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# Mitochondrial and Postmitochondrial Survival Signaling in Cancer

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## Abstract

Cancer cells are resistant to conventional chemotherapy and radiotherapy, however, the molecular mechanisms of resistance to therapy remain unclear. Cellular survival machinery protects mitochondrial integrity against endogenous or exogenous stresses. Prodeath molecules orchestrate around mitochondria to initiate and execute cell death in cancer, and also play an under appreciated role in survival of cancer cells. Prosurvival mechanisms can operate at mitochondrial and postmitochondrial levels to attenuate core apoptotic death program. It is intriguing to explore how prosurvival and prodeath molecules crosstalk to regulate mitochondrial functions leading to increased cancer cell survival. This review describes some putative survival mechanisms at mitochondria, which may play significant role in designing effective agents for cancer prevention and therapy. These survival pathways may also have significance in understanding other human pathophysiological conditions including diabetes, cardiovascular, autoimmune, and neurodegenerative diseases.

## 1). Introduction

Decreased apoptosis is associated with cancer and autoimmune diseases, whereas, excessive apoptosis is implicated in neurodegenerative and cardiovascular diseases (Fischer and Schulze-Osthoff, 2005; Horvitz, 1999; Olson and Kornbluth, 2001; Salvesen and Dixit, 1997). The process of apoptosis requires a sequence of events, which ultimately culminate into activation of cystein proteases known as caspases (Salvesen and Dixit, 1997). Mitochondrion functions as a critical signaling center for the activation of caspases. Various factors have been reported to regulate caspase activation during early and/or late phases of apoptosis. These factors encompass pre-mitochondrial, mitochondrial, and postmitochondrial levels; and regulate caspase activation induced by chemotherapeutic drugs, and endogenous and exogenous stresses such as toxicants or radiation exposure. Although tremendous progress has been made but how apoptosis is regulated at the mitochondrial and postmitochondrial levels is still not completely understood. Therefore,



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proper understanding of survival and apoptotic players during apoptotic process are critical in designing of drugs for various human diseases including cancer.

Recent studies suggest that proapoptotic proteins perform dual role, i.e., they regulate survival and apoptosis processes during stress. For example, p53 functions as proapoptotic molecule in apoptosis, but it can also act as a survival molecule by activating DNA repair signaling (Chipuk and Green, 2006; Gatz and Wiesmuller, 2006; Gudkov and Komarova, 2010; Kim et al., 2009). Similarly, cytochrome c functions as a survival or apoptotic molecule (Jiang and Wang, 2000; Kluck et al., 1997; Li et al., 1997; Poyton and McEwen, 1996; Zou et al., 1997). Although therapeutic interventions designed to induce or inhibit apoptosis are appealing, significant logistical hurdles such as efficacy and recurrence exist in clinics using these approaches. This review focuses on how survival and apoptotic mechanisms coordinate, and how these survival and apoptotic factors are instrumental in providing resistance to apoptosis.

## 2. Apoptotic pathways

Apoptosis is mediated by activation of caspases, which are generally synthesized as inactive zymogens (Salvesen and Dixit, 1997). Caspases are broadly divided into two groups: initiator caspases with long prodomain such as caspase-2, caspase-8, caspase-9, and caspase-10; and the executioner caspases with short prodomain like caspase-3, caspase-6, and caspase-7 (Boatright et al., 2003; Horvitz, 1999; Jiang and Wang, 2004; Salvesen and Dixit, 1997). Activation of caspases is tightly regulated and involves two major pathways: the intrinsic pathway that involves mitochondria, and the extrinsic pathway (death-receptor pathway) initiated by cell surface death receptors (Ashkenazi and Dixit, 1998; Boatright et al., 2003; Carrington et al., 2006; Luo et al., 1998). Intrinsic pathway is regulated by Bcl-2 family proteins and triggered by stresses such as DNA damaging agents, chemotherapeutics, serum deprivation, hypoxia, and oncogene activation (Danial and Korsmeyer, 2004; Fulda et al., 2010; Green and Kroemer, 2004; Sarosiek et al., 2013; Vieira and Kroemer, 1999). Stimulation of apoptosis with these agents initiates the release of proapoptotic proteins such as cytochrome c and second mitochondrial-derived activator of caspase/direct inhibitor of apoptosis protein-binding protein with low pI (Smac/Diablo) along with other proteins triggering caspase activation (Du et al., 2000; Fulda et al., 2010; Jiang and Wang, 2004; Sarosiek et al., 2013). The released cytochrome c interacts with an adaptor protein apoptotic protease activating factor 1 (Apaf-1), thus allows nucleotide binding and exchange, which initiates Apaf-1 oligomerization and apoptosome formation leading to the recruitment and activation of caspase-9 (Jiang and Wang, 2000; Kim et al., 2008; Reubold et al., 2009, 2011; Yuan and Akey, 2013). Active caspase-9 then processes executioner caspases such as caspase-3/7 to execute apoptosis (Bratton and Salvesen, 2010; Hu et al., 2013; Malladi et al., 2009; Shi, 2002; Wang, 2001). However, inhibitor of apoptosis proteins (IAPs) bind to active caspase-9 and -3 blocking the caspase cascade, and thus inhibit apoptosis (Bratton et al., 2001; Deveraux et al., 1997; Uren et al., 1996). Another proapoptotic protein, Smac/DIABLO released from the mitochondria interacts with and sequesters IAPs, and therefore, allows activation of caspases to progress during apoptotic induction (Du et al., 2000; Ekert et al., 2001; Srinivasula et al., 2000).

