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REVIEW ARTICLE

Oxidative stress: the mitochondria-dependent and mitochondria-independent pathways of apoptosis

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Abstract Oxidative stress basically defines a condition in which prooxidant–antioxidant balance in the cell is disturbed; cellular biomolecules undergo severe oxidative damage, ultimately compromising cells viability. In recent years, a number of studies have shown that oxidative stress could cause cellular apoptosis via both the mitochondria-dependent and mitochondria-independent pathways. Since these pathways are directly related to the survival or death of various cell types in normal as well as pathophysiological situations, a clear picture of these pathways for various active molecules in their biological functions would help designing novel therapeutic strategy. This review highlights the basic mechanisms of ROS production and their sites of formation; detail mechanism of both mitochondria-dependent and mitochondria-independent pathways of apoptosis as well as their regulation by ROS. Emphasis has been given on the redox-sensitive ASK1 signalosome and its downstream JNK pathway. This review also describes the involvement of oxidative stress under various environmental toxin- and drug-induced organ pathophysiology and diabetes-mediated apoptosis. We believe that this review would provide useful information about the most recent progress in understanding the mechanism of oxidative stress–mediated regulation of apoptotic pathways. It will also help to figure out the complex cross-talks between these pathways and their modulations by oxidative stress. The literature will also shed a light on the blind alleys of this field to be explored. Finally, readers would know about the ROS-regulated and apoptosis-mediated organ pathophysiology which might help to find their probable remedies in future.

Keywords Oxidative stress · Apoptosis · Mitochondria-dependent pathway · Mitochondria-independent pathway · ASK1-JNK signaling · Pathophysiology

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Introduction

We know that most of the living organisms need oxygen for their survival (Farrugia and Balzan 2012). Oxygen has the tendency to create reactive oxygen species (ROS) such as the hydroxyl radical (·OH) and the superoxide radical ($O_2{\cdot}^-$), etc. (Farrugia and Balzan 2012) even at the steady-state situation. Leakage of electron during the electron transport to the ultimate electron acceptor leads their binding to oxygen (O_2) and is considered to be the main source of ROS (Fig. 1). Numerous agents and factors, for example, heavy metals (Bhattacharyya et al. 2012; Pal et al. 2011, 2012, 2013; Das et al. 2009a, b), anticancer and other drugs (Das et al. 2011, 2012a, b, c; Pal et al. 2012; Ghosh et al. 2010a, b, c, d, 2011a, b), diabetes (Manna et al. 2009a, b; 2010a, b; Bhattacharya et al. 2013a, b; Das et al. 2012c), ultraviolet (UV) irradiation, air pollutants, xenobiotics, herbicides, and other exogenous factors can induce significant generation of ROS (Sarkar and Sil 2010; Halliwell and Cross 1994; Gille and Sigler 1995; Ghosh et al. 2012). In physiological state, a balance exists between the production of ROS and their neutralization in the system and no oxidative stress usually occurs (Turrens and Boveris 1980). Oxidative stress condition develops when the balance gets disturbed and an inequity among prooxidant and antioxidant occurs in which the level of

prooxidant increases (Farrugia and Balzan 2012). Oxidative stress generally imparts a condition in which vital cellular ingredients undergo severe oxidative damage, ultimately compromising cell viability (Sies 1991; Halliwell and Cross 1994). Actually, the ROS which are accumulated during oxidative stress are very transient species owing to their high reactivity, which gradually leads to impose oxidative damage on indispensable biomolecules such as proteins (Cabiscol et al. 2000), lipids (Bilinski et al. 1989), and nucleic acids (Yakes and VanHouten 1997). ROS are of three major types, namely hydrogen peroxide (H_2O_2), ·OH, and $O_2{\cdot}^-$ (Matés et al. 2012). H_2O_2 in the cell is formed directly by the action of oxidase enzyme or by the dismutation of $O_2{\cdot}^-$, while the constitutive presence of $O_2{\cdot}^-$ in cells arises due to the leakage from the mitochondrial respiratory chain. The ·OH, being a tremendously active reactive species, can modify DNA bases and also cause strand breaks, which ultimately results in DNA damage (Matés et al. 2010; Matés et al. 2012). Organisms, therefore, have to develop a suitable antioxidant defense system for protecting their cells from oxygen's noxious effect. To combat with oxidative stress, cells have their own antioxidant machineries consisting of several Phase II detoxification enzymes such as three isoforms of superoxide dismutases (SOD1, SOD2, SOD3), glutathione peroxidases (GPXs), catalase (CAT), glutathione S-transferase (GST), glutathione reductase (GR), peroxiredoxins (Prxs), glutaredoxin, two thioredoxin isoforms (TRX1 and TRX2) (Masutani and Yodoi 2002) as well as nonenzyme glutathione (GSH) and glutathione disulfide (GSSG). SOD usually scavenges $O_2{\cdot}^-$ and converts it into O_2 and H_2O_2; CAT, on the other hand, converts H_2O_2 into H_2O and O_2. GR catalyzes the conversion of GSH from GSSG, and GST plays a major role in radical-scavenging reaction of GSH. GPx helps consumption of H_2O_2 in combination with GSH.

The literature suggests that oxidative damage induced by ROS and subsequent cell death are associated with several human diseases such as diabetes (Das et al. 2012c; Das and Sil 2012; Rashid et al. 2012; Rashid et al. 2013; Manna and Sil 2012a, b), and neurodegenerative diseases such as Parkinson's disease (Hirsch 1993), Alzheimer's disease (Behl 1999) and amyotrophic lateral sclerosis (ALS) (Andrus et al. 1998). Besides, ROS have also been shown to play a key role in the progress of cancer (Ames et al. 1995; Farrugia and Balzan 2012) and in the aging process of humans (Orr and Sohal 1994). Moreover, ROS formation and buildup has long been found to play a vital role in mediating programmed cell death (PCD) (apoptosis or even necrosis) at a moderately high concentration, among different cell types (Pierce et al. 1991).

In this review, the apoptosis and its relationship with oxidative stress is of our prime importance. Recently, another important message has been conveyed to the researchers that ROS at a concentration below a specific threshold value could participate in cell signaling (Rhee 2006; Valko et al. 2007). However in this review, we will restrict our focus on the harmful effects of ROS.

Apoptosis and ROS

Apoptosis: an outline

The apoptosis is a type of cell suicide (Kam and Ferch 2000) regulated by a series of complex signaling pathways. It plays an important role in tissue homeostasis and embryonic development in all organisms (Hotchkiss et al. 2009). The term apoptosis was introduced by Kerr in the year 1971 (Zeiss 2003). But the morphological features of apoptosis were detected by Flemming in the year of 1885. Cells enter apoptosis upon intracellular damage and certain physiological cues. This is executed by specific cysteine proteases and caspases, for example caspase-2, -3, -6, -7, -8, -9, and -10 (Wyllie 2010). Based on the sequence of activation during apoptosis and structures, caspases can be further divided into two groups (Los et al. 1999), initiator caspases (caspase-2, -8, -9, and -10) and effector caspases (caspase-3, -6, and -7). Upon receiving death signals, initiator caspases activate by dimerization and initiate apoptotic signaling cascade. Downstream, these cleave effector caspases at internal Asp residues, thus converting them into their active forms by forming active hetero tetramers (Boatright and Salvesen 2003).

Cells undergoing apoptosis show several characteristic morphological and molecular changes (Strasser et al. 2000). Chromatin condensation, membrane surface blebbing, externalization of phosphatidylserine, oligonucleosomal DNA fragmentation and, ultimately, the breakdown of the cell into a series of membrane-bound fragments (called apoptotic bodies) are some of the distinct morphological and biochemical features (D'Emilio et al. 2010; Matés et al. 2012; Kerr et al. 1972) associated with apoptosis. In majority of the tissues, apoptotic bodies are phagocytosed by neighboring phagocytic cells. The phosphatidylserine acts as an "eat-me" signal which recruits macrophages to engulf the apoptotic bodies, and in that way, inflammatory response and damages to neighboring cells are prevented (Circu et al. 2012). Controlled autodigestion of the cell is also a characteristic of apoptosis (Tormo et al. 2009; Matés et al. 2012).

Molecular changes include a controlled set of target proteins that are cleaved selectively for the apoptosis-related morphological and biochemical features. Caspase-activated DNase (CAD) present in living cells binds to its inhibitor (inhibitor of CAD [ICAD]). This CAD in its

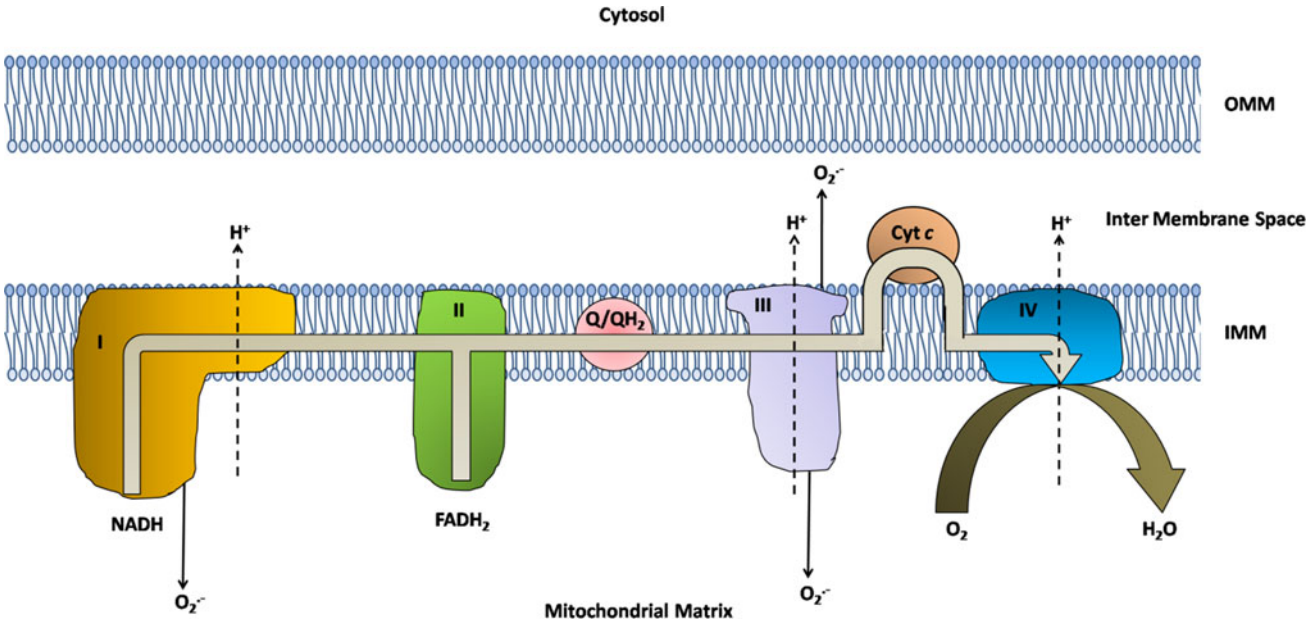

Fig. 1 Reactive oxygen species formation sites in mitochondrial respiratory chain (I, II, III, and IV represent respiratory chain complexes I, II, III, and IV of mitochondrial respiratory chain, respectively; [*arrows*] represents the formation of superoxide radical)

