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# Role for PKCδ on Apoptosis in the DNA Damage Response

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## 1. Introduction

Genotoxic stress induces cell cycle arrest, DNA repair, and apoptotic cell death. The decision by cells either to repair DNA lesions and continue through the cell cycle or to undergo apoptosis is relevant to the incidence of mutagenesis and, subsequently, carcinogenesis. In this regard, incomplete repair of DNA damage prior to replication or mitosis can result in the accumulation of heritable genetic changes. Therapeutic anti-cancer treatments that use genotoxic agents must strike a balance between induction of repair and apoptosis in order to maximize the therapeutic effect. However, the nature of the cellular signaling response that determines cell fate such as survival or death is far from being understood. Certain insights have been derived from the finding that diverse isozymes of the protein kinase C (PKC) family are activated in response to DNA damage. PKC-mediated signaling pathway modulates destiny of cells following genotoxic insults (Yoshida 2007a, Yoshida 2008a). In particular, recent studies have shown that certain isozyme of PKC controls function of the p53 tumor suppressor in induction of cell cycle arrest, DNA repair, and apoptosis. In the past 10 years, understanding the molecular mechanisms of apoptosis mediated by PKC has advanced considerably, and the primary focus of this review is to provide an overview of PKC and p53, its mode of action and its physiological role in DNA damage-induced apoptosis.

## 2. Protein kinase C

The protein kinase C (PKC) family of serine-threonine kinases was first described as a calcium-activated, phospholipid-dependent serine/threonine protein kinase (Takai et al. 1977). PKC is activated diacylglycerol (DAG) hydrolyzed from phosphatidylinositol (PI) by phospholipase C (PLC) under a different cell-signaling system (Nishizuka 1984, Nishizuka 1988, Nishizuka 1992, Nishizuka 1995). It has attracted attention as an intracellular receptor for tumor-promotor phorbol esters, such as 12-O-tetradecanoyl-13-phorbol acetate (TPA) (Niedel et al. 1983). Although PKC had been recognized as a protein kinase, subsequent studies have revealed that it belongs to a family of serine/threonine-specific protein kinases and is activated by diverse stimuli and participates in various cellular processes, such as growth, differentiation, apoptosis, and cellular senescence (Casabona 1997, Clemens et al. 1992, Goodnight et al. 1994, Hofmann 1997, Hug and Sarre 1993, Nishizuka 1984, Nishizuka 1988, Nishizuka 1992, Nishizuka 1995). PKC consists of at least 11 isozymes (α, βI, βII, γ, δ, ε, ζ, η, θ, ι/λ and μ) with selective tissue distribution, activators, and substrates. PKC isozymes

have been categorized into three groups: i) the classical/conventional PKCs (cPKCs: α, βI, βII γ), which are calcium dependent and activated by DAG; ii) the novel PKCs (nPKCs: δ, ε, θ, μ), which are calcium-independent and activated by DAG; and iii) the atypical PKCs (aPKCs: ζ, λ), which are calcium-independent and not activated by DAG (Casabona 1997, Goodnight et al. 1994, Hug and Sarre 1993, Nishizuka 1988, Nishizuka 1992, Nishizuka 1995). The cell-specific expression and subcellular localization of individual PKC isozymes indicate important isozyme-specific functions. To elucidate these functions, it should be necessary to study the individual features of each isozyme, such as expression, post-translational modification, substrate specificity, subcellular localization and signaling cross-talk with other proteins. Moreover, the involvement of a PKC isozyme in a signaling pathway resulting in a specific cellular response can be investigated by diverse distinct methods such as overexpression or inhibition of enzyme.