In the extrinsic or death-receptor pathway, death ligands such as Fas (CD95), tumor necrosis factors (TNF), death receptor (DR)-3 (Apo3), DR4 (TRAIL-R1) and DR5 (TRAIL-R2) trigger death-receptor trimerization leading to the recruitment of Fas-associated death domain (FADD) and formation of death-inducing signaling complex (DISC) with subsequent activation of caspase-8 (Ashkenazi and Dixit, 1998). Active caspase-8 then activates caspase-3 to execute apoptosis (Ashkenazi and Dixit, 1998; Shi, 2002). Death receptor pathway can be amplified by cleavage of a proapoptotic protein Bid, which translocates to mitochondria and initiates cytochrome c release, thus enhances caspase activation (Ashkenazi and Dixit, 1998; Barnhart et al., 2003; Luo et al., 1998; Shi, 2002).

Therefore, the release of mitochondrial cytochrome c represents the key event for both intrinsic and extrinsic pathways. The cytochrome c release is regulated by antiapoptotic Bcl-2 proteins such as Bcl-2 and Bcl-xL, which inactivate the proapoptotic channel forming function of multidomain Bax and Bak on the outer mitochondrial membrane (Brunelle and Letai, 2009; Danial and Korsmeyer, 2004; Kuwana and Newmeyer, 2003). Apoptotic stimuli activate proapoptotic BH3-only proteins such as Bid, Bim, and Puma, which inactivate antiapoptotic proteins Bcl-2 and Bcl-xL, and facilitate the formation of Bax and Bak channels on the mitochondrial membrane (Happo et al., 2012; Ren et al., 2010; Shamas-Din et al., 2011). Mitochondrially-localized protein, voltage-dependent anion channel (VDAC) also participates in the outer mitochondrial membrane (OMM) permeabilization (Boya et al., 2001; Keinan et al., 2010; Shimizu et al., 1999). VDAC is expressed as three isoforms VDAC1, VDAC2, and VDAC3. VDAC1 mostly interacts with Bax and participate in channel formation (Boya et al., 2001), whereas, VDAC2 acts as an antiapoptotic protein by sequestering Bak (Chandra et al., 2005; Cheng et al., 2003; Ren et al., 2009). TP53, a well-known tumor suppressor protein, regulates apoptosis by promoting the expression of various proapoptotic proteins such as Puma, Noxa, Fas and Apaf-1 (Chipuk and Green, 2006; Schuler and Green, 2005). TP53 can also directly interact and activate Bax and Bak to permeabilize mitochondria (Chipuk and Green, 2006; Chipuk et al., 2004; Green and Kroemer, 2009; Leu et al., 2004). Caspase-2 has also been associated with the induction of OMM permeabilization and therefore, cytochrome c release and apoptosis (Bouchier-Hayes and Green, 2012; Lassus et al., 2002).