active state is responsible for inter nucleosomal genomic DNA fragmentation (Wyllie 1980), a hallmark phenomenon of apoptosis. Caspase-3 and caspase-7 cleave this ICAD, resulting in the release of active CAD (Liu et al. 1997). Caspase proteolysis of further substrates is responsible for the other morphological changes related to apoptosis. Nuclear shrinkage and fragmentation occur through the cleavage of Lamins, the scaffold proteins of the nuclear envelope by effector caspases. Gelsolin, an actin depolymerizing enzyme, gets activated by caspases, resulting in the plasma membrane blebbing (Kothakota et al. 1997). Cleavage of cytoskeleton proteins such as fodrin (Kothakota et al. 1997) results in the loss of cell shape. Apoptotic cells are detached from the basement membrane and their neighbors by the cleavage of the focal adhesion complex's components. Phosphatidylserine (PS) externalization is another caspase-dependent process. In healthy cells, PS is localized actively on the inner leaflet of the plasma membrane and can be recognized by phagocytes as a signal for engulfment (Fadok et al. 1992). Its asymmetry of distribution has been reported to be lost in apoptotic cells. Although this phenomenon is caspase dependent, the exact mechanism has not been totally elucidated yet. It has further been speculated that a combined effect of the activation of a lipid scramblase and downregulation of a phospholipid translocase activity, observed in apoptotic lymphocytes, might contribute to PS exposure (Moreira and Barcinski 2004). PAK2, a member of the p21-activated kinase family and obtained by the caspase-mediated cleavage, participates in the formation of apoptotic bodies (Rudel and Bokoch 1997).

ROS and its generation

Free radicals are molecular fragments or molecules possessing one or more than one unpaired electrons in atomic or molecular orbitals (Halliwell and Gutteridge 2007). Free radicals become highly reactive due to this unpaired electron(s) (Valko et al. 2007). Within living systems, oxygen-derived free radicals are the most important class of radical species (Miller et al. 1990). Free radicals derived from oxygen (O_2), for instance superoxide anion ($O_2{\cdot}^-$) and hydroxyl (·OH) radicals, generally cumulatively called reactive oxygen species (ROS), which also includes H_2O_2 like O_2-derived nonradical species (Halliwell and Cross 1994; Matés et al. 2012; Farrugia and Balzan 2012). Oxygen itself in the molecular form (O_2) possesses a unique electronic configuration and could act as a radical. By accepting one electron, the molecular oxygen forms the superoxide anion radical ($O_2{\cdot}^-$), a relatively stable intermediate (Orrenius et al. 2007; Miller et al. 1990). Superoxide anion radical in the body can arise either from metabolic processes or following activation of oxygen by physical irradiation. This superoxide anion is considered as the primary ROS (Valko et al. 2007) and interacts with other molecules usually through enzyme- or metal-catalyzed processes or directly and produces secondary ROS (Valko et al. 2005). For instance, H_2O_2 is produced from superoxide anions by the dismutation reaction catalyzed by

SOD. Similarly, Haber–Weiss reaction or Fenton reaction produces highly reactive and toxic hydroxyl radical (·OH), through interaction between H_2O_2 and $O_2{\cdot}^-$ or H_2O_2 cleavage by Fe^{2+} (or Cu^{2+}), respectively (Circu and Aw 2010; Orrenius et al. 2007). In addition, to the respiratory chain, an outer mitochondrial membrane–resident flavoprotein, monoamine oxidase (MAO), also acts as another important source of ROS, specifically H_2O_2 (Orrenius et al. 2007; Andreyev et al. 2005). Additionally, a mitochondrial intermembrane space enzyme p66Shc (Migliaccio et al. 2006), matrix pH (Lambert and Brand 2004), and altered mitochondrial membrane potential (Korshunov et al. 1997) are also proven as few other important mitochondrial ROS sources (Circu and Aw 2010). Apart from superoxide anion ($O_2{\cdot}^-$), alkoxyl (RO·), hydroxyl (·OH), and hydrogen peroxide (H_2O_2), another type of reactive radicals resulting from oxygen in the living systems are peroxyl radicals (ROO·). Hydroperoxyl radical or perhydroxyl radical (HOO·) is the simplest peroxyl radical, which is basically the protonated form of superoxide ($O_2{\cdot}^-$). In a typical cell, only 0.3% of any superoxide in the cytosol is present as hydroperoxyl radical (De Grey 2002). Fatty acid hydroperoxide (LOOH)-independent and LOOH-dependent pathways are two parallel pathways in which hydroperoxyl radical initiates fatty acid peroxidation (Aikens and Dix 1991). The in vivo HOO· initiated and LOOH-dependent pathway of fatty acid peroxidation might have relevance to the mechanisms of lipid peroxidation.

Role of mitochondria in ROS formation

It is a well proven fact that mitochondria of living cells play a main role in the formation of free radicals (Circu and Aw 2010). Pyruvate is generated in the cell upon entry of glucose into the cell (which in turn promotes glycolysis), and this pyruvate is utilized in TCA cycle (Supale et al. 2012). Electrons get transferred from TCA cycle intermediates to the electron transport chain via NADH and $FADH_2$ (Fig. 1). TCA cycle occurs in mitochondrial matrix. In the cycle, NADH is formed by three dehydrogenases, namely isocitrate dehydrogenase, α-ketoglutarate dehydrogenase complex and malate dehydrogenase. $FADH_2$ is formed by the succinate dehydrogenase (Supale et al. 2012). The respiratory chain made up of five complexes containing subunits, which are encoded simultaneously in the mitochondrial and nuclear genomes (Wallace 1999). When electron transfer through respiratory chain occurs, proton from the mitochondrial matrix gets exported across the inner membrane, which in turn establishes strong mitochondrial membrane potential, positive on the outside. In inner mitochondrial membrane, complex I is the sole electron acceptor from NADH (Antinozzi et al. 2002), whereas electrons are transferred from $FADH_2$ to ubiquinone (Q) by complex II (succinate dehydrogenase) (Fig. 1) (Supale et al. 2012). On the other hand, water production and consumption of oxygen occur at complex IV (Supale et al. 2012) (Fig. 1). This is coupled to the ATP synthase (complex V) and promotes mitochondrial ATP formation from ADP and inorganic phosphate. The ATP, synthesized this way, is translocated to the cytosol. Adenine nucleotide translocator does this job in exchange for ADP (Supale et al. 2012). Hence, this electron transport chain of mitochondria is considered as the most important source of ATP in the mammalian cells and thus indispensable for living organism. Nevertheless, a small number of electrons escape to oxygen impulsively during the process of energy transduction. Thus, the oxygen free radical superoxide is generated (Fig. 1) (Kovacic et al. 2005; Supale et al. 2012). Actually, ROS is a by-product of normal mitochondrial respiration (Chance et al. 1979). Instead of reducing oxygen to water, 1–3% of all electrons in the electron transport chain of mitochondria escape to generate superoxide radicals (Orrenius et al. 2007; Valko et al. 2007). Several redox centers of the mitochondrial electron transport chain leak electrons to molecular oxygen and thus play the chief role of superoxide production (Andreyev et al. 2005). However, growing evidence suggests that most of the superoxide radicals generated by intact mammalian mitochondria (at least in vitro) are produced by complex I (Orrenius et al. 2007). Recently, it is established that complex I–dependent superoxide radical is released solely into the matrix by matrix-protruding iron–sulfur clusters of the hydrophilic arm (Fig. 1) (of complex I) (Orrenius et al. 2007; Brand et al. 2004). There is no measurable level of leaking from intact mitochondria (Muller et al. 2004). In the presence of the substrate of complex II, succinate, production of $O_2{\cdot}^-$ by complex I was found to be distinctly stimulated (Liu et al. 2002). This finding indicates the involvement of a reverse electron flow in this process (Liu et al. 2002). However, complex III is also considered as a significant site of $O_2{\cdot}^-$ production (Nishikawa et al. 2000) besides complex I (Turrens and Boveris 1980). In contrast with complex I, complex II–produced $O_2{}^-$ appears at both sides of the inner membrane (Fig. 1) (Muller et al. 2004). Ubiquinone is also considered as a major contributor to $O_2{}^-$ formation by complex III (Turrens et al. 1985). This ubiquinone as a part of mitochondrial respiratory chain connects Complexes I and II with III (Orrenius et al. 2007). In the process of electron transfer between these complexes, ubiquinone is reduced to intermediate unstable semiquinone, which is responsible for $O_2{\cdot}^-$ formation. Also, experimental evidence suggests that center "*o*" within complex III is responsible for $O_2{\cdot}^-$ generation (Orrenius et al. 2007). Till date, in addition to the respiratory chain complex, approximately 10 potential mitochondrial ROS-generating systems are identified as

source of mitochondrial $O_2{\cdot}^-$ and H_2O_2 (Andreyev et al. 2005). Among these, two are considered as major sources (Circu and Aw 2010). These two systems are Krebs cycle enzyme complexes: α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase (Andreyev et al. 2005). Conspicuously, mitochondrial α-KGDH produces high amount of H_2O_2 linked to increased amount of nicotinamide adenine dinucleotide, and it is obvious that this elevated oxidant burden increases additional ROS production from mitochondrial complex I, which in turn imparts elevated amount of oxidative stress to cells that promote cell death (Tretter and Adam-Vizi 2004).

