Protein kinase C δ ; Liver cancer; Subcellular localization; Tumor suppression; Tumor progression

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Protein kinase C δ (PKC δ) plays multifunctional roles in various cancers, including liver cancer. PKC δ has been shown to exert pleiotropic functions through various stimuli responsiveness, post-translational modifications, and subcellular localization. Recently, we found that PKC δ is secreted extracellularly and resides on the cell surface of liver cancer cells, which contributes to tumorigenesis. In this review, we focus on the localization of PKC δ to discuss its characteristic localization patterns and functions in liver cancer, and outline the involvement of PKC δ localized intra- and extracellularly with distinct functions in the progression of liver cancer.

quality classification

Grade A (Excellent): 0
 Grade B (Very good): 0
 Grade C (Good): C, C
 Grade D (Fair): D
 Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Received: March 26, 2021

Peer-review started: March 26, 2021

First decision: June 14, 2021

Revised: June 25, 2021

Accepted: December 31, 2021

Article in press: December 31, 2021

Published online: January 14, 2022

P-Reviewer: Huang T, Yao D

S-Editor: Zhang H

L-Editor: Webster JR

P-Editor: Zhang H



Citation: Yamada K, Yoshida K. Multiple subcellular localizations and functions of protein kinase C δ in liver cancer. *World J Gastroenterol* 2022; 28(2): 188-198

URL: <https://www.wjgnet.com/1007-9327/full/v28/i2/188.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v28.i2.188>

INTRODUCTION

The protein kinase C (PKC) family of serine/threonine kinase proteins in mammals, comprising the classical PKC (cPKC), novel PKC (nPKC), and atypical PKC (aPKC) subfamilies, is one of the defining families of AGC kinases[1,2]. To date, 10 isoforms of PKC have been identified in humans, including four cPKCs (PKC α , - β I, - β II, and - γ), four nPKCs (PKC δ , - ϵ , - η , and - θ), and two aPKCs (PKC ζ and - λ /i)[2,3]. PKC activation depends on the conformational activation of certain intracellular factors. Notably, PKC activation is regulated not only by binding to lipid factors, such as diacylglycerol (DAG) and phorbol esters, but also by protein phosphorylation[4]. PKC δ is often phosphorylated at several Tyr residues by various types of stimulations, including DNA-damaging reagents and oxidative stress[5,6]. Kinases that phosphorylate PKC δ at Tyr include the Src family of tyrosine kinases (*e.g.*, Src, Fyn, Lyn, and Lck) and c-Abl[6].

Among PKC families, PKC δ is a unique non-signal peptide-containing intracellular protein that has been reported to translocate to a diverse range of distributions, including the cytosol, nucleus, endoplasmic reticulum, Golgi, mitochondria, and plasma membrane, in response to different stimuli and cell types[8]. For example, a nuclear localization signal (NLS) was identified in the catalytic domain of PKC δ , which is necessary for the transport of PKC δ across the nuclear pore. Nuclear localization of PKC δ is associated with pro-apoptotic functions. Phosphorylation also affects the subcellular localization of PKC δ and its activation. Our recent study revealed that cytosolic PKC δ translocates to the extracellular space and acts as a growth factor for liver cancer cells or tumors[9]. In this review, we summarize studies reported to date regarding the intracellular function of PKC δ in cancerous phenotypes of liver cancer. We then focus on and discuss the relationship with subcellular localizations, which exist in extracellular and intracellular locations, and the functions of PKC δ . Increased knowledge on where PKC δ protein is localized and how it functions in living cells allows a more profound understanding of the functional diversity of PKC δ .

STRUCTURAL FEATURES OF PKC δ

PKC δ comprises an N-terminal regulatory domain and a C-terminal kinase core domain[5]. The C-terminal catalytic domain of PKC is conserved between isoforms and includes ATP- and substrate-binding sites and a kinase core[10,11]. The N-terminal regulatory domain is much less conserved and contains specific motifs for each isoform that are activated in response to unique signals. The regulatory modules in this N-terminal domain include the pseudosubstrate motif and C1 and C2 domains, which bind to Ca²⁺ and DAG. The affinity of the C1 and C2 domains for Ca²⁺ and DAG determines the cofactor requirements for the activation of specific PKC isoforms. cPKCs have functional C1 and C2 domains that bind to both Ca²⁺ and DAG[12-14], whereas nPKCs have a functional C1 domain that binds to DAG alone and a non-functional C2 domain, rendering these kinases independent of Ca²⁺ for activation[15].

Generally, upon PKC activation, growth factors and G protein-coupled receptors trigger the hydrolysis of membrane lipids by recruiting phospholipase C[16,17]. Phospholipase C generates DAG and inositol-1,4,5-triphosphate through the hydrolysis of membrane phosphoinositol. In response to DAG, PKC is translocated to the lipid membrane *via* the C1 domain, enabling interaction with its substrates and the phosphorylation response[18].

PKC δ confers distinct allosteric regulation *via* protein binding to the C1, C2, and V5 domains, tyrosine phosphorylation, and the removal of the regulatory domain by caspase cleavage (Figure 1). In particular, various reports have identified that a variety of tyrosine phosphorylation sites affect cellular functions. For example, many studies have demonstrated that tyrosine phosphorylation of PKC δ plays a critical role in cell death in response to apoptotic stimuli. Tyrosine residues important in the context of

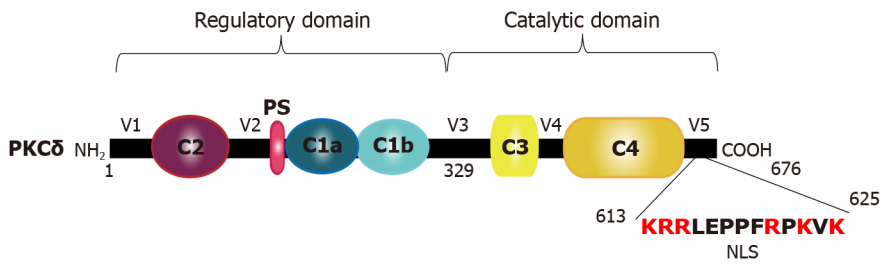


Figure 1 Schematic representation of protein kinase C δ domains. The N-terminal regulatory domain is composed of 1 to 329 amino acids, non-functional C2, pseudosubstrate, and lipid binding C1 (a and b) domains. The C-terminal catalytic domain is composed of 330 to 676 amino acids, ATP-binding C3, and kinase C4 domains. The 329 amino acids at the V3 region allow the cleavage site by caspase-3 to be constitutively active. The V5 region includes nuclear localization signal necessary for the nuclear transport of protein kinase C δ . NLS: Nuclear localization signal.

apoptosis include Tyr64, Tyr155, Tyr187, Tyr311, Tyr332, and Tyr512[18-20]. Furthermore, tyrosine phosphorylation of Tyr64 (C2 domain) and Tyr155 (C1a domain) is crucial for the exposure of PKC δ to NLS by disrupting the association between C2 and catalytic domains to enable nuclear transport.

FUNCTIONAL FEATURES OF INTRACELLULAR PKC δ IN LIVER CANCER

Tumor suppressive function

Studies on PKC $\delta^{-/-}$ mice have confirmed the pro-apoptotic role of this molecule in response to several stimuli, such as DNA damage. Although these mice developed normally and were fertile, increased B cell proliferation was observed[21]. Smooth muscle cells derived from PKC $\delta^{-/-}$ mouse aortas were also shown to be resistant to cell death in response to several stimuli. Hence, these studies with PKC $\delta^{-/-}$ mice demonstrated that PKC δ is not required for cell proliferation during development.