## 3. Endogenous prosurvival factors

Various signaling events orchestrate around mitochondria during apoptotic stimulation. Endogenous prosurvival molecules protect cells in response to apoptotic stimulation induced by exogenous or intrinsic stresses. These prosurvival molecules including antiapoptotic Bcl-2 family members (such as Bcl-2, Mcl-1, and Bcl-xL), serine-threonine kinase AKT (also known as protein kinase B, PKB), Ras/Raf/MEK/ERK pathways, anti-oxidant enzymes such as SOD (superoxide dismutase) and catalase, inhibitors of apoptosis (IAPs), and NF-κB act at multiple sites to attenuate or inhibit apoptosis. Small molecules such as nucleotides, sodium, potassium, calcium, and non-enzymatic antioxidants such as vitamin A, E, and C also function as endogenous prosurvival molecules. Additionally, apocytochrome c, p73, voltage-dependent anion channel 2 (VDAC2), cytochrome c oxidase (COX) subunits have prosurvival functions. Some of these endogenous prosurvival molecules are also known to possess proapoptotic functions. We have broadly classified these endogenous

survival molecules as mitochondrial or postmitochondrial factors depending upon their emulation of prosurvival functions. Prosurvival functions of some endogenous factors are discussed below.

### 3.1. Mitochondrial survival mechanisms

**3.1.1 Energy generating molecules as prosurvival factors—**One of the most important factors for cell survival is the generation of energy in the form of ATP. Mitochondria are considered as powerhouses of cells because most of the energy need is generated in the mitochondrion by the electron transport chain (ETC). Thus mitochondrial integrity is critical for cells to generate needed energy. Various proteins maintain proper functioning of mitochondria during normal or stress conditions. Cytochrome c is one of the key molecules involved in the mitochondrial ETC and is encoded by nuclear genome. Newly synthesized cytochrome c (i.e., apocytochrome c) translocates to mitochondria where a heme moiety is attached. This reaction is catalyzed by cytochrome c heme lyase, and in turns, apocytochrome c becomes holocytochrome c (Mayer et al., 1995; Nicholson et al., 1987), which transfers electron from complex III (cytochrome c reductase) to complex IV (cytochrome c oxidase) of the ETC. Although holocytochrome c participates in the ETC to generate energy for cell survival, persistent stress compromises mitochondrial integrity leading to the release of holocytochrome c from mitochondria, which triggers cell demise by initiating the process of apoptosis (Bossy-Wetzel et al., 1998; Kluck et al., 1997; Liu et al., 1996). How dual role of cytochrome c in balancing survival signaling and apoptosis is regulated remains elusive. But our studies along with others clearly indicate that cytochrome c is upregulated very early during apoptosis to keep cancer and normal cells healthy in response to multiple types of apoptotic inducers such as DNA damaging agents, mitochondrial toxins, intrinsic death stimuli, mitotic spindle inhibitors as well as endoplasmic reticulum stresses (Chandra et al., 2002; Heerdt et al., 1997; Joshi et al., 1999; Sanchez-Alcazar et al., 2000; Sanchez-Alcazar et al., 2001; Waterhouse et al., 2001). In addition to cytochrome c upregulation, cells also upregulate various proteins of ETC such as cytochrome c oxidase subunit I, II and IV (Chandra et al., 2002; Joshi et al., 1999; Sanchez-Alcazar et al., 2000; Sanchez-Alcazar et al., 2001). Some of these proteins are encoded by the mitochondrial genome, suggesting that both mitochondrial and nuclear encoded proteins were upregulated in response to a variety of chemotherapeutics drug or stresses (Chandra et al., 2002; Heerdt et al., 1997; Joshi et al., 1999; Sanchez-Alcazar et al., 2000; Sanchez-Alcazar et al., 2001). The question that still remains unanswered is how mitochondrial and nuclear genome coordinate to transcriptionally upregulate proteins required for energy production by the ETC.

#### 3.1.2 Mitochondrial integrity is critical for cell survival

**ATPase inhibitor factor 1 (IF1):** Mitochondrial oxidative phosphorylation requires multi subunit enzymes, $F_oF_1$-ATP synthase, that reversibly synthesize ATP driven by electrochemical potential ($\Delta\Psi_m$) across inner mitochondrial membrane (Boyer, 1997; Chandra and Singh, 2011; Senior et al., 2002; Yadav and Chandra, 2013). Disruption of $\Delta\Psi_m$ due to damage or mutations in genes encoding mitochondrial respiratory proteins compromises ATP generation. To cope with this situation, $F_oF_1$-ATP synthase acts as proton motive ATPase consuming ATP and translocating protons from the mitochondrial matrix to