Augmented free radical generation in mitochondria has been regarded as a result of two important phenomenons. The first one occurs when ATP production exceeds energy demand of cell, and in this very situation, the electron transport gets diminished. On the other hand, impairment and uncoupling (Khawaja et al. 2008; Hagenbuchner et al. 2012) of specific respiratory chain complexes under some stress conditions also favor the formation of free radicals (Ambrosio et al. 1993; Turrens and Boveris 1980). In this regard, members of FOXO subfamily transcription factors play an important role through Bim-mediated pathway (Hagenbuchner et al. 2012). Later, we will discuss this in detail. However, acute oxidative stress causes partial loss of electron transport chain components particularly in complex IV, and that could induce rapid downregulation in early mitochondrial events although expression of antioxidant enzymes in this situation is upregulated (Supale et al. 2012). This recent report is in line with the concept of mitochondrial hormesis (or mitohormesis), which states that ROS signaling promotes enhanced cellular defenses (Ristow and Zarse 2010).

ROS-mediated damage to mitochondria

As mitochondria are the major generator of ROS, they often become the target of elevated ROS exposure with deadly consequences, such as oxidative damage of mitochondrial DNA (mtDNA) (Circu et al. 2009; Rachek et al. 2009; Orrenius et al. 2007). The hydroxide ion in its neutral form, the hydroxyl radical (·OH), with a very short in vivo half-life of approximately 10–9 s, has elevated reactivity, which makes it a very hazardous radical (Pastor et al. 2000). Thus in vivo, its reaction site and site of formation are close. Elevated levels of $O_2{\cdot}^-$ and HO· associated with mtDNA damage are being considered to play a major role in cell apoptosis (Ricci et al. 2008), though the mechanism whereby mtDNA damage mediates apoptotic signaling is not properly understood (Circu and Aw 2010). In addition, oxidation and inactivation of iron–sulfur (Fe–S) proteins (e.g., aconitases) and the associated release of iron is another important mechanism of $O_2{\cdot}^-$-induced toxicity (Orrenius et al. 2007) in mitochondria. This aconitase inactivation is injurious to cells. Firstly, Fe^{2+} and H_2O_2 get released by the formation of an inactive $[3Fe\text{-}4S]^+$ cluster (Orrenius et al. 2007). This event produces equimolar amounts of H_2O_2 per mole of $O_2{\cdot}^-$ (Liochev and Fridovich 1999), which in turn causes elevated amount of oxidative burden to cells. H_2O_2 in turn directly affects the mitochondrial membrane lipid, modifying their structural and functional properties (Khawaja et al. 2008). Moreover, the released Fe^{2+} and H_2O_2 are the ingredients of the Fenton ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\cdot}OH + OH^-$) and Haber–Weiss ($O_2{\cdot}^- + H_2O_2 \rightarrow O_2 + {\cdot}OH + OH^-$) reactions. Hence, it can generate noxious hydroxyl radical, which in turn oxidizes DNA, mitochondrial proteins, and lipids. So, amplification of $O_2{\cdot}^-$-initiated oxidative damage occurs by this way (Orrenius et al. 2007).

Other cellular sources of ROS

Now coming to the "peroxisomes" which can also be considered as the major sites of oxygen consumption in the cell and are known to produce H_2O_2, but not $O_2{\cdot}^-$, under physiological conditions (Valko et al. 2004), they participate in several metabolic functions that use oxygen, leading to the formation of H_2O_2, which in turn is utilized for the oxidation of a variety of molecules. Catalase present in the organelle, on the other hand, decomposes H_2O_2 to H_2O and O_2 and thus prevents its accumulation and resulting toxic effect. The peroxisome, therefore, has to maintain a delicate balance with respect to the relative concentrations or activities of these enzymes to make sure that no net production of ROS could occur. The question, however, remains, "How does the organelle maintain this equilibrium?" with no clear answer so far. H_2O_2 usually releases into the cytosol after the damage of peroxisomes and subsequent downregulation of H_2O_2-consuming enzymes, resulting in a significant contribution to the oxidative stress (Valko et al. 2007). Alternatively, endoplasmic reticular (ER) monooxygenases cause augmented level of cellular H_2O_2 and $O_2{\cdot}^-$, endorse lipid peroxidation and mitochondrial dysfunction, change calcium homeostasis, and induce apoptosis. On the other hand, ligand–death receptor engagement (e.g., Fas ligand–Fas receptor [FasL-FasR], TNFα–TNF receptor 1 [TNFα-TNFR1]) in the extrinsic pathway of apoptosis induces lipid raft formation and recruitment and/or activation of Nox and also generation ROS (Finkel 2003; Xu et al. 2002) which signal activation of acid sphingomyelinase, ceramide production, and clustering of receptors (Circu and Aw 2010). A combination of all these processes together helps constituting lipid raft–derived signaling platforms, which in turn mediate death

receptor activation and induction of cellular apoptosis (Zhang et al. 2006a, b, 2007; Circu and Aw 2010).

SOD and XOR as regulator of ROS

In apoptosis, ROS is a vital regulatory signal (Matés et al. 2008), as inhibitors of SOD seems to favor apoptosis instead of proliferation (e.g., in fibroblasts) (Zwacka et al. 1998). Mn-SOD protects mitochondria from oxidative injury by removing $O_2{\cdot}^-$. Overexpression of Mn-SOD therefore reduces the intracellular ROS levels and might prevent cell death. Besides, Zwacka et al. (1998) showed that recombinant adenoviral vectors expressing the radical-scavenging enzymes Mn-SOD and Cu, Zn-SOD could reduce the level of apoptosis, suggesting that $O_2{\cdot}^-$ plays an important role in this process (Zwacka et al. 1998). Besides, Mn-SOD could provide protection against TNF-induced cytotoxicity, caspase-3 activation and antiproliferative effects in hematopoietic cells (Matés et al. 2012). Mn-SOD could also inhibit okadaic acid-, H_2O_2-, and taxol-induced apoptosis, but found to be ineffective in preventing vincristine, vinblastine, or daunomycin-induced apoptosis (Manna et al. 1998). The interconvertible forms xanthine oxidase (XO) and xanthine dehydrogenase (XD) could be obtained from the same enzyme, xanthine oxidoreductase (XOR) (Borges et al. 2002). XOR catalyzes the oxidative hydroxylation of hypoxanthine to xanthine and subsequently of xanthine to uric acid during purine catabolism. Uric acid so produced acts as a potent antioxidant and free radical scavenger (Valko et al. 2007). XOR has, therefore, been considered as an important species which functions as a cellular defense enzyme against oxidative stress. Besides, numerous ROS and RNS are synthesized from both XO and XD forms, particularly with the XO form (Vorbach et al. 2003; Valko et al. 2007). Thus, XOR could be pictured as an important protective regulator of the cellular redox potential because of its unique nature of the synthesis of both an antioxidant (uric acid) and numerous free radicals (ROS and RNS) makers (Valko et al. 2007).

Outline of the apoptotic signaling pathways

There are three major mechanisms that can lead to caspase activation. Firstly, a receptor–ligand binding leads to the activation of caspase-8; secondly, intercellular stresses lead to a mitochondria-dependent mechanism which occurs with the activation of caspase-9. Activation of Akt, a serine/threonine kinase, extracellular signal-regulated kinases (ERK1/2), p38, and c-Jun NH_2-terminal kinase (JNK) is a common requirement for this process (Gabai et al. 2000). The activation of these protease cascades is strongly synchronized by a number of polypeptides. Those include bcl-2 family members, inhibitor of apoptosis proteins, and a number of protein kinases. Finally, a process involving the endoplasmic reticulum with activation of caspase-12 (Nakagawa et al. 2000) could also lead to apoptosis. Among these three mechanisms, executioner caspase-3 is activated by former two (Guo and Hay 1999).

Death receptor–mediated apoptosis: the extrinsic pathway

Extrinsic pathways of apoptosis involve death receptors that are members of the tumor necrosis factor (TNF) receptor gene superfamily (Locksley et al. 2001). The receptors of TNF receptor superfamily have similar cysteine-rich extracellular domains and also share a cytoplasmic "death domain" which consist of about 80 amino acids (Ashkenazi and Dixit 1998). In the signaling pathways of transmitting the death signal from the surface to the inside of the cell, this death domain plays an important role. FasL/FasR, TNF-α/TNFR1, Apo3L/DR3, Apo2L/DR4, and Apo2L/DR5 are the best-characterized ligands and respective death receptors reported so far (Ashkenazi and Dixit 1998; Elmore 2007). Among these, the Fas ligand/Fas receptor (FasL/FasR) and tumor necrosis factor α/tumor necrosis factor receptor 1 (TNFα/TNFR1) are the best-characterized models (Elmore 2007) that define the sequence of events in the extrinsic phase of apoptosis. Figure 2 graphically represents the events.

Key biological functions of TNFα are mediated through death receptor TNFR1. TNFα–TNFR1 binding results in receptor trimerization and cross-linking via disulfide bond formation, which in turn release the inhibitory silencer of death domain (Jiang et al. 1999). This also results in the conscription of TNFR1-associated death domain (TRADD). Thus, complexes I and II are formed and activate divergent downstream signaling pathways, namely survival or apoptotic (Fig. 2) (Hsu et al. 1995).

TRADD plays the role of a scaffold for the receptor-interacting protein 1 (RIP1) and TNF-receptor-associated factor 2 (TRAF2) at complex I. This in turn facilitates the recruitment of TGF-β-activated kinase 1 and activation of NF-κB, Jun N-terminal protein kinase (JNK) and p38 (Shim et al. 2005). Along with NF-κB activation, antiapoptotic proteins such as c-FLIP, Bcl-xL, X-linked inhibitor of apoptosis (XIAP), and cellular inhibitors of apoptosis (c-IAP) 1 and 2 (Zong et al. 1999; Stehlik et al. 1998) are also activated (Fig. 2). Activation of apoptosis signal–regulating kinase 1 (ASK1) (a MAP3K) and proteasomal degradation of c-FLIP by ROS is also associated with JNK activation (Chang et al. 2006). Actually in this regard, TNFα signaling complex (TRADD-RIP1-TRAF2) gets recruited to ASK1 in which ASK1-interacting protein 1