PKC also binds to and is activated by tumor-promoting phorbol esters[4]. Therefore, PKC is considered a tumor-promoting protein. However, it has been reported that persistent treatment with phorbol esters causes degradation or downregulation of PKC [3,22-24]. In particular, PKC δ has been reported to enhance ubiquitin proteasomal degradation upon activation of PKC δ by lipids. Furthermore, accumulating evidence on PKC δ in cancer has shown that downregulation, rather than activation, of PKC δ is associated with tumor progression. Therefore, PKC δ is believed to act as a tumor suppressor because its downregulation facilitates tumor promotion and causes cell cycle arrest or induces apoptosis in response to various stimuli, such as H₂O₂, ceramide, tumor necrosis factor- α (TNF- α), ultraviolet radiation, cisplatin, and etoposide[22,25-27]. In fact, the *PKC δ* gene is deleted in many cancers[28]. Ectopic expression of PKC δ has been shown to decrease the anchorage-independent growth of NIH3T3 cells and reverse the transformation of rat fibroblasts and colonic epithelial cells by Src. Low levels of PKC δ have been reported in colon cancer, and overexpression of PKC δ suppresses the neoplastic phenotype of colon cancer cells[25]. A recent report suggested that PKC δ is lost in human squamous cell carcinoma due to transcriptional repression[29]. PKC δ has also been reported to decrease cell migration in breast cancer cells, whereas knockout of the PKC δ gene increases cell migration in mouse embryonic fibroblasts. These studies strongly support the role of PKC δ in tumor suppression.

Multiple reports suggest that PKC δ is responsible for apoptotic signaling in liver cancer cells (Table 1). In sorafenib-resistant hepatocellular carcinoma (HCC) cells, PKC δ activation was shown to induce cellular apoptosis *via* p38 activation[30]. Annexin A3 (ANXA3) interacts with PKC δ and thereafter suppresses PKC δ /p38-associated apoptosis and activates autophagy for cell survival. Thus, inhibition of ANXA3 by a monoclonal antibody is likely to impair cell survival and tumor growth. Although FTY720, a synthetic sphingosine immunosuppressor, has been known to have antitumor effects on HCC cells, PKC δ activation occurs in FTY720-treated HCC cells. FTY720 is thought to activate PKC δ *via* the generation of reactive oxygen species (ROS) and subsequent caspase 3-dependent cleavage to induce apoptosis. The relationship between intracellular activation of PKC δ and apoptosis in HCC cells has also been reported in the antitumor mechanism of an antagonist of FZD7, which is a membrane receptor overexpressed in HCC[31]. These lines of evidence suggest that PKC δ activation is not favorable for malignant transformation in liver cancer and may

Table 1 The relationship between subcellular localizations and functions of protein kinase C δ in liver cancer

| Response | Localization | Function | Mechanisms | Ref. |
|---------------------------|----------------------------------|--|---|------|
| ANXA3 expression | Cytosol/plasma membrane | Interacts with PKC δ and inhibits apoptosis | p38MAPK activation | [30] |
| ROS | Nucleus | Activates PKC δ and induces apoptosis | Activates caspase 3 and induces cleavage of PKC δ | [31] |
| Claudin-1 | Cytosol/plasma membrane | Enhances the ability of cell migration/invasion | Induces c-Abl-PKC δ signaling | [33] |
| mtROS | Plasma membrane | Induces gene expression for cell migration | Triggers oxidation of HSP60 and then induces MAPK activation | [34] |
| HIF-2 α expression | Cytosol/plasma membrane | Induces cell migration | Phosphorylates PKC δ at Tyr311 | [35] |
| HSP27 expression | Cytosol/plasma membrane | Inversely correlates with tumor malignancy | p38MAPK activation by PKC δ induces phosphorylation of HSP27 | [36] |
| No response | Extracellular space/cell surface | Enhances cell proliferation | Activates MAPK signaling | [9] |

mtROS: Mitochondrial reactive oxygen species; ANXA3: Annexin A3; PKC δ : Protein kinase C δ ; MAPK: Mitogen-activated protein kinase; HIF: Hypoxia-inducible factor; HSP: Heat shock protein.

be inactivated in these cells.

Tumor promotive function

Many studies have shown that PKC δ promotes the survival of multiple types of cancers, including non-small cell lung cancer, breast cancer, pancreatic cancer, chronic lymphocytic leukemia, and liver cancer.

PKC δ has been reported to induce signal survival. In fact, PKC δ promotes cell survival *via* several well-known pro-survival pathways, including NF- κ B, Akt, and extracellular signal-regulated kinase (ERK). It has been reported that PKC δ inhibits apoptosis by inhibiting apoptosis protein-2 and FLICE-like inhibitory protein *via* NF- κ B[32].

Numerous publications have reported that PKC δ is actively involved in the promotion of liver cancer, including cell migration, invasion, and tumor stage (Table 1). For example, claudin-1, a member of the tetraspanin family, plays a critical role in the acquisition of invasive capacity in human liver cells, and c-Abl-PKC δ signaling is important for malignant progression induced by claudin-1[33]. This c-Abl-PKC δ signaling pathway was shown to activate MMP-2, a key factor in cell migration and invasion. The cross talk between PKC and ROS may induce mitogen-activated protein kinase (MAPK) activation for cell migration and progression. Mandal *et al*[34] found that activation of PKC δ generated mitochondrial ROS triggers the oxidation of heat shock protein 60 (HSP60), a chaperone protein in the mitochondria, which induces the activation of ERK and c-Jun N-terminal kinase (JNK) in the cytosol, resulting in gene expression leading to migration in liver cancer. PKC δ and hypoxia have also been reported to be associated with cell migration in liver cancer. Hypoxia-inducible factor-2 α expression regulates CUB domain-containing protein 1, which stimulates the phosphorylation of PKC δ at Tyr311 to induce malignant migration in various cancer cells, such as liver cancer cells[35]. Furthermore, the levels of HSP27 are inversely correlated with tumor stage, as per the tumor, node and metastasis classification, in patients with HCC. Takai *et al*[36] showed that PKC δ activation regulates the phosphorylation of HSP27 *via* p38 MAPK.

There is supportive evidence that PKC δ acts as a tumor promoter in many types of cancers. For example, the mRNA levels of PKC δ were higher in estrogen receptor (ER)-positive tumors than in ER-negative tumors, and an increase in PKC δ mRNA was associated with reduced overall survival[37]. PKC δ knockdown decreased the survival of MCF-7 and MDA-MB-231 breast cancer cells[38]. Overexpression of PKC δ was also observed in human ductal pancreatic carcinomas compared to its normal counterparts. PKC δ has been reported to be associated with melanoma cell metastasis[39]. A recent study demonstrated that integrin α v β 3-mediated invasion of melanoma cells is mediated *via* PKC α and PKC δ .