maintain $\Delta\Psi_m$ as long as glycolytically generated ATP is available (Jennings et al., 1991; Kagawa et al., 2004). A nuclear encoded protein, the inhibitor factor 1 (IF1) binds with $F_oF_1$-ATP synthase and inhibits its ATPase activity to conserve ATP at the expense of $\Delta\Psi_m$ (Campanella et al., 2008; Gledhill et al., 2007). Overexpression of IF1 protect against ischemic injury, increase in mitochondrial cristae formation, increases $F_oF_1$-ATP synthase activity, whereas IF1 silencing induces autophagy (Campanella et al., 2009; Faccenda et al., 2013a; Faccenda et al., 2013b). Additionally, overexpression of IF1 in human carcinomas inhibits mitochondrial $F_oF_1$-ATP synthase activity causing metabolic shift in cancer cells to Warburg phenotype (Sanchez-Cenizo et al., 2010), promotes activation of NF-*k*B pathway, which leads to cellular proliferation and survival (Formentini et al., 2012). Overexpression of IF1 along with decreased expression of ATP synthase in various types of cancer lead to attenuation of cancer cell apoptosis (Cuezva et al., 2002; Faccenda et al., 2013a; Faccenda et al., 2013b; Lin et al., 2008; Sanchez-Arago et al., 2013). Altogether, IF1 maintains mitochondrial integrity in cancer cells, promotes Warburg phenotype, and supports the idea that IF1 could be an important molecule at the mitochondria to support survival of cancer cells (Campanella et al., 2008; Formentini et al., 2012; Sanchez-Cenizo et al., 2010).

**Antiapoptotic Bcl-2 family proteins:** Bcl-2 and Bcl-xL are considered to be the guardian of the mitochondria membrane integrity. These proteins block the release of proapoptotic proteins, and thereby, inhibit cell death (Brunelle and Letai, 2009; Danial and Korsmeyer, 2004; Kelly and Strasser, 2011; Kuwana and Newmeyer, 2003). Various posttranslational events can inhibit the prosurvival function of these antiapoptotic Bcl-2 family proteins. For example, after deamidation, in which amide group is removed from the two critical asparagine residues, Bcl-xL is no longer able to block the release of proapoptotic proteins, and eventually leads to cell death (Deverman et al., 2002). Surprisingly, deamidation is catalyzed by increase in pH due to upregulation of $Na^+/H^+$ exchanger isoform-1 (HNE-1), which participates in movement of positive ions across mitochondrial membrane (Zhao et al., 2007). This suggests that changes in the pH inside cells can also regulate survival and apoptosis signaling in cancer cells. Additionally, DNA damage-induced deamidation of Bcl-xL is also blocked by oncogenic tyrosine kinase, which then promotes survival of the cells (Weintraub et al., 2004; Zhao et al., 2004). Indeed, Bcl-xL deamidation is suppressed in multiple cancer cell types, which leads to restoration of prosurvival functions of Bcl-xL causing proliferation and survival of cancer cells (Takehara and Takahashi, 2003; Weintraub et al., 2004; Zhao et al., 2008). Since deamidation of Bcl-xL also promotes its degradation, the agents that promote deamidation of Bcl-xL or possibly other prosurvival Bcl-2 family proteins, could enhance apoptosis in cancer cells (Dho et al., 2013).

**AKT/PKB and mitochondria integrity:** Protein kinase B also known as AKT participates in maintenance of mitochondrial integrity (Betz et al., 2013; Dijkers et al., 2002; Gottlob et al., 2001; Marchi et al., 2012; Miyamoto et al., 2008; Roberts et al., 2013) by preventing intracellular acidification, attenuating apoptosis via inositol 1,4,5-trisphosphate receptor (IP3R) phosphorylation, hexokinase (HK) phosphorylation, mitochondrial hyperpolarization, and decline in oxidative phosphorylation. Unlike prosurvival protein Bcl-2, activated AKT requires association of glucose and HK to inhibit cytochrome c release from the mitochondrion (Majewski et al., 2004a; Majewski et al., 2004b). HK shuttles

between cytosolic and mitochondrial compartments and catalyze the conversion of glucose to glucose-6-phosphate, a critical prerequisite step in electron transport chain to generate energy (Gottlob et al., 2001; John et al., 2011; Plas et al., 2001; Rathmell et al., 2003). HK shuttling between cytosol and mitochondria is regulated by its molecular states. For example, cytosolic HK exists as monomer whereas mitochondrial HK (mtHK) forms tetramer on the outer mitochondrial membrane (Beutner et al., 1998; Xie and Wilson, 1990). MtHK associates with OMM through voltage-dependent anion channel-1 (VDAC1), however, it is unclear whether VDAC2 is also involved in this process (Abu-Hamad et al., 2008; Arzoine et al., 2009; Pastorino et al., 2002; Rosano, 2011; Shoshan-Barmatz et al., 2009; Zaid et al., 2005). Since VDAC2 binds and sequesters Bak in performing prosurvival function (Chandra et al., 2005; Cheng et al., 2003; Ren et al., 2009), it is reasonable to assume that mtHK may also associate with VDAC2 to maintain mitochondrial integrity, however further studies are needed to support this notion.