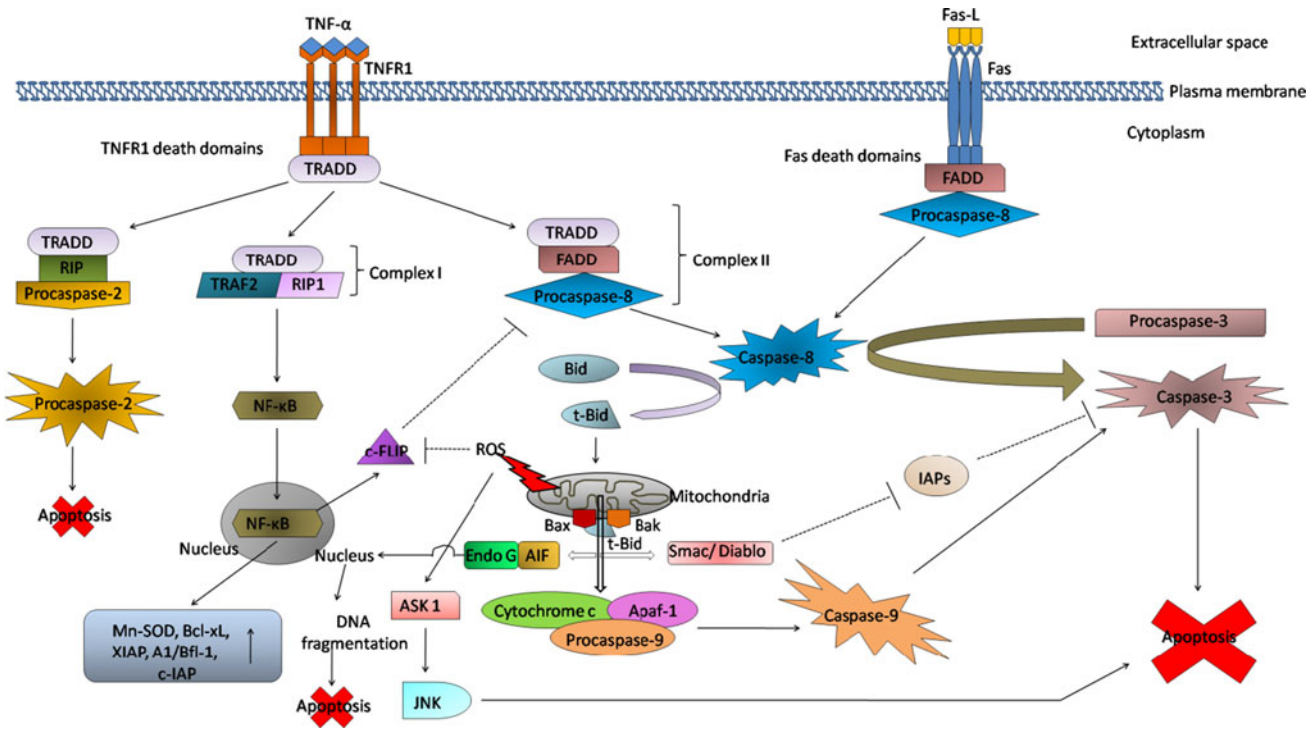

Fig. 2 Molecular mechanism of extrinsic pathway and its modulation by oxidative stress. ([*dashed line*] represents the inhibitory impact)

(AIP1) plays an important role as scaffolding protein (Zhang et al. 2004; Shiizaki et al. 2012). This scaffold protein also plays an important role in the association between ASK1 and PP2A (a serine/threonine phosphatase family member) induced by the TNFα (Min et al. 2008). Ser-966 residue of ASK1 becomes dephosphorylated by this PP2A, and thus ASK1 gets activated as a result of 14-3-3 proteins dissociation from it (Fig. 3) (Shiizaki et al. 2012). Kamata et al. (2005) show that ROS and MAP kinase phosphatases (MKP) interaction is a major regulator of JNK activation (Fig. 4). MAP kinase phosphatases (MKP) are inhibited by TNFα (in specific by TNFα induced ROS) and ultimately lead to sustained JNK activation and apoptosis (Fig. 4). TNFα also induces the activation of NF-κB as mentioned earlier in this section. This NF-κB activates MKP and MnSOD, which in turn prevents ROS accumulation (Fig. 4) (Kamata et al. 2005). Prevention of ROS accumulation in turn preserves the MKP activity (Kamata et al. 2005) and hence promotes cell survival by transiently activating JNK because here MKP acts as a JNK inhibitor. Thus, NF-κB acts as a major negative regulator of apoptosis (Karin and Lin 2002). It has also been reported that a Fas death domain–interacting protein, Daxx, also plays significant role in TNFα-induced apoptosis by Daxx-ASK1-JNK pathway (Fig. 4) (Shiizaki et al. 2012). Daxx becomes phosphorylated at Ser176 and Ser184 by activated ASK1 under the presence of TNFα signaling (Fukuyo et al. 2009) and becomes ubiquitinated at Lys122 by K-63-linked ubiquitination (Fig. 4) (Shiizaki et al. 2012). Then, ASK1 gets activated by polyubiquitinated Daxx in a positive feedback (Fig. 4) (Shiizaki et al. 2012).

Now coming to the complex II–mediated mechanism, complex II is formed within the cytosol after TNFR1 receptosome endocytosis and comprises TRADD, FADD, and caspase-8 (Fig. 2) (Schneider-Brachert et al. 2004). Here, an important checkpoint, whether TNFR1 induces apoptotic or survival signaling, depends upon the cellular status of c-FLIP and RIP1. Binding of caspase-8 at complex II and formation of DISC are competitively prohibited at high concentrations of c-FLIP (Fig. 2) (Micheau and Tschopp 2003). Also, caspase-8 cleavage of RIP1 mediates complex I dissolution, which also promotes formation complex II (Lin et al. 1999).

An alternative pathway can also be activated by TNFα where receptor-interacting protein (RIP) binds to TRADD and ultimately activates caspase-2 (Fig. 2).

As in the above-mentioned TNFα/TNFR1 signaling, receptor trimerization and the binding of the adapter protein Fas-associated DD (FADD) occur as a result of the binding of FasL to FasR, which in turn binds to procaspase-8 via dimerization of the death effector domain forms DISC promoting autocatalyting activation of procaspase-8 (Fig. 2) (Elmore 2007; Kischkel et al. 1995; Watanabe et al. 1988). In case of Fas-mediated signaling, besides the primary involvement of FADD and caspase-8 (Nagata 1999), the involvement of Daxx also occurs. Daxx becomes activated upon Fas signaling, which in turn activates ASK1

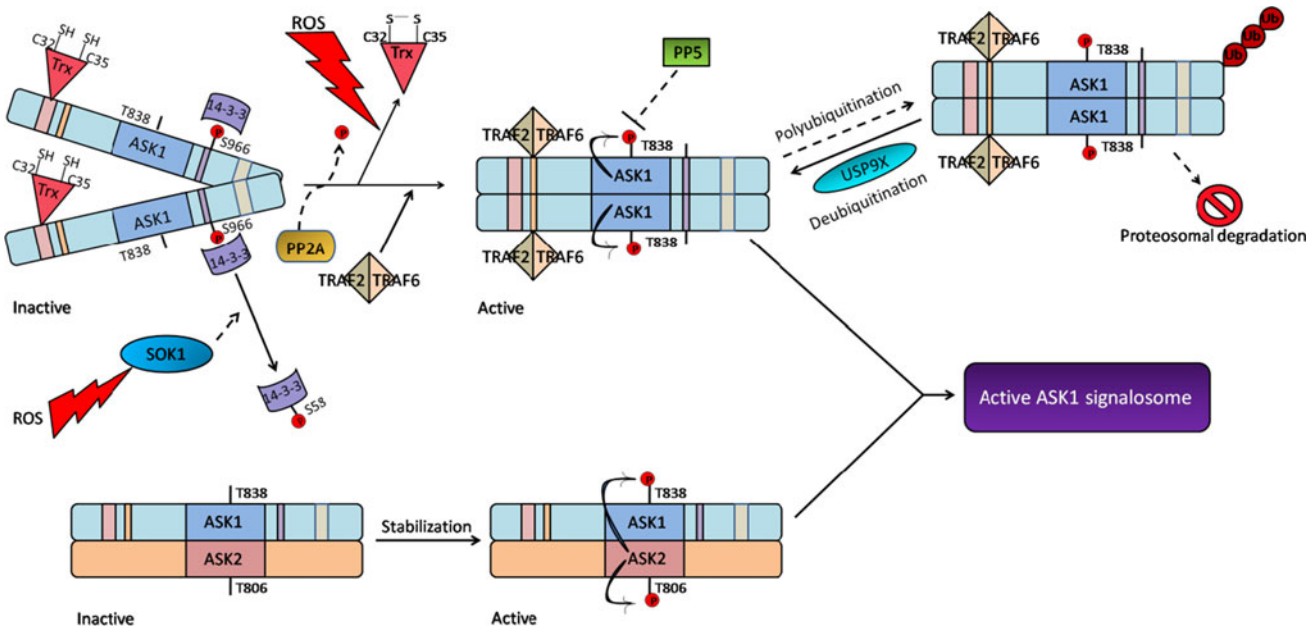

Fig. 3 Molecular mechanism of ASK1 signalosome formation. ([P] represents the phosphorylation state; *dashed line* shows inhibitory impact)