## 3. PKC and apoptotic cell death upon genotoxic insults

Novel PKCδ, θ, and μ are substrates for the effector caspase-3, and proteolytic activation of these novel PKCs has been associated with cell death (Datta et al. 1997, Emoto et al. 1995, Endo et al. 2000). However, recent studies have shown that PKC acts upstream of caspases to regulate cell death. For example, PKC activators enhanced caspase activation, whereas an inhibitor of PKC prevented caspase activation in response to DNA damage (Basu et al. 2001). In particular, studies with PKCδ$^{-/-}$ mice suggest that PKCδ plays pivotal roles in the regulation of cell proliferation and apoptosis (Humphries et al. 2006, Leitges et al. 2001). PKCδ is activated by a variety of stimuli including ionizing radiation, anti-cancer agents, reactive oxygen species (ROS), ultraviolet radiation, growth factors and cytokines (Carpenter et al. 2002, Chen et al. 1999, Denning et al. 1996, Konishi et al. 2001, Reyland et al. 1999, Yoshida and Kufe 2001, Yoshida et al. 2002). Molecular mechanisms such as tyrosine phosphorylation and proteolytic cleavage by caspase-3 are of importance to understand the pro-apoptotic role for PKCδ activation. PKC isozymes have been implicated in the growth factor signal transduction pathway (Nishizuka 1992). By contrast, activation of PKCδ inhibits cell cycle progression and down-regulation of PKCδ is linked to tumor promotion, suggesting that PKCδ may have a negative effect on cell survival (Lu et al. 1997, Watanabe et al. 1992). In many cases, the growth-inhibitory effects of PKCδ have been linked to changes in the expression of factors that influence cell cycle progression. Furthermore, PKCδ plays a pivotal role in the genotoxic stress response leading to apoptosis in various cell types (Brodie and Blumberg 2003, Reyland 2007, Yoshida 2007a). In addition, cells derived from PKCδ$^{-/-}$ mice were shown to be defective in mitochondria-dependent apoptosis (Humphries et al. 2006, Leitges et al. 2001). These findings thus support our proposition of a pro-genotoxic role for PKCδ. PKCδ is activated in response to diverse cellular stimuli by various processes, including membrane translocation (Joseloff et al. 2002, Wang et al. 1999), protein-protein interaction (Benes et al. 2005), tyrosine phosphorylation (Denning et al. 1996, Kaul et al. 2005), and proteolytic cleavage (Emoto et al. 1995, Ghayur et al. 1996, Yoshida 2007a, Yoshida et al. 2003). The translocation of PKCδ to discrete subcellular compartments and/or proteolytic cleavage can be induced by numerous stimuli, such as ceramide, TNFα, UV irradiation, ionizing radiation, oxidative stress, and etoposide (DeVries et al. 2002, Majumder et al. 2000, Matassa et al. 2001, Reyland et al. 1999, Yamaguchi et al. 2007b, Yoshida 2007a, Yoshida et al. 2006a, Yoshida et al. 2002, Yoshida et al. 2003, Yoshida et al. 2006b). Importantly, recent

studies have shown that genotoxin-induced PKCδ activation is in part dependent upon Ataxia telangiectasia mutated (ATM) (Yoshida et al. 2003). Whereas ATM activates c-Abl, and c-Abl activates PKCδ, a potential explanation is that DNA damage induces an ATM→c-Abl→PKCδ pathway (Yoshida 2007b, Yoshida and Miki 2005, Yoshida et al. 2005). Alternatively, ATM may directly activate PKCδ in the DNA damage response. In either case, nuclear targeting of PKCδ is pre-requisite for ATM-mediated full activation of PKCδ.

## 4. Nuclear translocation of PKCδ in the apoptotic responses

Translocation of PKCδ into the nucleus has been demonstrated in various cells (Blass et al. 2002, DeVries et al. 2002, DeVries-Seimon et al. 2007, Eitel et al. 2003, Scheel-Toellner et al. 1999, Yoshida et al. 2003, Yuan et al. 1998). Recent study showed that PKCδ translocates to nucleus after exposure of cells with 1-β-D-arabinofuranosylcytosine (ara-C) (Yoshida et al. 2003). Moreover, pretreatment with PKCδ inhibitor, rottlerin, attenuates nuclear targeting of PKCδ (Yoshida et al. 2003), suggesting that its kinase activity is required for nuclear translocation. A putative nuclear localization signal has been identified at the C-terminus of the catalytic domain of PKCδ (DeVries et al. 2002). Numerous PKCδ targets and substrates, including the p53 tumor suppressor, are nuclear proteins that function in induction of apoptosis.