How AKT performs prosurvival function through HK? Various pieces of evidence support that AKT phosphorylates HK and increases HK association with mitochondria (Gottlob et al., 2001; Majewski et al., 2004a; Miyamoto et al., 2008; Roberts et al., 2013). MtHK inhibits Bax translocation to and its oligomerization on mitochondria. MtHK also inhibits Bak oligomerization. Lack of Bax and/or Bak activation and their oligomerization lead to the inhibition of mitochondrial permeabilization and cytochrome c release, causing blockage of apoptosis (Majewski et al., 2004b; Verma et al., 2013). It is also known that HK dissociation with mitochondria can promote release of cytochrome c in the absence of Bax and Bak, and this process is not inhibited by overexpression of Bcl-2, suggesting that association of HK with mitochondria may function parallel to Bcl-2 function in regulating cell survival (Majewski et al., 2004a). Since HK antagonizes proapoptotic proteins as silencing of HK induces Bax oligomerization (Schindler and Foley, 2013), stabilization of HK at mitochondria via cyclophilin D and VDAC suppresses apoptosis in cancer cells (Krasnov et al., 2013; Machida et al., 2006).

AKT is a master regulator of survival/apoptosis and targets various proteins including HK. For example, AKT phosphorylates Bad, thus inhibits proapoptotic activity of Bad (Datta et al., 2002). AKT directly phosphorylates inhibitor of κB kinase (IKKβ), which allows translocation of NF-κB to the nucleus and upregulation of various prosurvival molecules (Datta et al., 2002). Caspase-9 is one of the main initiator caspases in apoptosis signaling and is phosphorylated by AKT leading to the inhibition of caspase-9 cleavage and apoptosis (Cardone et al., 1998). AKT also mediates phosphorylation of forkhead box O3a (FOXO3a), which then translocates out from the mitochondria and promote survival by inhibiting transcription of proapoptotic proteins (Brunet et al., 1999). In addition, AKT activates endothelial NO synthase (eNOS) leading to the increase levels of NO, which participates in survival mechanisms (Fulton et al., 1999; Gao et al., 2002). Together, AKT acts at multiple levels to protect mitochondrial integrity and functions causing inhibition of apoptosis, thus inhibiting of AKT function may provide avenues to cancer prevention and therapy.

**Voltage-dependent anion channel (VDAC):** VDAC is considered an endogenous survival protein and is localized as integral protein on outer mitochondrial membrane. VDAC is generally expressed in three isoforms with VDAC1 and VDAC2 being most prevalent

(Blachly-Dyson et al., 1994; Blachly-Dyson et al., 1993). VDAC1 in open state allows free shuttling of ATP and ADP. Mitochondrial generated ATP is transported to the cytosol for the exchange with ADP, which is utilized in the oxidative phosphoryalation to generate ATP (Blachly-Dyson et al., 1994; Blachly-Dyson et al., 1993). Thus VDAC1 participates in electron transport chain to generate energy and support survival. On the other hand, VDAC2 perform prosurvival role by sequestering Bak and inhibiting proapoptotic function of Bak (Cheng et al., 2003; Ren et al., 2009). How VDAC2 and Bak interaction is maintained and sustained is not clearly known but our findings clearly suggest that in the presence of Bax, VDAC2 interacts with Bak causing inhibition of its proapoptotic function. Although VDAC2 does not interact with Bax but the presence of Bax seems to be important for VDAC2-Bak association, because in the absence of Bax, interaction between Bak and VDAC2 is lost either with or without apoptotic stimulation (Chandra et al., 2005). Absence of Bak-VDAC2 interactions, and thus lack of inhibitory effects of VDAC2 may underlie the critical role of Bak in dictating the apoptotic sensitivity of Bax-deficient cells (Chandra et al., 2005). Above discussion suggests a prosurvival role for VDAC2, another study shows that in the absence of Bak, VDAC2 play an important role in Bax activation during apoptosis (Yamagata et al., 2009). It is also suggested that VDAC2-mediated recruitment of Bak to the mitochondria plays a role in truncated Bid-induced mitochondrial apoptosis (Roy et al., 2009). In the absence of apoptotic stimuli, inactive Bak exists as a large protein complex involving VDAC2 (Lazarou et al., 2010; Ma et al., 2013), thus in order to induce robust Bak activation, dissociation of VDAC2 from the Bak-VDAC2 complex will be a better approach to induce efficient apoptosis in cancer cells. Indeed, Bcl-$x_S$-mediated disruption of Bak-VDAC2 interaction induces efficient apoptosis in melanoma cells (Plotz et al., 2012).