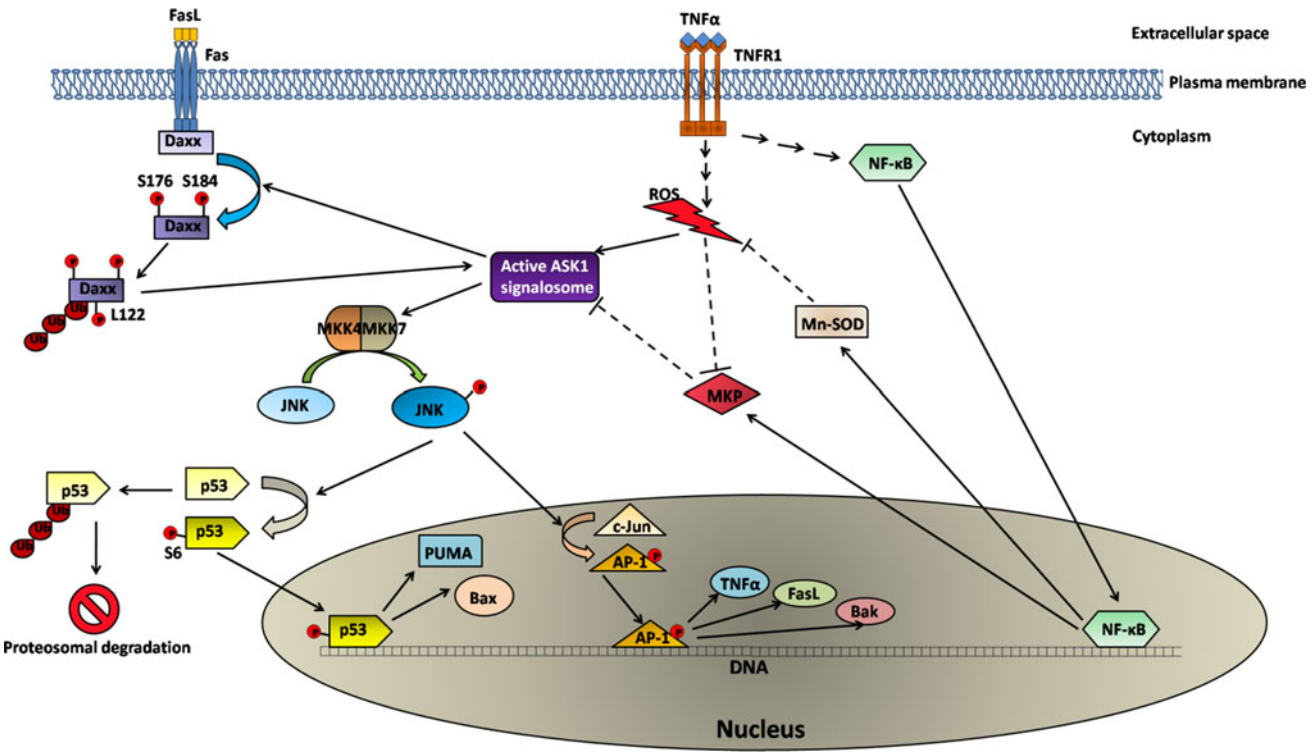

Fig. 4 Relationship of oxidative stress with intrinsic apoptotic pathway (Ub represents ubiquitination; [*dashed line*] shows inhibitory impact; [P] represents the phosphorylation state; [*triple arrows*] represents intermediate steps)

and then JNK and p38 (Chang et al. 1998). But many experimental proofs also suggest the dispensability of this pathway in case of Fas-induced death signaling, at least in few cells (e.g., MEFs, thymocytes) (Shiizaki et al. 2012). In T cells, Fas-induced apoptosis can be blocked by a protein called Toso, which inhibits the processing of caspase-8 (Hitoshi et al. 1998; Elmore 2007).

After the activation of caspase-8, the execution phase of apoptosis begins. Nevertheless, the extent of activated caspase-8 at the DISC determines two different types of

mechanisms (Type 1 or Type 2). Normal caspase-8 activation activates caspase-3 (Type 1) directly; low caspase-8-induced caspase-3 activation, on the other hand, involves the mitochondria via an amplification loop (Fig. 2) (Barnhart et al. 2003). For the Type 2 apoptosis, the proapoptotic Bid is cleaved by activated caspase-8 to tBid (Luo et al. 1998; Huang et al. 2007). Interactions of tBid with Bax/Bak permeabilize outer mitochondrial membrane, which results in the release of apoptogenic cytochrome *c*. Moreover, H_2O_2 and $O_2{\cdot}^-$ generated by NADPH oxidase are induced by Fas (Circu and Aw 2010). This phenomenon results in either c-FLIP ubiquitination/proteasomal degradation or preventing c-FLIP S-nitrosation and cytoprotection by nitric oxide (NO) scavenging (Wang et al. 2008). Hence, both the phenomena ultimately downregulate the antiapoptotic c-FLIP. This ROS–NO-controlled c-FLIP downregulation could be considered as a key regulator of Fas-induced apoptosis (Wang et al. 2008) and could likely have a significant impact on pathophysiological situations of altered ROS and NO availability, as evident in ischemia reperfusion or chronic inflammation (Circu and Aw 2010).

In this respect, it is important to mention that there are other kinds of receptors which upon ligand binding cannot transmit an apoptotic signal. Those receptors lack functional cytosolic domains. These are called decoy receptors. TRAIL-R3, TRAIL-R4, and the soluble receptor osteoprotegerin are three decoy receptors (Circu and Aw 2010; LeBlanc and Ashkenazi 2003).

Mitochondria-mediated pathways: the intrinsic pathway

Mitochondria are involved and play a central role in the integration and circulation of death signals initiating inside the cells (such as oxidative stress, DNA damage) in regulating cell death pathways (Kaufmann and Earnshaw 2000; Green and Reed 1998; Wang 2001; Green and Kroemer 2004). Cytotoxic agents such as radiation, nitrogen monoxide, arsenic (Das et al. 2009a, b, 2010a; Manna et al. 2007a, b, 2008a, b; Sinha et al. 2007a, 2008a, b), alloxan (Rashid et al. 2012; Bhattacharya et al. 2011), streptozotocin (Manna et al. 2009a, b, c), doxorubicin (Pal et al. 2012), mercury (Pal et al. 2012; Ghosh and Sil 2008), copper nano structures (Manna et al. 2012; Sarkar et al. 2011) induce apoptosis involving the mitochondria. Theses stimuli result in the formation of pores at mitochondrial membranes. At IMM, MPTP is formed (Ca^{2+} and cyclosporin A [CsA] sensitive) while the OMM gets perforated by Bax/Bak-dependent mechanism (Mg^{2+} sensitive, but cyclophilin D (CyD) insensitive) (Orrenius et al. 2007). We will discuss those mechanisms later in this chapter. At this moment, we are going to focus on the consequences.

Due to the formation of OMM pores, the integrity of mitochondrial membranes gets disturbed, resulting in the decrease in the mitochondrial transmembrane potential ($\Delta\Psi_m$) and release of two main groups of proapoptotic proteins, which normally become sequestered at intermembrane space into the cytosol (Saelens et al. 2004; Elmore 2007). Here, it is necessary to mention that the release of mitochondrial factors in turn cause disturbance of $\Delta\Psi_m$ and cause a loss of the biochemical homeostasis of the cells; for example, synthesis of ATP is prevented, NADH, NADPH, and glutathione (GSH) are oxidized, and excess ROS is produced. In this connection, overproduction of ROS causes oxidation of lipids, nucleic acids, and proteins, in a straightforward fashion, and as a consequence, loss of $\Delta\Psi_m$ as part of a positive response is developed. Coming back to the topic, it can be said that a group of proteins are related to the caspase-dependent mitochondrial way of apoptosis. Those are cytochrome *c*, Smac/DIABLO, and HtrA2/Omi (Verhagen et al. 2000). The other group contains AIF, EndoG, and CAD (Orrenius et al. 2007). These are related to caspase-independent mitochondrial way of apoptosis. Among all these, the most important factor is the cytochrome *c*. As described elsewhere, along with cytochrome *c* and Apaf-1, procaspase-9 forms multiprotein apoptosome, which ultimately produces active caspase-9 and leads to apoptosis (Fig. 2), whereas Smac/DIABLO and HtrA2/Omi inhibit IAPs and thus indirectly promote apoptosis by indirectly activating caspase-3. On the other hand, AIF, EndoG, and CAD upon release from mitochondria directly go to the nucleus and cleave DNA, irrespective of any interaction with the caspases (Fig. 5). It is to mention here that this mechanism is kept aside by cells as a late event and only occurs after the cell has committed to suicide (Elmore 2007).

Now, we are coming to the regulatory mechanisms of the most important factor (i.e., cytochrome *c*). Cytochrome *c* is an intermembrane space protein of mitochondria, restricted on the outer side of the inner mitochondrial membrane, binding to the anionic, mitochondria endemic phospholipid, cardiolipin (Hirsch et al. 1997; Orrenius et al. 2007), which holds an important place in the intracellular electron transport chain reaction. Now the question comes, "How does it get released from mitochondrial intramembrane space?" Well, the oxidative stress holds the answer! Studies show that the oxidation of cardiolipin (CL) decreases its affinity of binding to cytochrome *c* and also facilitates cytochrome *c* mobilization from the IMM (Fig. 5) (Ott et al. 2002; Orrenius et al. 2007; Manna et al. 1998). In this case, in the presence of cardiolipin, cytochrome *c* shows peroxidase activity (Kagan et al. 2005). In complex with cardiolipin, cytochrome *c* catalyzes the H_2O_2-dependent cardiolipin peroxidation (Orrenius et al. 2007). Also, Perier et al. (2005) have shown that

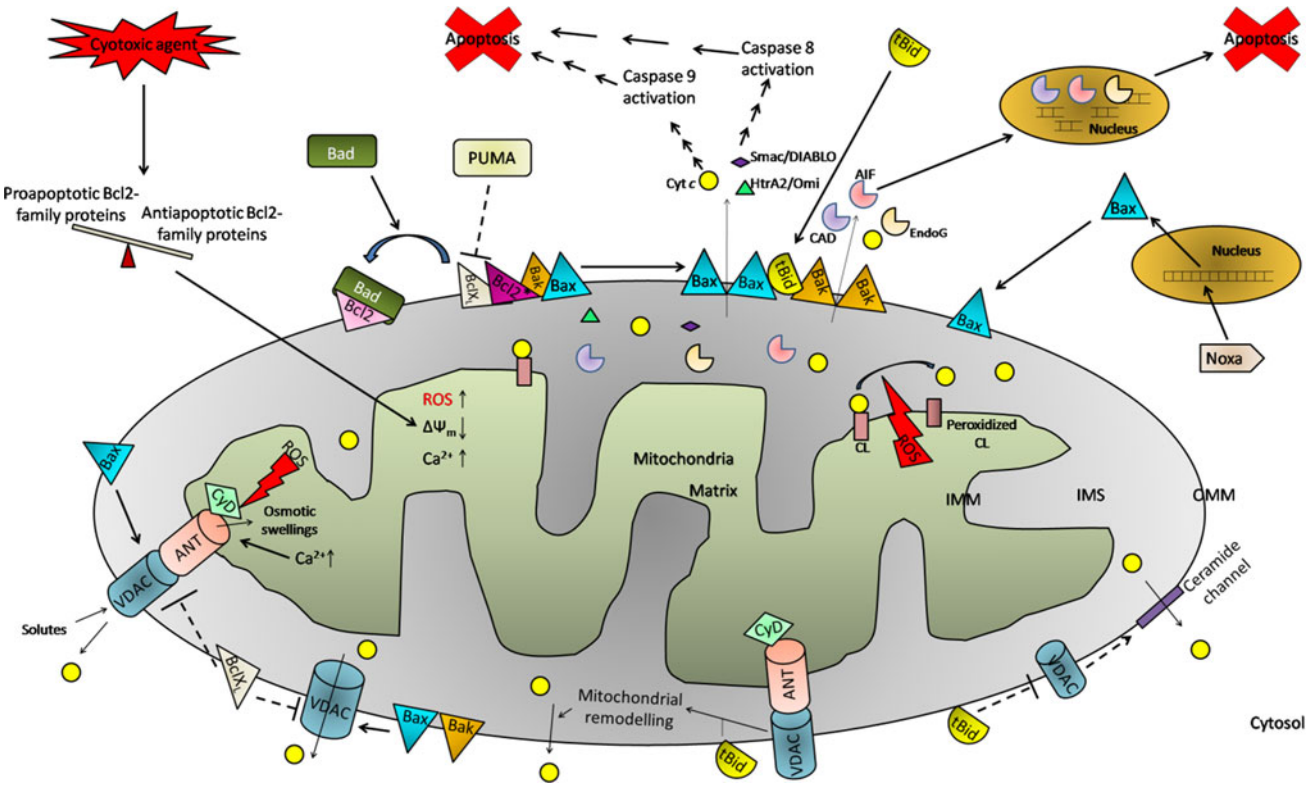

Fig. 5 Molecular mechanism of intrinsic pathway and its modulation by oxidative stress ([*dashed line*] shows inhibitory impact; [*triple arrows*] represents intermediate steps)

