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The Activation Role of Protein Kinase D1 Important In Mitochondria and Oxidative Stress in Association with Pancreatic Cancer

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Abstract: *In this study, the mitochondrial efficiency and metabolic activity regulation of cancer cells were discussed, which revealed that the reactive oxygen species (ROS) plays the co-related role with the generate cancer cells. For inhibition of cytotoxic and facilitating tumorigenic signals, mechanism of ROS must be controlled. The molecules signal that was rich to nucleus plays key rules in regulating antioxidant genes by increased oxidative stress. ROS sensors have many proteins one of these proteins Protein kinase D1 (PKD1). In this survey, we focus on the effect of ROS to activate the PKD1 as well as pancreatic cancer progress.*

Keywords*: cancer cells, reactive oxygen species, protein kinase D1, pancreatic cancer*

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I. Introduction

Burg effect cancer cells having the warburg effect increased levels of production by two factors: glycolytic metabolism via to cells and (ROS) reactive oxygen species in mitochondria which is lead to modified in oxidative phosphorylation (1). Raising the level of ROS are rarely accompanied up an organization of antioxidant devices in tumor initiation (2, 3). The modification of antioxidant devices holds over ROS at scales where they are protumorigenic and promote cell subsistent and reproduction, but does not encourage apoptosis or necrotic cell dimes. In this review focuses on signaling pathway a ROS sensor that key regulates tumor cell detoxification, activation of protein kinase D1 (PKD1) lead to reproduction, and survival through kinase D1 count as one of three members of the PKD family of serine/threonine kinases. The structure of PKD1 consist of an N-terminal work as a regulatory part and a C- terminal Kinase domain. The regulation has two main source cysteine-rich (C1) domains responsible for lipid binding and pleckstrin homology (PH) domain which is important for protein-lipid and protein-protein interactions and binds (4). The location of PKDs in different cellular parts and simplify of Golgi convey process also in mitochondria as well as cytosolic and nuclear signaling (5). The impact of rising oxidative stress causes to PKD1 locates in mitochondria (6). ROS-activated PKD1, initiate cytosolic signaling pathways and nucleus distribution (6-9). The signaling pathway that targets to the activation of PKD1 decide by oxidative stress seems individual because it combines tyrosine phosphorylation of the molecule at many residues (8-11), which is not important occurrences of PKD1 which is activated by receptor receive signaling (7).

1. PKD activation downstream of ROS

Intracellular oxidative stress levels can be controlled Protein kinase D1 activates, two ways to activate PKD such as the addition of hydrogen peroxide or induced by glutathione depletion (7, 8, and 12). The activation of PKD1 also leads to an increase in mitochondrial ROS (mROS) give rise by inhibitors of the mitochondrial respiratory chain (13). In addition, these also include retention, diphenyleneiodonium inhibitor, and mitochondrial complex I, an inhibitor of the NADPH cytochrome P450 reductase (6). Furthermore, oncogenes are responsible for activating PKD1 that leads to increasing mROS levels, such as the mutation in version (G12D, G12V) of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRas) (14). Mitochondria (and cellular) with high levels of ROS cause to form a chain of tyrosine phosphorylations (Y95, Y432, Y463,

and Y502) in PKD1 (8, 10, 11), which are arranged by the (proto-oncogene,tyrosine-protein kinase Src) directly or either by the downstream of Src (10, 11). It is well un-known and not fully understood that how Src mechanism is activated downstream of ROS, and these changes due to upright oxidation of cysteine residues, tyrosine nitration, or redox inactivation of inhibitory protein tyrosine phosphatases help to increase activity. In this review, we clarify that the activation of PKD1 related to the levels of ROS-responsive receptor-like PTP alpha, whereas PKD1 in response to hydrogen peroxide (15), the mechanism was not available in details. For Src-mediated phosphorylations of PKD1 at Y432 and Y502, non-functional consequences have been imputed, Phosphorylation of PKD1 at Y95 is immediately caused by Src (10), so far, Y463 has been improved to be phosphorylated by Abelson murine leukemia viral oncogene homolog 1 (Abel), the source was activated (11). PKD1 phosphorylation at Y463 in PH domain shows to be starting step that causes of conformational change, which starts membrane anchoring at the mitochondria (16). Binding to diacylglycerol that can be created through activation of phospholipase D1 downstream of mROS (16). It should be the remarked that it was also clearly shown that the multifunctional chaperone p32 can work as an adapter that binds to PKD1 and PKCδ with mitochondrial membranes (17), but so far the important role for p32 in ROSinitiated activation of PKD1 has not yet been investigated. The phosphorylation of PKD1 at Y95 by Src as the next step. This creates the associate motif for the C2 domain of PKCδ (10), whereas the other knows that is also activated downstream of oxidative stress and Src (18). PKCδleads to phosphorylates the PKD1 activation loop serines (S738 and S742), leading to kinase activates completely (7, 10).