**3.1.3 Reactive oxygen species dismutation and cell survival—**Although activation of mitochondrial function is critical for energy generation, increased electron transport chain activity is also associated with generation of reactive oxygen species (ROS). It is estimated that cells produce enormous amount of ROS everyday, and there is tremendous need to attenuate ROS in cells (Handy and Loscalzo, 2012; Mailloux et al., 2013; Sena and Chandel, 2012; Trachootham et al., 2008). ROS cause damage to mitochondrial and nuclear genome, which leads to direct and indirect changes in the cell microenvironment triggering tumorigenesis (Chandra and Singh, 2011; Penta et al., 2001; Wallace, 2005; Yadav and Chandra, 2013). Cells also contain various endogenous molecules such as glutathione to attenuate the detrimental effects of ROS, and therefore, protect DNA from oxidative damage (Beckman and Ames, 1997; Handy and Loscalzo, 2012; Mailloux et al., 2013; Nakamura and Swenberg, 1999; Sena and Chandel, 2012; Trachootham et al., 2008). Cells have also evolved multiple mechanisms including upregulation of antioxidants and/or oxidative attenuator mitochondrial MnSOD and Cu/ZnSOD to cope with the stresses (Mailloux et al., 2013; Valko et al., 2006).

How is the level of Cu/ZnSOD and MnSOD upregulated to attenuate detrimental effect of ROS? We have previously demonstrated that following apoptotic stimulation, these antioxidant proteins are induced at the transcriptional level, thus implicating the involvement of transcription factors. We observed an increased expression of transcription

factor FOXO3a, which regulates MnSOD and perhaps Cu/ZnSOD (Liu et al., 2005). Although signals that transcriptionally activate FOXO3a and potentially other transcription factors are not well defined, but ROS may play critical role to activate transcription factors (Dansen, 2011; de Keizer et al., 2011; Liu et al., 2005; Ponugoti et al., 2012; Storz, 2011; Vurusaner et al., 2012). FOXO3a and other transcription factors including NF-κB, and p53 are regulated by ROS and these transcription factors also respond to oxidative stress (Finkel and Holbrook, 2000; Hoogeboom et al., 2008; Nemoto and Finkel, 2002; Zhang et al., 2011). For example, increased expression of FOXO3a confers resistance to oxidative stress, and FOXO transcription factors promote cell survival in response to oxidative stress (Kops et al., 2002; Li et al., 2012; Oh et al., 2011; Sengupta et al., 2011).

In multiple cancer cell types, we observed that apoptotic stimuli trigger early mitochondrial activation, leading to rapid generation of ROS causing activation of master transcription factor such as FOXO3a, which, in turn, activate multiple target genes, with either proapoptotic or anti-apoptotic functions (Liu et al., 2005). The levels of ROS production is also important in determining the fate of cells because cancer cells produce higher amount of ROS in order to support their survival and proliferation (Sena and Chandel, 2012; Wang and Yi, 2008; Wangpaichitr et al., 2012). Thus activation of antioxidant system may lead to suppression of death-causing levels of ROS leading to survival of cancer cells. It is also critical to note that strengths and timings of ROS-dependent or -independent pro-survival and pro-death signals may determine the ultimate fate of cancer cells during stress (Handy and Loscalzo, 2012; Liu et al., 2005; Sena and Chandel, 2012; Trachootham et al., 2008).