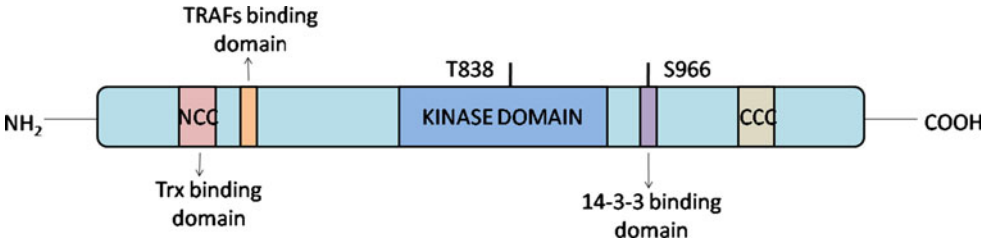

Fig. 6 Structure of ASK1 molecule indicating its active sites

intramitochondrial oxidative stress is increased with the suppression of activity of complex I. Additionally, p66Shc, a redox protein, produces H_2O_2 in the intermembrane space (Giorgio et al. 2005). This in turn augments the soluble and releasable pool of cytochrome *c* (Perier et al. 2005). However, subsequently, this soluble cytochrome *c* releases into the cytoplasm through the pores that form in the mitochondrial membrane.

Before discussing the pore-forming mechanism, it is noteworthy to mention that these apoptotic mitochondrial events are controlled by the Bcl-2 family proteins which can be of two types: pro- and antiapoptotic (Cory and Adams 2002). There exists a balance between the proapoptotic (Bax, Bak, Bok, Bid, Bim, Bik, Bad, Bmf, Hrk, Noxa, Puma, Blk, etc.) and antiapoptotic (Bcl-2, Bcl-X_L, Bcl-w, A1, Mcl-1, etc.) members of the Bcl-2 family proteins (Cory and Adams 2002) and their up- and downregulations usually determine the fate of the cells by either undergoing apoptosis or surviving in an organ pathophysiology (Fig. 5) (Das et al. 2008, 2009b, 2010a; Ghosh and Sil 2008; Roy et al. 2009; Sinha et al. 2007a, b, 2008c, d, e, 2009; Manna et al. 2007a, 2007b, 2008b, 2008c, 2008d, 2009a; Bhattacharjee and Sil 2007). Upon activation, proapoptotic family members are able to form pores in the OMM where the antiapoptotic members inhibit the activity of these proapoptotic proteins by preventing oligomerization (Orrenius et al. 2007). OMM permeabilization occurs due to oligomerization of Bax and/or Bak, which is also triggered by tBid (generated through the cleavage of Bid by caspase-8 as mentioned earlier) (Fig. 5) (Wei et al. 2000) (this is the cross-link between the receptor–ligand-mediated pathway and mitochondrial pathway). Actually under steady-state condition, Bax/Bak remains inactive by binding to Bcl2, Bcl-X_L. Upon

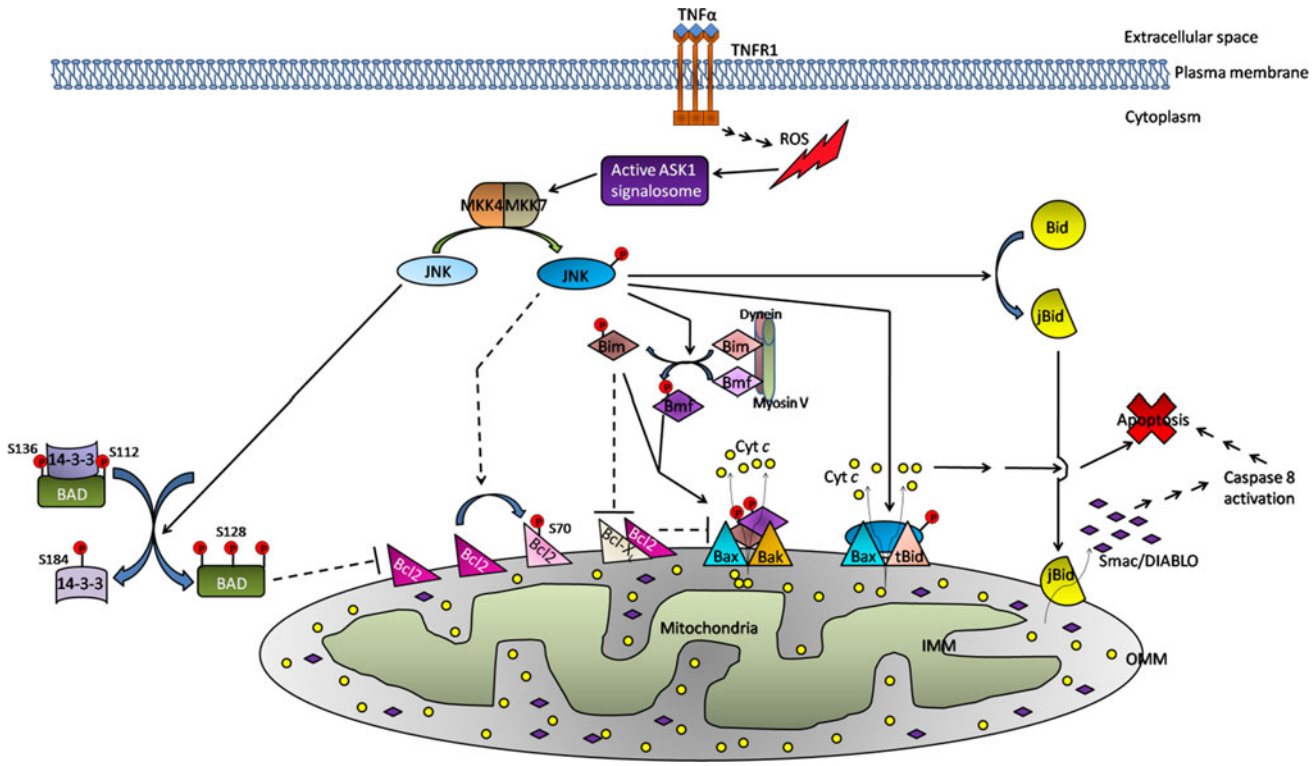

Fig. 7 Relationship of oxidative stress with extrinsic apoptotic pathway. ([*dashed line*] shows inhibitory impact; [●] represents the phosphorylation state; [*triple arrows*] represents intermediate steps)

receiving death signal, Bad gets activated by phosphorylation and inhibits Bcl2 and Bcl-X_L by heterodimerization (Yang et al. 1995). Noxa also inhibits antiapoptotic Bcl2 family member (Oda et al. 2000), whereas PUMA increases the expression and conformational change of Bax, in turn helping pore formation (Fig. 5) (Liu et al. 2003).

Now coming to the Ca^{2+}-mediated mitochondrial membrane pore-forming mechanism, the MPTP-mediated one, MPTP is located at contact sites between the inner and outer mitochondrial membranes and comprised of voltage-dependent anion channel (VDAC), adenine nucleotide translocase (ANT), and cyclophilin D (CyD) (Fig. 5) (Rasola and Bernardi 2007). Only CyD is a permanent ingredient and modulator of MPTP (Circu and Aw 2010). Alternation of mitochondrial membrane potential ($\Delta\Psi_{m)}$, elevated Ca^{2+} level, oxidative stress, thiol oxidation, or altered pyridine nucleotide status could modulate MPTP opening. Oxidative stress plays an important role in the MPT mechanism. ROS-mediated modification of thiol group of ANT is crucial in this respect (Fig. 5) (Bustamante et al. 2005). Also Bcl2 family proteins modulate the induction of MPT (Orrenius et al. 2011). Bcl2 resists MPT which, on the other hand, is augmented by Bax (Fig. 5) (Evtodienko et al. 1999; Pastorino et al. 1998). Also, Bax and Bak directly interact with VDAC in an MPT-independent manner and help to increase the pore size to that extent which permits the release of cytochrome *c,* while Bcl-X_L opposes this mechanism (Shimizu et al. 1999). In contrast, sometimes VDAC closure leads to formation of ceramide channels which helps in cytochrome *c* release, and this process is mediated by tBid (Fig. 5) (Rostovtseva and TanW 2005). ROS-mediated oxidation of cardiolipin helps the binding of tBid with VDAC (Orrenius et al. 2011). However, tBid is also involved in MPTP-dependent structural remodeling of mitochondria, which also makes the intermembrane space to be opened and hence facilitates the release of cytochrome *c* (Fig. 8) (Scorrano et al. 2002).

Although the notion that mitochondrial release of apoptogenic factors occurs through MPTP or Bax, the exact mechanism of OMM permeabilization still remains an open question.