2. Signaling through ROS-Activated PKD1 and functional consequences

Previous found the activation of PKD1 is also related to cell survival and detoxification which controlled by several signaling molecules. The aiming target is the nuclear factor transcription factor kappa-light-chain-enhancer of B cells (NF-κB) activate. ROS/Src/Abl/PKCδ pathway helps to activate, PKD1 induces canonical NF-κB signaling by IκB kinase β and suborder down the investigation of the inhibitor of kappa-light-chain-enhancer of B cells alpha activate (8). However, the date of the molecular mechanism is still unknown. Cell survival, cytokine production, and inflammatory signaling are under the control of protein known as NF-κB. In addition, downstream of PKD1 control activation of protein NF-KP was also correlated to rise level expression of SOD2.SOD2 gene encoding (MnSOD) manganese superoxide dismutase (6). Manganese superoxide dismutase produces hydrogen peroxide, bona fide signaling is necessary for controlling tumor cell growth (2). Intermediation of PKD1 action of NF-Kb leads to rising expression of epidermal growth factor receptor(EGFR) and its responsible channels TGFα and EGF (14).In addition, Both of NF-κB activation and PKD1 are including in other signaling pathways to cell survival developed under-response of oxidative stress, in mitochondria, the cofilin2 translocated and reacted with the proapoptotic molecule Bax (19). Cofilin phosphatase inhibited by PKD1 prevent 1L acceleration (20).In addition, there is a signaling reduce of cofilin2 translocation to mitochondria and protect mitochondria after oxidative stress resulted in cell survivals (19). Besides, Using various pathway of how PKD1 promotes cell existence is by regulating signal of kinases ½ in the extracellular activate which improve chronic oxidative stress (21, 22). C-Jun N-terminal kinase (JNK) signaling downregulating that promote cell death (21, 22). As same as,p38 MAPK signaling by PKD1 downregulation confers to hydrogen peroxide has shown the efficiency of cell survive from apoptosis (23). ROS activated PKD1 has another target known as heat shock protein Hsp27, which is phosphorylated by PKD1 at S82 (24). Binding of PKD1-phosphorylated and Hsp27 to cell death signal-regulating kinase 1 to stop JNK-induced cell death (25). Chemoresistance of Various cancers has been implicated by Hsp27 (26,27). Furthermore, protein kinase phosphorylates and activate PKD1 death-associated with tumor suppressor correlated with oxidative damage (28). Like signaling effects of autophagy, caused PKD1-mediated phosphorylation of Vps34 lead to increases of formation autophagosome and lipid kinase activity (29).

3. Conclusion

ROS- sensing signaling play role important in the regulation balance of oxidative stress in tumor cells. This work as a target channel for tumor cells (46). In this review, we prove that ROS, control PKD1 via various factors through given signals. In mitochondria depolarization, PKD1 determination leads to ROS release (53). In addition, PKD1 downstream signaling may control ROS levels for tumor cell. Previously, different PKD inhibitors have been improved in preclinical models. Provide an example, PKD inhibitor CRT0066101 in orthotopically implanted pancreatic cancer cells improve that effects on pre-I-tumor (54). Therefore, if the inhibitor can be used it is still unknown for final stage tumors. Further studies are clearly needed it to prove that the target ROS-PKD signal levels evaluate the cancer therapy.

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