## 5. Role for p53 in response to DNA damage

The tumor suppressor protein p53 plays a central role in mediating stress and DNA damage-induced cell cycle arrest and apoptosis (Vogelstein et al. 2000). The p53 protein controls normal responses to DNA damage and other forms of genotoxic stress and is an indispensable element in maintaining genomic stability (Vogelstein et al. 2000). In fact, *p53* is the most frequently mutated gene in human cancers (Nigro et al. 1989). The level of p53 protein is mostly undetectable in normal cells but rapidly increases in response to a variety of stress stimuli. The mechanism by which the p53 protein is stabilized is not completely understood, but post-translational modification plays a crucial role (Shieh et al. 1997). Mutations in the *p53* gene are frequently correlated with generation of human cancers; however, the p53 pathway can be also derailed by diverse oncogenic molecules (Oren et al. 2002). The *p53* gene knocked-out mice develop tumors with an increased rate (Donehower et al. 1992). It is reasonable that many agents may inhibit the p53 pathway as part of the road toward tumor promotion. However, mechanisms for action of many chemical agents that promote tumor development have not been elucidated. With the central role of p53 in mind, agents that promote tumor formation might block the p53 pathway. Importantly, p53 is regulated primarily via post-translational modifications, especially phosphorylation, and the accumulation of p53 is the first step following cellular stress (Oren 1999). The *mdm2* gene is a transcriptional target of p53, and once synthesized, the MDM2 protein can bind to p53 at its NH2 terminus leading to its rapid degradation through the ubiquitin proteasome-mediated pathway (Kubbutat and Vousden 1998, Oren 1999, Ryan et al. 2001). Upon DNA damage, p53 is phosphorylated at multiple sites at the NH2 terminus, thereby inhibiting MDM2 binding (Burns and El-Deiry 1999, Canman et al. 1998, Kubbutat and Vousden 1998, Oren 1999, Ryan et al. 2001, Siliciano et al. 1997). As a result, p53 degradation stops and p53 accumulates. p53 can also be phosphorylated at its COOH-terminal regulatory domain, which influences its DNA binding

(Meek 1998). In this context, constitutive phosphorylation of p53 by PKC at its COOH-terminal domain can lead to its degradation through ubiquitin proteasome-mediated pathway (Chernov et al. 2001). Moreover, treatment with PKC inhibitors, such as H7 or bisindolylmaleimide I, prohibited COOH-terminal phosphorylation of p53 and increased accumulation of p53 without any effect on the formation of the p53-MDM2 complex (Chernov et al. 2001). However, PKC inhibitors were incapable of p53 accumulation in human papilloma virus-positive HeLa cells (Chernov et al. 2001, Chernov et al. 1998).

## 6. PKCδ regulation of p53

The p53 tumor suppressor is activated following genotoxic stress. Transactivation of p53 target genes dictates cell cycle arrest and DNA repair or apoptosis. Accumulating studies have demonstrated that PKCδ regulates p53 expression at the transcriptional and post-translational levels.

### 6.1 Control at the transcription

Recent reports document that PKCδ transactivates expression of *p53* at the transcriptional level (Abbas et al. 2004, Liu et al. 2007, Yoshida 2008a). The tumor-promoting phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) hinders DNA damage-induced up-regulation of p53 by down-regulating PKCδ. TPA initiates tumor formation in a variety of mice and tissue culture models, and this has been correlated with the down-regulation of PKC (Hansen et al. 1990). TPA initially induces and then diminishes the activity of the diacylglycerol-dependent PKC isoforms (Fournier and Murray 1987, Hansen et al. 1990). Previous studies showed that the tumor-promoting activities of TPA are mediated at least in part by down-regulating PKCδ (Lu et al. 1997). Moreover, transgenic mice over-expressing PKCδ were resistant to tumor promotion by TPA (Reddig et al. 1999). In this regard, previous studies implied that TPA can inhibit the DNA damage-mediated induction of p53 (Magnelli et al. 1995). Moreover, other studies with protein kinase inhibitors suggested that PKCδ regulates the p53 signalsome pathway (Ghosh et al. 1999). Regulation of p53 upon stress most commonly occurs by inhibiting ubiquitination and degradation of the p53 protein. In contrast, repression of p53 by inhibiting PKCδ is caused by the prevention of p53 synthesis, not augmented degradation of p53 protein. Inhibiting PKCδ blocks both basal transcription of the human *p53* gene and initiation of transcription from the human *p53* promoter. The DNA damage-elicited increase in *p53* accumulation is drastically inhibited by pre-treatment with TPA. In addition, the PKCδ inhibitor, rottlerin, is also able to block the DNA damage-mediated induction of *p53*. More importantly, pre-treatment of cells with TPA or treatment with rottlerin results in the inhibition of basal *p53* transcription. In this regard, accumulation of *p53* could not be achieved by any means, including proteasome inhibition, after TPA or rottlerin treatment, since *p53* transcription is hindered. Thus, the tumor-suppressing effects for PKCδ are mediated at least in part through activating *p53* transcription. Suppression of the *p53* promoter has been implied as a mechanism for tumor promotion (Raman et al. 2000, Stuart et al. 1995). Damaged genes in tumor cells are generally the mechanistic drivers toward oncogenesis. However, abrogation of endogenous genes, specifically tumor suppressors, may be also a crucial regulatory mechanism for tumor promotion. In this context, agents that interfere with the activity of PKCδ may inhibit p53 responses.