FOXO subfamily of transcription factors and mitochondria-dependent pathway

Mitochondria-independent pathway is also regulated by the members of FOXO subfamily of transcription factors. Mitochondrial respiration gets uncouple by FOXO3, and this uncoupling produces increased amount of ROS (Hagenbuchner et al. 2012). Translocation of FOXO3 is triggered by stress-responsive kinases, JNK, and mammalian-Ste20-like kinase-1 (MST1) (Fig. 8) (Lehtinen et al. 2006;

Essers et al. 2004). Many apoptotic stimuli (e.g., chemotherapeutic agents such as etoposide) directly damage nuclear DNA, which provokes the tyrosine kinase c-Abl (Hagenbuchner et al. 2012). c-Abl phosphorylates MST1 at Tyr433. This phosphorylation activates and stabilizes MST1 while improving its interaction with FOXO3 and triggers the nuclear translocation of FOXO3 (Fig. 8) (Hagenbuchner et al. 2012). In addition, ataxia telangiectasia mutated (ATM) also favors the nuclear accumulation of FOXO3 in the same situation as mentioned above (Tsai et al. 2008). Hagenbuchner et al. (2012) have also shown increased level of ROS, specifically H_2O_2, triggers the nuclear accumulation of FOXO3. In the downstream, nuclear translocation of FOXO proteins transactivates the expression of Bim, BCL6, and Noxa (Hagenbuchner et al. 2012; Khawaja et al. 2008). On the other hand, irrespective of JNK activity, Bim translocates to mitochondria, and it creates a ROS burst by uncoupling and disrupting mitochondrial respiration there (Fig. 8) (Khawaja et al. 2008; Hagenbuchner et al. 2012). Khawaja et al. (2008) proposed a mechanism of ROS-induced Bim accumulation at mitochondria. In this proposal, they mention that the microtubular network provides the rails for mitochondria trafficking, thereby directly affecting the interaction between microtubules with Bim and ROS (H_2O_2) and translocating Bim to adjacent mitochondria. Sidewise, BCL6 downregulates the activation of antiapoptotic Bcl-X_L (Fig. 8), damaging the cell's ability to combat with increased ROS and proapoptotic BH3-only proteins (Hagenbuchner et al. 2012). Whatever may be the cases, these complex expression, activation, and/or repression and proper targeted translocation of pro- and/or antiapoptotic Bcl2 proteins may cause transient MPTP opening, which promotes ROS accumulation (Hagenbuchner et al. 2012) and also directly or indirectly favors the Bax- and/or Bak-mediated OMM permeabilization along with subsequent generation of ROS and facilitates the release of mitochondria–resident apoptogenic factors (e.g., cytochrome *c*). All these consequences ultimately converge into apoptotic cell death.

Oxidative stress signaling

Misbalancing of the fine-tuning between the levels of ROS and endogenous antioxidants leads to oxidative stress and, in worse conditions, apoptosis. ROS are the most effective activators of ASK1 (Soga et al. 2012). It is well known that various types of cytotoxic stressors such as anticancer drugs and UV irradiation activate ASK1 by producing ROS and thus induce apoptosis (Saeki et al. 2002; Laethem et al. 2006; Hattori et al. 2009; Matsukawa et al. 2004; Takeda et al. 2003). ASK1 plays a pivotal role in oxidative stress signaling (Ray et al. 2012; Tobiume et al. 2001). Using the dominant-negative and constitutive active mutants of ASK1, it has been undoubtedly proved that the former reduces apoptosis caused by TNFα and oxidative stress, whereas the later induces apoptosis in an augmented fashion (Matsuzawa and Ichijo 2008). Being a redox sensor, ASK1 may also sense the degree and duration of oxidative stress and channelize the cells into apoptosis pathways only after the extensive damage of cells caused by excess and prolonged oxidative stress exposure. Thus in redox signaling, cell fate, such as survival, differentiation, or apoptosis, seems to be regulated by ASK1. Details of this signaling have been discussed under the following subheadings.

Formation of a redox switch: The ASK1 signalosome

Apoptosis signal-regulating kinase 1 (ASK1) is a MAP3 K family member. Human ASK1 contains 1,374 amino acids (Shiizaki et al. 2012; Circu and Aw 2010). In the middle part of the ASK1 molecule, a serine/threonine kinase domain exists flanked by two coiled-coil domain, N-terminal coiled-coil domain (NCC), and C-terminal coiled-coil domain (CCC) (Fig. 6) (Shiizaki et al. 2012). Homo-oligomerization of ASK1 occurs through the CCC and NCC domain interaction (Fig. 3). Recently, it has been shown that the interaction between C-terminal coiled-coil (CCC) domain forms a complex of high molecular mass, approximately 1,500 kDa (Matsuzawa and Ichijo 2008). This high molecular mass complex contains very important redox-sensitive regulatory protein thioredoxin (Trx) and controls the activation of ASK1 and is hence named ASK1 signalosome (Fig. 3) (Noguchi et al. 2005; Fujino et al. 2006). In unstimulated cells, Trx directly binds to the NCC and constitutively disrupts the homophilic interactions by these domains leading to negative regulation of the ASK1 activity (Fig. 3) (Fujino et al. 2007; Matsuzawa and Ichijo 2008; Saitoh et al. 1998; Ray et al. 2012). Upon ROS-dependent oxidation of two cysteine residues (Cys-32 and Cys-35) in the redox center, Trx forms an intramolecular disulfide bond that makes it inactive and results in its dissociation from ASK1 by forming intramolecular disulfide bond (Fig. 3) (Ray et al. 2012; Matsuzawa and Ichijo 2008). This phenomenon allows complete oligomerization of ASK1 by subsequent N-terminal homophilic interaction in addition to the basal interaction through the CCC, while tumor necrosis factor α receptor-associated factors (TRAF) further support this binding (Saitoh et al. 1998; Fujino et al. 2007; Ray et al. 2012; Liu et al. 2000). To be specific, tumor necrosis factor receptor-associated factor 2 (TRAF2) and TRAF6 are recruited to ASK1 signalosome upon activation with H_2O_2, and this event helps to positively control the activity of ASK1 (Fig. 3) (Shiizaki et al. 2012).

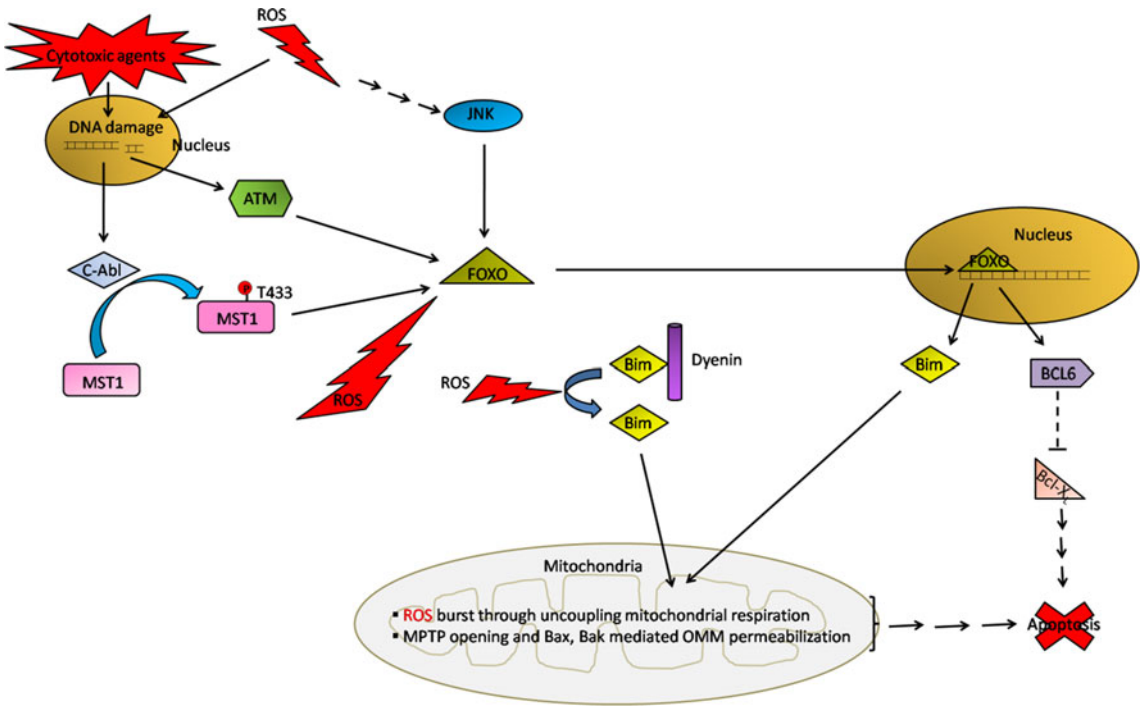

Fig. 8 Relationship between FOXO, Bim, and mitochondria-dependent pathway of apoptosis. ([*dashed line*] shows inhibitory impact; [●] represents the phosphorylation state; [*triple arrows*] represents intermediate steps)

This phenomenon activates ASK1 (Matsuzawa and Ichijo 2008). Subsequently, the oligomer undergoes autophosphorylation at conserved threonine residue (Thr-838 in human) present in the ASK1 activation loop (Tobiume et al. 2002). This phosphorylation of the threonine residue (Thr-838 of human) within the serine/threonine kinase domain of ASK1 is very much important in its activation (Shiizaki et al. 2012) and is done by trans-autophosphorylation mechanism under oxidative stress (Tobiume et al. 2002). In addition, the kinase activity of ASK1 also depends on the phosphorylation state of Thr-845. Here, it is also to be noted that the protein phosphatase 5 (PP5) negatively regulates the activity of ASK1 kinase at this level by dephosphorylating the threonine residue (Fig. 3) (Morita et al. 2001; Matsuzawa and Ichijo 2008). Besides the homo-oligomerization, ASK1 also hetero-oligomerizes with another ASK family serine/threonine MAPKKK, the ASK2 (Ray et al. 2012). ASK2 is a recently characterized member of the ASK family and is a functional binding partner of ASK1 (Takeda et al. 2007; Wang et al. 1998). ASK2 gets stabilized by binding of ASK1 to its C-terminal domain, which leads to the autophosphorylation of ASK2 at the conserved threonine Thr-806 in the activation loop (in human) (Fig. 3) (Ray et al. 2012). At this time, the hetero-oligomer is activated by phosphorylation of ASK1 at Thr-838 by ASK2 (Takeda et al. 2007). Active ASK2 exhibits sufficient activity in the direction of the JNK and p38 pathways and is also accompanied by the activation of caspase-3. H_2O_2-induced JNK activation in the absence of ASK2 is undoubtedly diminished. This finding signifies the obvious role of ASK2 as a novel component of the ASK1 signalosome, and this ASK1/ASK2 heteromeric complex plays a decisive role in the signaling pathway of oxidative stress response (Matsuzawa and Ichijo 2008). In the following section, this will be discussed in details.