SUBCELLULAR LOCALIZATIONS AND FUNCTIONS OF PKC δ

Cytosol and plasma membrane

PKC δ is translated on the ribosome in the cytosol and generates its inactive cytosolic form. Similar to other PKC families, in response to DAG, PKC δ is also translocated to the plasma membrane *via* the C1 domain, which exerts a subsequent phosphorylation response. PKC δ activation is also required for Akt activation by Ras[40] (1-98). Activating mutations with Ras or PI3K increases PKC δ levels and induces Akt activation. PKC δ also induces ERK1/2 activation[41,42]. Akt and ERK1/2 activation have been implicated in the PKC δ -mediated increase in anchorage-independent growth and resistance of pancreatic ductal cancer cells to apoptotic stimuli[43]. Conversely, cytosolic PKC δ reportedly triggers apoptosis by activating p38 MAPK to inhibit Akt[8], indicating that PKC δ activation can behave as both a prosurvival and pro-apoptotic factor. Liver damage has been reported to induce inflammation and PKC δ translocation to the plasma membrane[44,45]. PKC δ activation has been observed in the tissues of patients with non-alcoholic steatohepatitis and non-alcoholic fatty liver disease and in a mouse model of hepatic cirrhosis[46-49].

Nucleus

Importantly, PKC δ is a PKC isoform that has been identified as a substrate for caspase-3[50]. Cleavage of PKC δ by caspase-3 separates the regulatory domain and catalytic fragment to allow constitutive activation of PKC δ even in the absence of any co-factors[22] and then translocates to the nucleus, where the catalytic fragment of PKC δ induces apoptosis[22]. Others and we have shown that full-length or fragmented PKC δ is translocated to the nucleus by transiting the nuclear pore[6,51]. Nuclear PKC δ interacts with and phosphorylates its substrates such as α -Abl, p53, p73, lamin B, Rad9, topoisomerase II, heterogeneous nuclear ribonucleoprotein K (hnRNP-K), and DNA-dependent protein kinase[22,52-54]. Moreover, nuclear PKC δ regulates the transcription of target genes in response to cellular stresses such as DNA damage, which is implicated in pro-apoptotic functions.

Upon oxidative stress, we previously showed that PKC δ associates with and activates IKK α in the nucleus[55]. Although IKK α activates NF- κ B by phosphorylating I κ B in the cytoplasm, which leads to prosurvival signaling, PKC δ -mediated IKK α activation at the nucleus causes phosphorylation of p53 at Ser20; however, it does not affect NF- κ B activation.

The tumor suppressor p53 is a master regulator of cellular processes, such as cell cycle arrest, DNA repair, or apoptosis[56,57]. Several studies have suggested that p53 is located downstream of PKC δ . In response to genotoxic stress, PKC δ phosphorylates p53 at Ser46 to trigger p53-mediated apoptosis.

In the nucleus, PKC δ also regulates p53 expression by increasing p53 transcription. We previously reported that PKC δ interacts with the death-promoting transcription factor Btf to induce Btf-mediated p53 gene transcription and apoptosis[58]. In addition, TNF- α treatment induces translocation of PKC δ into the nucleus[59]. PKC δ can bind to the NF- κ B RelA subunit and subsequently induce the transactivation of p65/RelA[59]. These findings demonstrate that NF- κ B is involved in PKC δ -mediated TNF/TNF-related apoptosis-inducing ligand (TRAIL) resistance. PKC δ inhibition or knockdown decreased NF- κ B expression and sensitized MCF7 cells to TNF/TRAIL-induced cell death[60].

Mitochondria

Bax and Bak are pro-apoptotic factors, and the Bcl-2 family regulates mitochondrial membrane permeability to induce apoptosis[61]. Upon exposure to ionizing radiation, Bax and Bak are activated *via* the c-Abl-PKC δ -p38 pathway to trigger mitochondrial cell death[30,62]. Mcl-1, an anti-apoptotic Bcl-2 family member, is a direct target of PKC δ . The catalytic fragment of PKC δ phosphorylates Mcl-1 and degrades it, leading to cell death. During the early stages of hypoxic stress, PKC δ induces autophagy *via* JNK-mediated phosphorylation of Bcl-2 to dissociate the Bcl-2/beclin-1 complex, and prolonged hypoxic stress induces PKC δ cleavage[63].

Cell surface

We recently showed that PKC δ is localized at the cell surface of liver cancer cell lines (Figure 2). Cell surface PKC δ was found to be anchored by other cell surface proteins, such as heparan sulfate proteoglycans (HSPGs). Some growth factors, such as fibroblast growth factors, vascular endothelial growth factor, and hepatocyte growth factor[64,65] have cationic amino acid clusters that can interact with heparan sulfate,

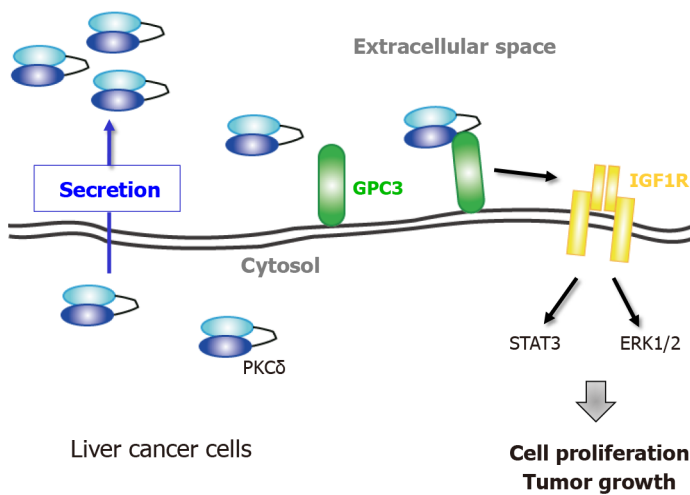


Figure 2 Extracellular protein kinase C δ shows oncogenic property in liver cancer. Model of the proliferative regulation of extracellular protein kinase C δ (PKC δ) in liver cancer cells. PKC δ is secreted from living cells and resides at the plasma membrane through its association with glypican 3, leading to an increase in insulin-like growth factor 1 receptor activation and enhancement of subsequent proliferative signaling to increase cell growth. PKC δ : Protein kinase C δ ; GPC3: Glypican 3; ERK: Extracellular signal-regulated kinase; IGF1R: Insulin-like growth factor 1 receptor.

which is composed of one or more unbranched anionic polysaccharide(s) known as glycosaminoglycans[65-67]. The cationic amino acid clusters closely resemble the NLS of intracellular proteins[68]. In fact, extracellular NLS-containing proteins, such as importin α 1, hnRNP-K, and PKC δ are detected at the cell surface of human cells[9,69,70]. These extracellular NLS-containing proteins are more likely to be located at the cell surface by binding to HSPGs.

Furthermore, glypican3, a liver cancer-specific HSPG, was identified as a receptor for cell surface PKC δ [71]. Both Cheng *et al*[72,73] and we showed that GPC3 regulates the activation of insulin-like growth factor 1 receptor (IGF1R)[9]. In fact, we found that extracellular PKC δ induces activation of IGF1R *via* association with GPC3 and its downstream signaling molecules, such as ERK1/2 and STAT3. Thus, these lines of evidence strongly suggest that cell surface PKC δ acts as a growth factor. In addition, we showed that anti-PKC δ monoclonal antibody (mAb) inhibits the proliferation and tumorigenesis of liver cancer cells, but not PKC δ -CRISPR knockout cells. Thus, cell surface PKC δ may be a potential therapeutic target for liver cancer.