Recent study also demonstrated that PKCδ induces the promoter activity of p53 via the p53 core promoter element (CPE-p53) and that such induction is enhanced after DNA damage. Upon genotoxic insults, PKCδ is activated and interacts with the death-promoting transcription factor Btf (Bcl-2-associated transcription factor) to co-occupy CPE-p53. Inhibition of PKCδ decreases the affinity of Btf to CPE-p53, thereby reducing *p53* expression. Concomitant with these results, abrogation of Btf-mediated *p53* transcription by RNA interference leads to repression of p53-mediated apoptosis in response to genotoxic stress. These findings demonstrate that activation of *p53* transcription by PKCδ induces p53-dependent apoptosis following DNA damage (Liu et al. 2007).

### 6.2 Control at the post-translation

Recent study demonstrated that both PKCδ and IKKα, but not IKKβ, are targeted to the nucleus after oxidative stress (Yamaguchi et al. 2007a, Yamaguchi et al. 2007b). PKCδ interacts with and activates IKKα. Significantly, upon exposure to oxidative stress, PKCδ-mediated IKKα activation does not contribute to NF-κB activation; rather, nuclear IKK controls transcription activity of p53 by phosphorylation on Ser20. These findings indicate a novel mechanism in which the PKCδ→IKKα signaling pathway contributes to ROS-induced p53 activation. Recent studies have also demonstrated that phosphorylation of p53 at Ser46 induces p53AIP1 expression, resulting in the commitment to the apoptotic cell death (Matsuda et al. 2002, Oda et al. 2000, Taira et al. 2007, Yoshida 2008b). Furthermore, upon genotoxic stress, p53DINP1 is induced and then recruits a kinase(s) to p53, which specifically phosphorylate Ser46 (Okamura et al. 2001). We initially found that PKCδ is associated with Ser46 phosphorylation (Yoshida et al. 2006a). This phosphorylation was required for the interaction of PKCδ to p53. Importantly, p53DINP1 associated with PKCδ in response to anti-cancer agents. In concert with these findings, PKCδ potentiates p53-dependent apoptotic cell death by Ser46 phosphorylation. Taken together, PKCδ controls p53 to induce apoptosis in the cellular response to DNA damage (Yoshida et al. 2006a). Of note, our subsequent studies have demonstrated that another kinase DYRK2 plays a major and direct role on apoptosis induction by phosphorylating p53 at Ser46 in response to DNA damage (Taira et al. 2007, Taira et al. 2010). We also recently found that PKCδ regulates MDM2 expression independently of p53. Given that *Mdm2* mRNA change was detected in p53-proficient, but not deficient cells, PKCδ affected Mdm2 at the post-translational level. In this context, treatment of proteasome inhibitor MG132 restored Mdm2 expression to the steady-state level. Moreover, PKCδ inhibited Mdm2 ubiquitination in p53-deficient cells and loss of PKCδ resulted in an increase in Mdm2 proteasomal degradation. P300/CBP-associated factor (PCAF), an ubiquitin ligase 3 for Mdm2, was observed to participate in Mdm2 ubiquitination by PKCδ inhibition and PCAF silencing rescued Mdm2 diminution. We thus conclude that PKCδ regulates Mdm2 expression distinctively of p53 pathway by affecting Mdm2 ubiquitination and maintenance of Mdm2 expression by PKCδ is important to ensure normal genotoxic cell death response in human cancer cells (Hew et al. 2011).

## 7. Future perspective

PKCδ plays a pivotal role in the control of apoptotic cell death in response to a diverse array of stress stimuli. Thus PKCδ is a pro-apoptotic kinase activated by multiple mechanisms, including subcellular translocation and proteolysis. The proteolytic activation of PKCδ is also important not only in activating the downstream apoptotic cascade including p53, but

also in amplifying upstream caspase signaling. Most of the studies mentioned above suggest that the role of PKCδ in the induction of apoptosis is tightly associated with its caspase-dependent cleavage and the regulation of p53. However, functional regulation of p53 by PKCδ remains largely unclear. In this regard, thorough investigation coupled with PKCδ and p53 should be enhanced from multiple views. In the encounter with genotoxic insults, ATM controls various cellular responses, such as cell cycle arrest, transcription, DNA repair, and apoptosis. In this context, DNA damage-induced PKCδ is modulated under ATM, suggesting the notion that establishment of the ATM→PKCδ→p53 signaling cascade provides new mechanistic light on how PKCδ functions as the pro-apoptotic kinase in the nucleus (Figure 1) (Yoshida 2007a, Yoshida 2008a). While dysregulation of the PKCδ signalsome confers resistance to anticancer drugs (Meinhardt et al. 1999), there is little