### 3.2 Post mitochondrial survival events

Holocytochrome c (i.e., heme-containing mitochondrial cytochrome c) released from the mitochondrion initiates the apoptosome-mediated caspase activation, and is generally believed that it represents the point of no return. Evidence reported in the last few years clearly suggest that apoptotic signaling can still be curtailed even after cytochrome c release from the mitochondrion. Some of the well-known molecules such as heat shock proteins (HSPs) inhibit the apoptosome formation while IAPs bind with active caspases to inhibit the caspase cascade. Although Hsp70 binds with CARD domain of Apaf-1 and inhibits recruitment of caspase-9 and thus its activation (Beere et al., 2000; Saleh et al., 2000), later findings suggest that Hsp70 confers protective effect by inhibiting cytochrome c release from mitochondria not at the level of apoptosome formation (Clemons et al., 2005; Stankiewicz et al., 2005; Steel et al., 2004). It is also known that Hsp70 promotes cell survival by antagonizing apoptosis-inducing factor (AIF) to inhibit caspase-independent apoptosis (Ravagnan et al., 2001), and by inhibiting lysosomal membrane permeabilization (Nylandsted et al., 2004). Similarly, Hsp90 inhibits apoptosome formation and caspase activation (Kurokawa et al., 2008; Pandey et al., 2000) whereas Hsp27 inhibits caspase activation by sequestering caspase-3 and cytochrome c (Concannon et al., 2001; Garrido et al., 1999; Samali et al., 2001).

Various small molecules, notably nucleotides, play a critical role in apoptosome formation and caspase activation. Elegant studies demonstrate that micromolar concentration of nucleotides such as dATP or ATP initiate Apaf-1 oligomerization (Cain et al., 2000; Jiang

and Wang, 2000; Zou et al., 1999). Mammalian cells contain intracellular ATP and nucleotide pool at high mM (Craig and Wallace, 1991; Mesner et al., 1999), and we demonstrated that physiological levels of nucleotides (i.e., in mM levels) inhibits cytochrome c-Apaf-1 interaction by binding with cytochrome c, and therefore, inhibits the most upstream events in apoptosome assembly that is at the levels of cytochrome c-Apaf-1 interaction (Chandra et al., 2006). Nucleotides such as ADP bind with Apaf-1 and promote conformational changes leading to its inactivation (Riedl et al., 2005). ATP also binds with procaspase-9 and inhibits caspase-9 processing (Chereau et al., 2005). These evidences clearly suggest that nucleotides act on various target molecules to inhibit apoptosome assembly and function as critical prosurvival molecules. On the other hand, these evidences also indicate that apoptosome formation/function is a complicated process and needs further investigation. In this direction, few recent evidence on nucleotide binding and apoptosome structure clarify that under normal circumstances, nucleotides such as dATP or ATP or ADP is prebound with Apaf-1 and causes its inactivation (Kim et al., 2005; Reubold et al., 2009, 2011; Riedl et al., 2005; Yuan and Akey, 2013; Yuan et al., 2013; Yuan et al., 2011). ATP binding to caspase-9 also inhibits its activation (Chereau et al., 2005). During apoptosis, the levels of nucleotides decrease significantly to allow cytochrome c-Apaf-1 interaction, which initiate nucleotide exchange by nucleotide exchange factor consisting of PHAP-1, CAS and Hsp70 (Chandra et al., 2006; Kim et al., 2008). The hydrolysis of bound nucleotide during nucleotide exchange triggers the formation of apoptosome and activate caspases (Kim et al., 2008), however, later studies suggest that ATP hydrolysis may not be required for apoptosome formation (Reubold et al., 2009). It is not clear how prosurvival and proapoptotic function of Hsp70 are regulated but further studies are required to understand/ resolve the dual function of Hsp70. The formation and function of apoptosome is also regulated by t-RNAs, which bind cytochrome c and inhibits cytochrome c-Apaf-1 interaction leading to the inhibition of apoptosome formation and function (Mei et al., 2010). Additionally, mM levels of calcium also seems to inhibit apoptosome assembly by binding to Apaf-1 (Bao et al., 2007).

Various other proteins such as oncoprotein prothymosine-αProT(Jiang et al., 2003), silencing of acetylcholineesterase (Park et al., 2004), Apaf-1 interacting protein (Cao et al., 2004), and protein kinase A (Martin et al., 2005) negatively regulate caspase-9 activation by inhibiting apoptosome formation. Likewise, certain compounds/salts also inhibit apoptosome formation and caspase activation such as diarylurea compounds (Lademann et al., 2003), Taurine (Takatani et al., 2004), and physiological concentrations of $K^+$ and $Na^+$ inhibit caspase activation and apoptosome formation (Cain et al., 2001; Thompson et al., 2001). Similarly, acidic pH (Brooks et al., 2005), NO or NO derived species interfere with caspase-9/Apaf-1 interactions and prevent correct assembly of the apoptosome (Zech et al., 2003). In spite of various reports, the mechanistic aspect of regulation of apoptosome formation and caspase activation in *in-vivo/in-vitro* systems triggered by cytochrome c is not clearly understood. Importantly, apocytochrome c i.e., freshly synthesized cytochrome c that does not contain heme-moiety also interacts with apaf-1 and inhibits apoptosome assembly (Martin et al., 2004). These studies clearly suggest that apocytochrome c functions as prosurvival molecule, while holocytochrome c serves as key survival molecules as a part of