Extracellular space

We also found that PKC δ is secreted into the extracellular space in liver cancer[9]. Extracellular accumulation of PKC δ was detected in different liver cancer cell lines but not in hepatocytes, suggesting that PKC δ secretion may be specific to liver cancer cells. Interestingly, our proteomics study showed that PKC, rather than PKC δ , was not detected in the culture medium of liver cancer cell lines. This means that PKC δ is a unique isoform of the PKC superfamily that is secreted extracellularly. Furthermore, higher levels of PKC δ were detected in the serum of patients with liver cancer, but not in patients with chronic hepatitis, hepatic cirrhosis, or healthy donors. This increase in serum PKC δ levels was also noted in a limited number of AFP- and PIVKA-II-negative liver cancer patients. Based on these clinical data, we propose that serum PKC δ may be a novel biomarker for liver cancer.

Recently, we and other groups have reported the extracellular localization of proteins with no signal peptide-containing proteins, such as FGF1, FGF2, HMGB1, hnRNP-K, importin α 1, and IL-1 β [69,70,74-77]. Secretion of these proteins is referred to as unconventional secretion[74,78]. Since the *PKC δ* gene does not encode a signal peptide, the extracellular secretion of PKC δ is also categorized as unconventional secretion. PKC δ has been shown to be full-length in the extracellular space and continues to be released from growing cells[9]. Many studies have reported that IL-1 β secretion often occurs in immune cells after induction of inflammatory stimulation[77,79,80]. There are some differences in the secretion modes between immune and cancer cells. Unlike immune cells (IL-1 β), liver cancer cells constitutively secrete importin α 1 and PKC δ even under physiological culture conditions (using 10% FBS medium)[9,69]. Conversely, some features were common between immune and liver cells, including the induction of unconventional secretion by ATP treatment[81] and independent of brefeldin A, an inhibitor in the “conventional” secretion pathway of

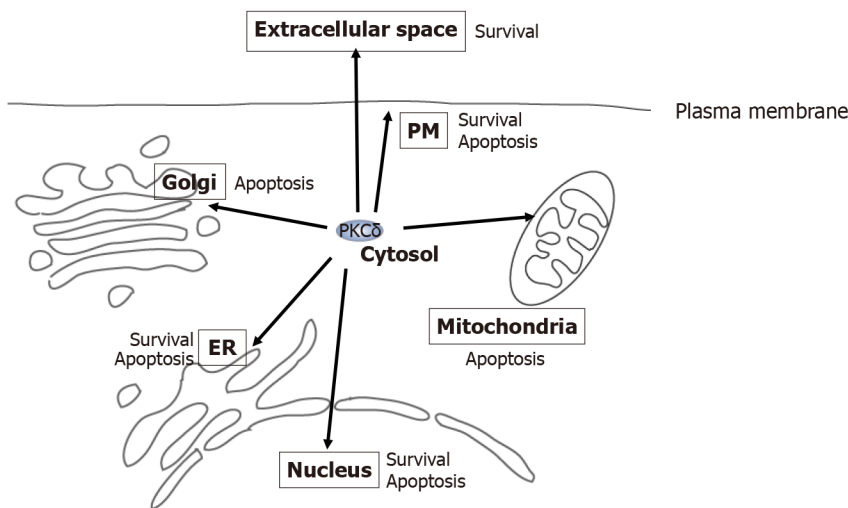


Figure 3 Multi-localization and functional diversity of protein kinase C δ . Protein kinase C δ (PKC δ) resides at various locations, including the cytosol, nucleus, estrogen receptor (ER), mitochondria, Golgi, extracellular space, and plasma membrane (inside and outside the cell). At each location, PKC δ acts as an apoptotic or survival factor in response to various stimuli, such as genotoxic stresses, phorbol ester, DNA damage, ER stress, tumor necrosis factor (TNF)- α , and TNF-related apoptosis-inducing ligand. PKC δ : Protein kinase C δ ; ER: Estrogen receptor; PM: Plasma membrane.

signal peptide-containing proteins[82].

We found that PKC δ secretion was initiated in the cytosol. Phorbol ester treatment inhibited PKC δ secretion, and the NLS active mutant was not secreted into the extracellular space. In fact, secreted PKC δ showed a lower level of phosphorylation (Tyr311 and Thr505). These lines of evidence support the possibility that cytosolic PKC δ , as a starting point for extracellular localization, could contribute to tumor progression in liver cancer.

Other organelles

A previous study has shown that PKC δ is translocated to the ER in response to ER stress and interacts with ER-bound c-Abl[83]. This PKC δ -c-Abl complex consequently moves to the mitochondria to trigger apoptosis[83]. It has been reported that tyrosine phosphorylation of PKC δ is associated with this interaction with c-Abl[84]. The chemical inhibitor rottlerin blocks the translocation of the PKC δ -c-Abl complex from the ER to the mitochondria, which confers protection against apoptosis[83]. Another ER protein, p23 (Tnp21), interacts with PKC δ , which enables the retention of PKC δ in the ER[85]. Translocation of PKC δ to the ER has also been reported in cells with Sindbis virus and in glioma cells treated with TRAIL, where PKC δ exerts an anti-apoptotic effect. Furthermore, a small amount of PKC δ has been observed in the Golgi apparatus. Ceramide or IFN- γ stimulation has been shown to translocate PKC δ to the Golgi apparatus, which is associated with ceramide-induced apoptosis in HeLa cells.

CONCLUSION

The apoptotic and survival functions of PKC δ are defined by cell and tissue types and their cellular conditions (Figure 3). In response to cellular stresses, PKC δ may be translocated to different organelles (including the cytosol and extracellular space), where PKC δ executes distinct functions in each location. Among the many types of tissues and cells, liver cancer cells have the most patterns of localization of PKC δ , including conventional intracellular and extracellular localization. Notably, extracellular PKC δ is involved in the tumorigenesis of liver cancer; therefore, it is a promising novel diagnostic and therapeutic target for liver cancer. Additional studies are required to elucidate further the various roles of PKC δ in liver cancer cells, which are dependent on the expression, subcellular distribution, and tumor microenvironment.