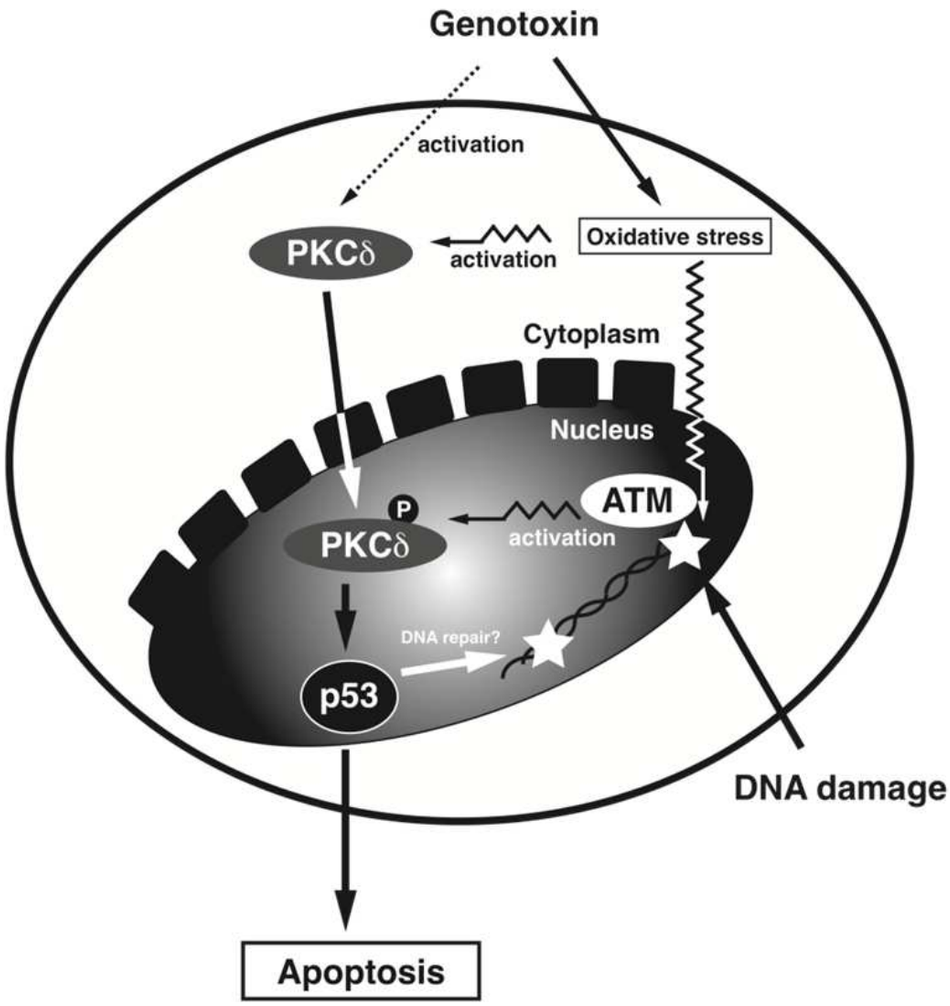


Fig. 1. A hypothetical schema for nuclear targeting of PKCδ in response to DNA damage. Following DNA damage, PKCδ translocates from the cytoplasm into the nucleus. In addition, some genotoxic stress also exerts cytoplasmic oxidative stress to activate PKCδ. In the nucleus, PKCδ is activated by ATM, then induces apoptosis (or DNA repair) in a p53-dependent manner.

understanding of how the PKCδ signaling pathway is influenced when cancer cells acquire resistance to chemotherapeutic drugs. Considering the importance of PKCδ in genotoxic stress-induced apoptosis, a thorough understanding of how it controls apoptosis should benefit cancer therapeutic potentials. Finally, novel PKCδ-based therapy may be used in combination with other agents to confer synergism and prevent the development for drug resistance.

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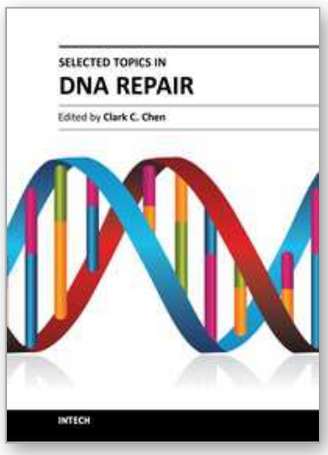


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This book is intended for students and scientists working in the field of DNA repair, focusing on a number of topics ranging from DNA damaging agents and mechanistic insights to methods in DNA repair and insights into therapeutic strategies. These topics demonstrate how scientific ideas are developed, tested, dialogued, and matured as it is meant to discuss key concepts in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

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