electron transport chain. Only heme-containing mitochondrial cytochrome c when released in the cytosol initiates the caspase cascade and subsequently apoptotic cell death.

Since the Apaf-1 apoptosome is a key complex triggering caspase-dependent apoptosis (Bratton and Salvesen, 2010; Reubold and Eschenburg, 2012; Yuan and Akey, 2013), proper functioning of the apoptosome is critical for efficient cancer therapy. Multiple types of cancer harbor apoptosome dysfunction causing inhibition of cancer cell apoptosis and may be associated with the development of resistance during cancer therapy (Corvaro et al., 2007; Fadeel et al., 2008; Hajra and Liu, 2004; Ledgerwood and Morison, 2009; Liu et al., 2002; Schafer and Kornbluth, 2006; Yang et al., 2003). In this direction, multiple small molecules targeting apoptosome have been discovered, which may restore apoptosome function and enhance apoptotic cell death in cancer (Qi et al., 2010; Rodina et al., 2007; Tan et al., 2011; Yang et al., 2003).

## 4. Conclusions and future perspectives

Based on available evidence, we conclude that various prosurvival signaling converge on mitochondria to promote survival of cancer cells. Findings from the last few years further demonstrate that some of the key apoptotic proteins also possess non-apoptotic and/or prosurvival functions. For example, a key proapoptotic BH3-only protein, Bim (Gogada et al., 2013), NOXA (Liu et al., 2011; Ploner et al., 2008), Apaf-1 (Zermati et al., 2007), FADD (Pellegrini et al., 2005), and caspases (Schwerk and Schulze-Osthoff, 2003) show prosurvival or non-apoptotic functions. In addition, prosurvival molecules could also have proapoptotic functions. For example, we and others have identified that prosurvival protein XIAP could also participate in regulation of cytochrome c release (Gogada et al., 2011; Owens et al., 2010). Therefore, in order to induce efficient apoptosis, these prosurvival machinery need to be deactivated as well as proapoptotic function of prosurvival molecules needs to be harnessed. Although significant development has been made towards targeting mitochondria for cancer prevention and therapy, these strategies do not address all defects associated with survival of cancer cells. Future studies on: enhancing the release of cytochrome c and other proapoptotic proteins may allow the formation of functional apoptosome; and screening of small molecules that can restore apoptosome function would lead to efficient apoptosome-mediated caspase activation, and thus apoptosis.

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## Abbreviations

| | |
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| **AKT/PKB** | protein kinase B |
| **Apaf-1** | apoptotic protease activating factor 1 |
| **ERK** | extracellular signal-regulated kinase |

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| **ETC** | electron transport chain |
| **FADD** | Fas-associated death domain |
| **FOXO3a** | forkhead-box protein O3a |
| **HK** | hexokinase |
| **HNE-1** | $Na^+/H^+$ exchanger isoform-1 |
| **HSPs** | heat shock proteins |
| **IAPs** | inhibitor of apoptosis proteins |
| **IF1** | inhibitor factor 1 |
| **IKK** | I-kappa-B kinase |
| **MAPK** | mitogen-activated protein kinase |
| **OMM** | outer mitochondrial membrane |
| **ROS** | reactive oxygen species |
| **SIRT-1** | sirtuin 1 |
| **SOD** | superoxide dismutase |
| **VDAC** | voltage-dependent anion channel |
| **$\Delta\Psi_m$** | electrochemical potential |
| **Smac/Diablo** | second mitochondrial-derived activator of caspase/direct inhibitor of apoptosis protein-binding protein with low pI |

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## Highlights

- Mitochondrion functions as a key-signaling center for survival and death of cancer cells.
- Survival signaling molecules can operate at pre-mitochondrial, mitochondrial and post-mitochondrial levels.
- Proapoptotic molecules possess non-apoptotic and/or prosurvival functions