REFERENCES

- 1 **Manning G**, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. *Science* 2002; **298**: 1912-1934 [PMID: [12471243](#) DOI: [10.1126/science.1075762](#)]
- 2 **Newton AC**. Protein kinase C: structural and spatial regulation by phosphorylation, cofactors, and macromolecular interactions. *Chem Rev* 2001; **101**: 2353-2364 [PMID: [11749377](#) DOI: [10.1021/cr0002801](#)]
- 3 **Ohno S**, Nishizuka Y. Protein kinase C isotypes and their specific functions: prologue. *J Biochem* 2002; **132**: 509-511 [PMID: [12359062](#) DOI: [10.1093/oxfordjournals.jbchem.a003249](#)]
- 4 **Griner EM**, Kazanietz MG. Protein kinase C and other diacylglycerol effectors in cancer. *Nat Rev Cancer* 2007; **7**: 281-294 [PMID: [17384583](#) DOI: [10.1038/nrc2110](#)]
- 5 **Steinberg SF**. Structural basis of protein kinase C isoform function. *Physiol Rev* 2008; **88**: 1341-1378 [PMID: [18923184](#) DOI: [10.1152/physrev.00034.2007](#)]
- 6 **Yoshida K**. PKCdelta signaling: mechanisms of DNA damage response and apoptosis. *Cell Signal* 2007; **19**: 892-901 [PMID: [17336499](#) DOI: [10.1016/j.cellsig.2007.01.027](#)]
- 7 **Lu W**, Finnis S, Xiang C, Lee HK, Markowitz Y, Okhrimenko H, Brodie C. Tyrosine 311 is phosphorylated by c-Abl and promotes the apoptotic effect of PKCdelta in glioma cells. *Biochem Biophys Res Commun* 2007; **352**: 431-436 [PMID: [17126298](#) DOI: [10.1016/j.bbrc.2006.11.028](#)]
- 8 **Gomel R**, Xiang C, Finnis S, Lee HK, Lu W, Okhrimenko H, Brodie C. The localization of protein kinase Cdelta in different subcellular sites affects its proapoptotic and antiapoptotic functions and the activation of distinct downstream signaling pathways. *Mol Cancer Res* 2007; **5**: 627-639 [PMID: [17579121](#) DOI: [10.1158/1541-7786.MCR-06-0255](#)]
- 9 **Yamada K**, Oikawa T, Kizawa R, Motohashi S, Yoshida S, Kumamoto T, Sacki C, Nakagawa C, Shimoyama Y, Aoki K, Tachibana T, Saruta M, Ono M, Yoshida K. Unconventional Secretion of PKC δ Exerts Tumorigenic Function via Stimulation of ERK1/2 Signaling in Liver Cancer. *Cancer Res* 2021; **81**: 414-425 [PMID: [33318039](#) DOI: [10.1158/0008-5472.CAN-20-2009](#)]
- 10 **Gold MG**, Barford D, Komander D. Lining the pockets of kinases and phosphatases. *Curr Opin Struct Biol* 2006; **16**: 693-701 [PMID: [17084073](#) DOI: [10.1016/j.sbi.2006.10.006](#)]
- 11 **Mellor H**, Parker PJ. The extended protein kinase C superfamily. *Biochem J* 1998; **332** (Pt 2): 281-292 [PMID: [9601053](#) DOI: [10.1042/bj3320281](#)]
- 12 **Johnson JE**, Giorgione J, Newton AC. The C1 and C2 domains of protein kinase C are independent membrane targeting modules, with specificity for phosphatidylserine conferred by the C1 domain. *Biochemistry* 2000; **39**: 11360-11369 [PMID: [10985781](#) DOI: [10.1021/bi000902c](#)]
- 13 **Nalefski EA**, Falke JJ. The C2 domain calcium-binding motif: structural and functional diversity. *Protein Sci* 1996; **5**: 2375-2390 [PMID: [8976547](#) DOI: [10.1002/pro.5560051201](#)]
- 14 **Orr JW**, Newton AC. Interaction of protein kinase C with phosphatidylserine. 2. Specificity and regulation. *Biochemistry* 1992; **31**: 4667-4673 [PMID: [1581317](#) DOI: [10.1021/bi00134a019](#)]
- 15 **Ohno S**, Akita Y, Konno Y, Imajoh S, Suzuki K. A novel phorbol ester receptor/protein kinase, nPKC, distantly related to the protein kinase C family. *Cell* 1988; **53**: 731-741 [PMID: [3370672](#) DOI: [10.1016/0092-8674\(88\)90091-8](#)]
- 16 **Kharait S**, Dhir R, Lauffenburger D, Wells A. Protein kinase Cdelta signaling downstream of the EGF receptor mediates migration and invasiveness of prostate cancer cells. *Biochem Biophys Res Commun* 2006; **343**: 848-856 [PMID: [16564022](#) DOI: [10.1016/j.bbrc.2006.03.044](#)]
- 17 **Parker PJ**, Brown SJ, Calleja V, Chakravarty P, Cobbaut M, Linch M, Marshall JJT, Martini S, McDonald NQ, Soliman T, Watson L. Equivocal, explicit and emergent actions of PKC isoforms in cancer. *Nat Rev Cancer* 2021; **21**: 51-63 [PMID: [33177705](#) DOI: [10.1038/s41568-020-00310-4](#)]
- 18 **Newton AC**. Regulation of the ABC kinases by phosphorylation: protein kinase C as a paradigm. *Biochem J* 2003; **370**: 361-371 [PMID: [12495431](#) DOI: [10.1042/BJ20021626](#)]
- 19 **Konishi H**, Yamauchi E, Taniguchi H, Yamamoto T, Matsuzaki H, Takemura Y, Ohmae K, Kikkawa U, Nishizuka Y. Phosphorylation sites of protein kinase C delta in H₂O₂-treated cells and its activation by tyrosine kinase in vitro. *Proc Natl Acad Sci U S A* 2001; **98**: 6587-6592 [PMID: [11381116](#) DOI: [10.1073/pnas.111158798](#)]
- 20 **Gridling M**, Ficarro SB, Breitwieser FP, Song L, Parapatics K, Colinge J, Haura EB, Marto JA, Superti-Furga G, Bennett KL, Rix U. Identification of kinase inhibitor targets in the lung cancer microenvironment by chemical and phosphoproteomics. *Mol Cancer Ther* 2014; **13**: 2751-2762 [PMID: [25189542](#) DOI: [10.1158/1535-7163.MCT-14-0152](#)]
- 21 **Miyamoto A**, Nakayama K, Imaki H, Hirose S, Jiang Y, Abe M, Tsukiyama T, Nagahama H, Ohno S, Hatakeyama S, Nakayama KI. Increased proliferation of B cells and auto-immunity in mice lacking protein kinase Cdelta. *Nature* 2002; **416**: 865-869 [PMID: [11976687](#) DOI: [10.1038/416865a](#)]
- 22 **Basu A**. Involvement of protein kinase C-delta in DNA damage-induced apoptosis. *J Cell Mol Med* 2003; **7**: 341-350 [PMID: [14754503](#) DOI: [10.1111/j.1582-4934.2003.tb00237.x](#)]
- 23 **Roffey J**, Rosse C, Linch M, Hibbert A, McDonald NQ, Parker PJ. Protein kinase C intervention: the state of play. *Curr Opin Cell Biol* 2009; **21**: 268-279 [PMID: [19233632](#) DOI: [10.1016/j.ceb.2009.01.019](#)]
- 24 **Gould CM**, Newton AC. The life and death of protein kinase C. *Curr Drug Targets* 2008; **9**: 614-625 [PMID: [18691009](#) DOI: [10.2174/138945008785132411](#)]
- 25 **Perletti G**, Terrian DM. Distinctive cellular roles for novel protein kinase C isoenzymes. *Curr Pharm Des* 2006; **12**: 3117-3133 [PMID: [16918438](#) DOI: [10.2174/1381612067797947498](#)]

- 26 **Reyland ME.** Protein kinase Cdelta and apoptosis. *Biochem Soc Trans* 2007; **35**: 1001-1004 [PMID: [17956263](#) DOI: [10.1042/BST0351001](#)]
- 27 **Emoto Y, Manome Y, Meinhardt G, Kisaki H, Kharbanda S, Robertson M, Ghayur T, Wong WW, Kamen R, Weichselbaum R.** Proteolytic activation of protein kinase C delta by an ICE-like protease in apoptotic cells. *EMBO J* 1995; **14**: 6148-6156 [PMID: [8557034](#) DOI: [10.1002/j.1460-2075.1995.tb00305.x](#)]
- 28 **Jackson DN, Foster DA.** The enigmatic protein kinase Cdelta: complex roles in cell proliferation and survival. *FASEB J* 2004; **18**: 627-636 [PMID: [15054085](#) DOI: [10.1096/fj.03-0979rev](#)]
- 29 **Yadav V, Yanez NC, Fenton SE, Denning MF.** Loss of protein kinase C delta gene expression in human squamous cell carcinomas: a laser capture microdissection study. *Am J Pathol* 2010; **176**: 1091-1096 [PMID: [20093486](#) DOI: [10.2353/ajpath.2010.090816](#)]
- 30 **Omar HA, Chou CC, Berman-Booty LD, Ma Y, Hung JH, Wang D, Kogure T, Patel T, Terracciano L, Muthusamy N, Byrd JC, Kulp SK, Chen CS.** Antitumor effects of OSU-2S, a nonimmunosuppressive analogue of FTY720, in hepatocellular carcinoma. *Hepatology* 2011; **53**: 1943-1958 [PMID: [21391227](#) DOI: [10.1002/hep.24293](#)]
- 31 **Nambotin SB, Lefrancois L, Sainsily X, Berthillon P, Kim M, Wands JR, Chevallier M, Jalinot P, Scoazec JY, Trepo C, Zoulim F, Merle P.** Pharmacological inhibition of Frizzled-7 displays anti-tumor properties in hepatocellular carcinoma. *J Hepatol* 2011; **54**: 288-299 [PMID: [21055837](#) DOI: [10.1016/j.jhep.2010.06.033](#)]
- 32 **Tong M, Che N, Zhou L, Luk ST, Kau PW, Chai S, Ngan ES, Lo CM, Man K, Ding J, Lee TK, Ma S.** Efficacy of annexin A3 blockade in sensitizing hepatocellular carcinoma to sorafenib and regorafenib. *J Hepatol* 2018; **69**: 826-839 [PMID: [29885413](#) DOI: [10.1016/j.jhep.2018.05.034](#)]
- 33 **Wang Q, Wang X, Evers BM.** Induction of cIAP-2 in human colon cancer cells through PKC delta/NF-kappa B. *J Biol Chem* 2003; **278**: 51091-51099 [PMID: [14527959](#) DOI: [10.1074/jbc.M306541200](#)]
- 34 **Mandal JP, Shiue CN, Chen YC, Lee MC, Yang HH, Chang HH, Hu CT, Liao PC, Hui LC, You RI, Wu WS.** PKC δ mediates mitochondrial ROS generation and oxidation of HSP60 to relieve RKIP inhibition on MAPK pathway for HCC progression. *Free Radic Biol Med* 2021; **163**: 69-87 [PMID: [33307168](#) DOI: [10.1016/j.freeradbiomed.2020.12.003](#)]
- 35 **Cao M, Gao J, Zhou H, Huang J, You A, Guo Z, Fang F, Zhang W, Song T, Zhang T.** HIF-2 α regulates CDCP1 to promote PKC δ -mediated migration in hepatocellular carcinoma. *Tumour Biol* 2016; **37**: 1651-1662 [PMID: [26307391](#) DOI: [10.1007/s13277-015-3527-7](#)]
- 36 **Takai S, Matsushima-Nishiwaki R, Tokuda H, Yasuda E, Toyoda H, Kaneoka Y, Yamaguchi A, Kumada T, Kozawa O.** Protein kinase C delta regulates the phosphorylation of heat shock protein 27 in human hepatocellular carcinoma. *Life Sci* 2007; **81**: 585-591 [PMID: [17673262](#) DOI: [10.1016/j.lfs.2007.06.018](#)]
- 37 **McKiernan E, O'Brien K, Grebenchtchikov N, Geurts-Moespot A, Sieuwerts AM, Martens JW, Magdolen V, Evoy D, McDermott E, Crown J, Sweep FC, Duffy MJ.** Protein kinase Cdelta expression in breast cancer as measured by real-time PCR, western blotting and ELISA. *Br J Cancer* 2008; **99**: 1644-1650 [PMID: [19002183](#) DOI: [10.1038/sj.bjc.6604728](#)]
- 38 **McCracken MA, Miraglia LJ, McKay RA, Strobl JS.** Protein kinase C delta is a prosurvival factor in human breast tumor cell lines. *Mol Cancer Ther* 2003; **2**: 273-281 [PMID: [12657722](#)]
- 39 **Savoia P, Fava P, Osella-Abate S, Nardò T, Comessatti A, Quaglino P, Bernengo MG.** Melanoma of unknown primary site: a 33-year experience at the Turin Melanoma Centre. *Melanoma Res* 2010; **20**: 227-232 [PMID: [20449885](#)]
- 40 **Xia S, Chen Z, Forman LW, Faller DV.** PKCdelta survival signaling in cells containing an activated p21Ras protein requires PDK1. *Cell Signal* 2009; **21**: 502-508 [PMID: [19146951](#) DOI: [10.1016/j.cellsig.2008.12.002](#)]
- 41 **He P, Shen N, Gao G, Jiang X, Sun H, Zhou D, Xu N, Nong L, Ren K.** Periodic Mechanical Stress Activates PKC δ -Dependent EGFR Mitogenic Signals in Rat Chondrocytes via PI3K-Akt and ERK1/2. *Cell Physiol Biochem* 2016; **39**: 1281-1294 [PMID: [27606614](#) DOI: [10.1159/000447833](#)]
- 42 **Yan D, Chen D, Im HJ.** Fibroblast growth factor-2 promotes catabolism via FGFR1-Ras-Raf-MEK1/2-ERK1/2 axis that coordinates with the PKC δ pathway in human articular chondrocytes. *J Cell Biochem* 2012; **113**: 2856-2865 [PMID: [22488450](#) DOI: [10.1002/jcb.24160](#)]
- 43 **Mauro LV, Grossoni VC, Urtreger AJ, Yang C, Colombo LL, Morandi A, Pallotta MG, Kazanietz MG, Bal de Kier Joffé ED, Puricelli LL.** PKC Delta (PKCdelta) promotes tumoral progression of human ductal pancreatic cancer. *Pancreas* 2010; **39**: e31-e41 [PMID: [19924022](#) DOI: [10.1097/MPA.0b013e3181bce796](#)]
- 44 **Huynh DTN, Back N, Sim S, Myung CS, Heo KS.** Minor Ginsenoside Rg2 and Rh1 Attenuates LPS-Induced Acute Liver and Kidney Damages via Downregulating Activation of TLR4-STAT1 and Inflammatory Cytokine Production in Macrophages. *Int J Mol Sci* 2020; **21** [PMID: [32932915](#) DOI: [10.3390/ijms21186656](#)]
- 45 **Renu K, Saravanan A, Elangovan A, Ramesh S, Annamalai S, Namachivayam A, Abel P, Madhyastha H, Madhyastha R, Maruyama M, Balachandrar V, Valsala Gopalakrishnan A.** An appraisal on molecular and biochemical signalling cascades during arsenic-induced hepatotoxicity. *Life Sci* 2020; **260**: 118438 [PMID: [32949585](#) DOI: [10.1016/j.lfs.2020.118438](#)]
- 46 **Dzierlenga AL, Cherrington NJ.** Misregulation of membrane trafficking processes in human nonalcoholic steatohepatitis. *J Biochem Mol Toxicol* 2018; **32**: e22035 [PMID: [29341352](#) DOI: [10.1002/jbt.22035](#)]

- 47 **Yang M**, Chen Z, Xiang S, Xia F, Tang W, Yao X, Zhou B. Hugin Qingzhi medication ameliorates free fatty acid-induced L02 hepatocyte endoplasmic reticulum stress by regulating the activation of PKC- δ . *BMC Complement Med Ther* 2020; **20**: 377 [PMID: [33308192](#) DOI: [10.1186/s12906-020-03164-3](#)]
- 48 **Koh EH**, Yoon JE, Ko MS, Leem J, Yun JY, Hong CH, Cho YK, Lee SE, Jang JE, Baek JY, Yoo HJ, Kim SJ, Sung CO, Lim JS, Jeong WI, Baek SH, Baek JJ, Torres S, Solsona-Vilarrasa E, Conde de la Rosa L, Garcia-Ruiz C, Feldstein AE, Fernandez-Checa JC, Lee KU. Sphingomyelin synthase 1 mediates hepatocyte pyroptosis to trigger non-alcoholic steatohepatitis. *Gut* 2021; **70**: 1954-1964 [PMID: [33208407](#) DOI: [10.1136/gutjnl-2020-322509](#)]
- 49 **Lee SJ**, Kim SJ, Lee HS, Kwon OS. PKC δ Mediates NF- κ B Inflammatory Response and Downregulates SIRT1 Expression in Liver Fibrosis. *Int J Mol Sci* 2019; **20** [PMID: [31533364](#) DOI: [10.3390/ijms20184607](#)]
- 50 **Ghayur T**, Hugunin M, Talanian RV, Ratnofsky S, Quinlan C, Emoto Y, Pandey P, Datta R, Huang Y, Kharbanda S, Allen H, Kamen R, Wong W, Kufe D. Proteolytic activation of protein kinase C delta by an ICE/CED 3-like protease induces characteristics of apoptosis. *J Exp Med* 1996; **184**: 2399-2404 [PMID: [8976194](#) DOI: [10.1084/jem.184.6.2399](#)]
- 51 **DeVries TA**, Neville MC, Reyland ME. Nuclear import of PKCdelta is required for apoptosis: identification of a novel nuclear import sequence. *EMBO J* 2002; **21**: 6050-6060 [PMID: [12426377](#) DOI: [10.1093/emboj/cdf606](#)]
- 52 **Yoshida K**. Nuclear trafficking of pro-apoptotic kinases in response to DNA damage. *Trends Mol Med* 2008; **14**: 305-313 [PMID: [18539531](#) DOI: [10.1016/j.molmed.2008.05.003](#)]
- 53 **Cross T**, Griffiths G, Deacon E, Sallis R, Gough M, Watters D, Lord JM. PKC-delta is an apoptotic lamin kinase. *Oncogene* 2000; **19**: 2331-2337 [PMID: [10822384](#) DOI: [10.1038/sj.onc.1203555](#)]
- 54 **Gao FH**, Wu YL, Zhao M, Liu CX, Wang LS, Chen GQ. Protein kinase C-delta mediates down-regulation of heterogeneous nuclear ribonucleoprotein K protein: involvement in apoptosis induction. *Exp Cell Res* 2009; **315**: 3250-3258 [PMID: [19747914](#) DOI: [10.1016/j.yexcr.2009.09.005](#)]
- 55 **Yamaguchi T**, Miki Y, Yoshida K. Protein kinase C delta activates IkappaB-kinase alpha to induce the p53 tumor suppressor in response to oxidative stress. *Cell Signal* 2007; **19**: 2088-2097 [PMID: [17644309](#) DOI: [10.1016/j.cellsig.2007.06.002](#)]
- 56 **Lane DP**. Cancer. p53, guardian of the genome. *Nature* 1992; **358**: 15-16 [PMID: [1614522](#) DOI: [10.1038/358015a0](#)]
- 57 **Reinhardt HC**, Schumacher B. The p53 network: cellular and systemic DNA damage responses in aging and cancer. *Trends Genet* 2012; **28**: 128-136 [PMID: [22265392](#) DOI: [10.1016/j.tig.2011.12.002](#)]
- 58 **Liu H**, Lu ZG, Miki Y, Yoshida K. Protein kinase C delta induces transcription of the TP53 tumor suppressor gene by controlling death-promoting factor Btf in the apoptotic response to DNA damage. *Mol Cell Biol* 2007; **27**: 8480-8491 [PMID: [17938203](#) DOI: [10.1128/MCB.01126-07](#)]
- 59 **Lu ZG**, Liu H, Yamaguchi T, Miki Y, Yoshida K. Protein kinase Cdelta activates RelA/p65 and nuclear factor-kappaB signaling in response to tumor necrosis factor-alpha. *Cancer Res* 2009; **69**: 5927-5935 [PMID: [19549902](#) DOI: [10.1158/0008-5472.CAN-08-4786](#)]
- 60 **Zhang J**, Liu N, Zhang J, Liu S, Liu Y, Zheng D. PKCdelta protects human breast tumor MCF-7 cells against tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis. *J Cell Biochem* 2005; **96**: 522-532 [PMID: [16114000](#) DOI: [10.1002/jcb.20535](#)]
- 61 **Yamada K**, Yoshida K. Mechanical insights into the regulation of programmed cell death by p53 via mitochondria. *Biochim Biophys Acta Mol Cell Res* 2019; **1866**: 839-848 [PMID: [30790591](#) DOI: [10.1016/j.bbamcr.2019.02.009](#)]
- 62 **Owens TW**, Valentijn AJ, Upton JP, Keeble J, Zhang L, Lindsay J, Zouq NK, Gilmore AP. Apoptosis commitment and activation of mitochondrial Bax during anoikis is regulated by p38MAPK. *Cell Death Differ* 2009; **16**: 1551-1562 [PMID: [19662026](#) DOI: [10.1038/cdd.2009.102](#)]
- 63 **Chen JL**, Lin HH, Kim KJ, Lin A, Ou JH, Ann DK. PKC delta signaling: a dual role in regulating hypoxic stress-induced autophagy and apoptosis. *Autophagy* 2009; **5**: 244-246 [PMID: [19098423](#) DOI: [10.4161/auto.5.2.7549](#)]
- 64 **Wesche J**, Malecki J, Wiedlocha A, Ehsani M, Marcinkowska E, Nilsen T, Olsnes S. Two nuclear localization signals required for transport from the cytosol to the nucleus of externally added FGF-1 translocated into cells. *Biochemistry* 2005; **44**: 6071-6080 [PMID: [15835896](#) DOI: [10.1021/bi047403m](#)]
- 65 **Chiodelli P**, Bugatti A, Urbinati C, Rusnati M. Heparin/Heparan sulfate proteoglycans glycomic interactome in angiogenesis: biological implications and therapeutic use. *Molecules* 2015; **20**: 6342-6388 [PMID: [25867824](#) DOI: [10.3390/molecules20046342](#)]
- 66 **Lin X**. Functions of heparan sulfate proteoglycans in cell signaling during development. *Development* 2004; **131**: 6009-6021 [PMID: [15563523](#) DOI: [10.1242/dev.01522](#)]
- 67 **Matsuo I**, Kimura-Yoshida C. Extracellular modulation of Fibroblast Growth Factor signaling through heparan sulfate proteoglycans in mammalian development. *Curr Opin Genet Dev* 2013; **23**: 399-407 [PMID: [23465883](#) DOI: [10.1016/j.gde.2013.02.004](#)]
- 68 **Miyamoto Y**, Yamada K, Yoneda Y. Importin α : a key molecule in nuclear transport and non-transport functions. *J Biochem* 2016; **160**: 69-75 [PMID: [27289017](#) DOI: [10.1093/jb/mvw036](#)]
- 69 **Yamada K**, Miyamoto Y, Tsujii A, Moriyama T, Ikuno Y, Shiromizu T, Serada S, Fujimoto M, Tomonaga T, Naka T, Yoneda Y, Oka M. Cell surface localization of importin α 1/KPNA2 affects cancer cell proliferation by regulating FGF1 signalling. *Sci Rep* 2016; **6**: 21410 [PMID: [26887791](#)]

- DOI: [10.1038/srep21410](https://doi.org/10.1038/srep21410)]
- 70 **Yang L**, Fujimoto M, Murota H, Serada S, Honda H, Yamada K, Suzuki K, Nishikawa A, Hosono Y, Yoneda Y, Takehara K, Imura Y, Mimori T, Takeuchi T, Katayama I, Naka T. Proteomic identification of heterogeneous nuclear ribonucleoprotein K as a novel cold-associated autoantigen in patients with secondary Raynaud's phenomenon. *Rheumatology (Oxford)* 2015; **54**: 349-358 [PMID: [25172934](https://pubmed.ncbi.nlm.nih.gov/25172934/) DOI: [10.1093/rheumatology/keu325](https://doi.org/10.1093/rheumatology/keu325)]
 - 71 **Ghouri YA**, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. *J Carcinog* 2017; **16**: 1 [PMID: [28694740](https://pubmed.ncbi.nlm.nih.gov/28694740/) DOI: [10.4103/jcar.JCar_9_16](https://doi.org/10.4103/jcar.JCar_9_16)]
 - 72 **Cheng W**, Huang PC, Chao HM, Jeng YM, Hsu HC, Pan HW, Hwu WL, Lee YM. Glypican-3 induces oncogenicity by preventing IGF-1R degradation, a process that can be blocked by Grb10. *Oncotarget* 2017; **8**: 80429-80442 [PMID: [29113314](https://pubmed.ncbi.nlm.nih.gov/29113314/) DOI: [10.18632/oncotarget.19035](https://doi.org/10.18632/oncotarget.19035)]
 - 73 **Cheng W**, Tseng CJ, Lin TT, Cheng I, Pan HW, Hsu HC, Lee YM. Glypican-3-mediated oncogenesis involves the Insulin-like growth factor-signaling pathway. *Carcinogenesis* 2008; **29**: 1319-1326 [PMID: [18413366](https://pubmed.ncbi.nlm.nih.gov/18413366/) DOI: [10.1093/carcin/bgn091](https://doi.org/10.1093/carcin/bgn091)]
 - 74 **Nickel W**, Rabouille C. Mechanisms of regulated unconventional protein secretion. *Nat Rev Mol Cell Biol* 2009; **10**: 148-155 [PMID: [19122676](https://pubmed.ncbi.nlm.nih.gov/19122676/) DOI: [10.1038/nrm2617](https://doi.org/10.1038/nrm2617)]
 - 75 **Giuliani F**, Grieve A, Rabouille C. Unconventional secretion: a stress on GRASP. *Curr Opin Cell Biol* 2011; **23**: 498-504 [PMID: [21571519](https://pubmed.ncbi.nlm.nih.gov/21571519/) DOI: [10.1016/j.ceb.2011.04.005](https://doi.org/10.1016/j.ceb.2011.04.005)]
 - 76 **Gardella S**, Andrei C, Ferrera D, Lotti LV, Torrisi MR, Bianchi ME, Rubartelli A. The nuclear protein HMGB1 is secreted by monocytes *via* a non-classical, vesicle-mediated secretory pathway. *EMBO Rep* 2002; **3**: 995-1001 [PMID: [12231511](https://pubmed.ncbi.nlm.nih.gov/12231511/) DOI: [10.1093/embo-reports/kvf198](https://doi.org/10.1093/embo-reports/kvf198)]
 - 77 **Man SM**, Karki R, Kanneganti TD. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. *Immunol Rev* 2017; **277**: 61-75 [PMID: [28462526](https://pubmed.ncbi.nlm.nih.gov/28462526/) DOI: [10.1111/imr.12534](https://doi.org/10.1111/imr.12534)]
 - 78 **Rabouille C**. Pathways of Unconventional Protein Secretion. *Trends Cell Biol* 2017; **27**: 230-240 [PMID: [27989656](https://pubmed.ncbi.nlm.nih.gov/27989656/) DOI: [10.1016/j.tcb.2016.11.007](https://doi.org/10.1016/j.tcb.2016.11.007)]
 - 79 **Kimura T**, Jain A, Choi SW, Mandell MA, Johansen T, Deretic V. TRIM-directed selective autophagy regulates immune activation. *Autophagy* 2017; **13**: 989-990 [PMID: [26983397](https://pubmed.ncbi.nlm.nih.gov/26983397/) DOI: [10.1080/15548627.2016.1154254](https://doi.org/10.1080/15548627.2016.1154254)]
 - 80 **Zhang M**, Kenny SJ, Ge L, Xu K, Schekman R. Translocation of interleukin-1 β into a vesicle intermediate in autophagy-mediated secretion. *Elife* 2015; **4**: e11205 [PMID: [26523392](https://pubmed.ncbi.nlm.nih.gov/26523392/) DOI: [10.7554/eLife.11205](https://doi.org/10.7554/eLife.11205)]
 - 81 **Andrei C**, Dazzi C, Lotti L, Torrisi MR, Chimini G, Rubartelli A. The secretory route of the leaderless protein interleukin 1beta involves exocytosis of endolysosome-related vesicles. *Mol Biol Cell* 1999; **10**: 1463-1475 [PMID: [10233156](https://pubmed.ncbi.nlm.nih.gov/10233156/) DOI: [10.1091/mbc.10.5.1463](https://doi.org/10.1091/mbc.10.5.1463)]
 - 82 **Frye BC**, Halfter S, Djurdjaj S, Muehlenberg P, Weber S, Raffetseder U, En-Nia A, Knott H, Baron JM, Dooley S, Bernhagen J, Mertens PR. Y-box protein-1 is actively secreted through a non-classical pathway and acts as an extracellular mitogen. *EMBO Rep* 2009; **10**: 783-789 [PMID: [19483673](https://pubmed.ncbi.nlm.nih.gov/19483673/) DOI: [10.1038/embor.2009.81](https://doi.org/10.1038/embor.2009.81)]
 - 83 **Qi X**, Mochly-Rosen D. The PKCdelta -Abl complex communicates ER stress to the mitochondria - an essential step in subsequent apoptosis. *J Cell Sci* 2008; **121**: 804-813 [PMID: [18285444](https://pubmed.ncbi.nlm.nih.gov/18285444/) DOI: [10.1242/jcs.024653](https://doi.org/10.1242/jcs.024653)]
 - 84 **Kajimoto T**, Ohmori S, Shirai Y, Sakai N, Saito N. Subtype-specific translocation of the delta subtype of protein kinase C and its activation by tyrosine phosphorylation induced by ceramide in HeLa cells. *Mol Cell Biol* 2001; **21**: 1769-1783 [PMID: [11238914](https://pubmed.ncbi.nlm.nih.gov/11238914/) DOI: [10.1128/MCB.21.5.1769-1783.2001](https://doi.org/10.1128/MCB.21.5.1769-1783.2001)]
 - 85 **Wang H**, Xiao L, Kazanietz MG. p23/Tmp21 associates with protein kinase Cdelta (PKCdelta) and modulates its apoptotic function. *J Biol Chem* 2011; **286**: 15821-15831 [PMID: [21454541](https://pubmed.ncbi.nlm.nih.gov/21454541/) DOI: [10.1074/jbc.M111.227991](https://doi.org/10.1074/jbc.M111.227991)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