Other regulators of ASK1 and its redox connection

As a result of the disassociation of Trx from ASK1, the ASK1 signalosome forms a higher-molecular-mass complex than the resting one (∼ 3000 kDa) (Noguchi et al. 2005). This finding suggests the recruitment of other factors to the signalosome (Matsuzawa and Ichijo 2008). In addition to thioredoxin (Trx), as mentioned earlier, ASK1 activity is also modulated by other few redox proteins. Redox proteins such as glutaredoxin (Grx) and glutathione S-transferase Mu1-1, heat shock proteins (Hsp90, Hsp72), 14-3-3 and TRAF proteins, ASK1-interacting protein 1, Daxx, and JASP/JIP3, respectively, inhibit (Song and Lee 2003; Saitoh et al. 1998; Song et al. 2002; Zhang et al. 1999; Park et al. 2002; Dorion et al. 2002; Matsuzawa and Ichijo 2008) and activate ASK1 (Zhang et al. 2004; Chang et al. 1998; Matsuura et al. 2002). Active ASK1 phosphorylates MAPKKs, namely MKK4, MKK3, MKK6, and MKK7 (Ichijo et al. 1997). Both

MAP2K4/MAP2K7 (MKK4/MKK7)-JNK and MAP2K3/MAP2K6 (MKK3/MKK6)-p38 pathways are activated by ASK1 (Ichijo et al. 1997) upon oxidative stress.

Now we are going to discuss redox regulation of ASK1, in the downstream of Trx regulation in detail:

ASK1 can be negatively regulated by 14-3-3 proteins which bind ASK1 at a Ser-966-containing site, under steady-state condition when the Ser-966 residue remains phosphorylated (Fig. 3) (Goldman et al. 2004; Shiizaki et al. 2012). This Ser-966 becomes dephosphorylated under oxidative stress conditions (mediated by PP2A mentioned earlier) and results in the dissociation of 14-3-3 proteins from ASK1 leading to its activation (Zhang et al. 1999; Shiizaki et al. 2012). Additionally, the mammalian sterile 20 (Mst) family member SOK-1 becomes activated under oxidative stress conditions, which in turn phosphorylates Ser-58 residue of 14-3-3ζ, and this phosphorylation also induces the dissociation of 14-3-3ζ from ASK1 (Fig. 3) (Zhou et al. 2009). TNF-α-induced activation of ASK1 also involves 14-3-3 proteins (Shiizaki et al. 2012). Now, it should also be kept in mind that the negative regulation is not the only way to regulate the ASK1 activity, but positive regulators also play significant role in the activation of ASK1. In this regard, TRAFs play a very important role. TRAF2, TRAF5, and TRAF6 activate ASK1 (Nishitoh et al. 1998; Shiizaki et al. 2012). Liu et al. (2000) have shown that TRAF2 enhances the ASK1 homo-oligomerization and activation by binding to amino-terminal region (amino acids 384–655) of ASK1 (Fujino et al. 2007). TRAF6 also binds to its amino-terminal region (Fig. 3) (Fujino et al. 2007; Shiizaki et al. 2012). Thus, NCC-mediated and ROS-induced homophilic interaction of ASK1 also depends on the association of TRAF2/TRAF6 (Shiizaki et al. 2012). In brief, ROS stimulation dissociates Trx from the ASK1 and simultaneously recruits TRAF2/TRAF6 to ASK1 signalosome, which assists in the autophosphorylation of ASK1 (Noguchi et al. 2005; Shiizaki et al. 2012).

Oxidative stress can also regulate ASK1 by ubiquitin-proteasome system where ubiquitin-specific peptidase 9, X-linked (USP9X) may act as a fine-tuner and key regulator component of ASK1-dependent signaling cascade (Fig. 3) (Nagai et al. 2009). Oxidative stress makes ASK1 ubiquitinated and thus it degrades while USP9X paradoxically saves the ASK1 by binding and deubiquitinating it in response to oxidative stress (Shiizaki et al. 2012). Thus, USP9X modulates the duration and/or magnitude of ASK1 activity under oxidative stress and determines cell fate (Nagai et al. 2009; Shiizaki et al. 2012). It can, therefore, be conclusively said that TRAF-dependent autophosphorylation and PP5-dependent dephosphorylation (Morita et al. 2001) can directly and ubiquitin-dependent degradation and USP9X-mediated deubiquitination can indirectly synchronize the ASK1 kinase activity (Nagai et al. 2009).

Downstream to ASK1: The JNKs

JNKs are the last component of the tripartite kinase cascade comprising of MAP kinase kinase kinase (MAP3 K), MAP kinase kinase (MAP2 K), and MAP kinase (MAPK) (Dhanasekaran and Reddy 1998; Dhanasekaran and Johnson 2007). Upon specific stimulation, JNKs become activated by phosphorylation of Thr and Tyr residues within the activation loop of JNKs by the penultimate dual specificity kinases of the kinase pathway, either MKK4 or MKK7 (Fig. 4) (Dhanasekaran and Reddy 1998). Various apoptotic stimuli such as TNFα and ROS can activate ASK1, ultimately resulting in the stimulation of JNK module and apoptosis (Matsuzawa and Ichijo 2001; Nagai et al. 2007). It is noteworthy to mention here that the cell fate depends on the degree and/or duration of activation of MAPKs. There are reports that strongly support that oxidative stress- and TNFα-induced transient activation of JNK leads to cell survival/differentiation by inducing NF-κB-induced antiapoptotic gene expression, while on the other hand sustained activations of JNK have been reported to induce apoptosis (Liu et al. 2002; Deng et al. 2003; Chen et al. 1996; Guo et al. 1998; Roulston et al. 1998). Nevertheless, ASK1 activity is very important for JNK activation. Though the transient activations JNK and p38 were indistinguishable between ASK1-deficient cells and cells with wild-type ASK1 activity, but the sustained activations of these two MAPKs strongly need wild-type ASK1 activity (Matsuzawa and Ichijo 2008). Similar activation of JNK and p38-MAPK has been observed in arsenic-induced hepatic apoptosis (Das et al. 2010a). Now coming back to the topic, it is to mention that JNKs follow two different strategies, one direct and another indirect one, in activating apoptotic signaling. In the direct strategy, the activities of mitochondrial pro- and antiapoptotic proteins can be directly modulated by phosphorylation through JNKs. But in the indirect one, it can be done by the transactivation of specific transcription factors such as c-Jun, which in turn upregulates proapoptotic genes (Fig. 4) (Dhanasekaran and Reddy 2008).

Both of the intrinsic and extrinsic pathways have JNK as a central modulator. Still, multiple splice variants of JNKs have been identified which are encoded by three discrete genes: JNK1, JNK2, and JNK3 (Davis 2000; Johnson and Nakamura 2007; Dhanasekaran and Reddy 2008). Apoptotic signaling is stimulated by all three JNKs. As per direct experimental proof concerned, JNK1- or JNK2-mutant MEFs ($JNK1^{-/-}$ or $JNK2^{-/-}$ respectively) showed resistance to apoptosis induced by apoptosis-inducing agents (Dhanasekaran and Reddy 2008; Tournier et al. 2000).

JNK-mediated activation of apoptotic signaling: The direct strategy

In this strategy, functions of the mitochondrial anti- and proapoptotic proteins have been modified by JNKs (Aoki et al. 2002; Schroeter et al. 2003). JNK promotes apoptosis by directly inhibiting Bcl2, the antiapoptotic protein, through phosphorylating it at Ser-70 (Fig. 7) (Srivastava et al. 1999; Yamamoto et al. 1999). On other hand, upon activation JNK gets translocated to mitochondria and releases cytochrome *c* from inner membrane space (Tournier et al. 2000; Kharbanda et al. 2000; Chauhan et al. 2003), the mechanism of which seems to be mediated by an analogous pathway to that of caspase-8-dependent one, involving proapoptotic proteins Bid and Bax (Fig. 7) (Dhanasekaran and Reddy 2008). This ultimately leads to apoptosis through the caspase-8-dependent pathway, as mentioned earlier in this review. Evidence indicates that activated JNK cleaves the Bid (proapoptotic BH3-only member of Bcl2 family of apoptotic proteins), by an unknown mechanism, resulting in a 21-kDa fragment of Bid (jBid) in caspase-8-independent manner (Fig. 7) (Madesh et al. 2002; Dhanasekaran and Reddy 2008). On translocation to mitochondria, jBid releases the proapoptotic protein Smac/DIABLO (Deng et al. 2003), which in turn induces apoptosis by indirectly activating caspase-8 in mechanism described elsewhere. Other BH3-only proapoptotic proteins, namely Bim, Bad, and Bmf, get activated by phosphorylation through the activities of JNK (Lei and Davis 2003). Upon phosphorylation, Bim and Bmf are released from the hold of the sequestering dynein and myosin V motor complexes and activate proapoptotic Bax and/or Bak (Letai et al. 2002; Lei et al. 2002; Marani et al. 2002). On the other hand, antiapoptotic Bcl2 family proteins Bcl2 and Bcl-X_L are neutralized by activated Bim (Puthalakath et al. 1999; Puthalakath and Strasser 2002). In the case of the other proapoptotic protein BAD, phosphorylation occurs at Ser-128 (Donovan et al. 2002) and releases it from the hold of the sequestering 14-3-3 family of proteins (Gross et al. 1999). Now it is significant to note that Ser-112/136-phosphorylated BAD can be sequestered by 14-3-3 family of proteins. However, the apoptosis-inducing effect of the activated BAD is exerted through inhibiting the activity of prosurvival Bcl-2 proteins (Gross et al. 1999; Wang et al. 2007). In addition, JNK phosphorylates 14-3- 3ζ at Ser-184 (Tsuruta et al. 2004), which further helps the 14-3-3 to release BAD (Sunayama et al. 2005).

JNK-mediated activation of apoptotic signaling: The indirect strategy

After activation, the phosphorylated JNK translocates to the nucleus where it transactivates c-Jun by phosphorylation (Davis 2000; Chang and Karin 2001; Behrens et al. 1999), leading to the formation of activator protein 1 (AP-1) (Fig. 4). AP1 in turn leads to the transcription of different proteins including proapoptotic factors, for instances TNFα, Fas-L, and Bak (Fan and Chambers 2001; Dhanasekaran and Johnson 2007; Dhanasekaran and Reddy 2008; Raman et al. 2007; Turjanski et al. 2007). But the requirement of JNK-c-Jun/AP1 pathway for apoptotic signaling is very much cell type dependent and apoptotic stimuli specific (Dhanasekaran and Reddy 2008; Barone et al. 2008; Kolomeichuk et al. 2008). Experiments have shown that though JNK activation has a critical role in apoptosis, but the requirement of c-Jun/AP-1 pathway is not obligatory, considering that JNK can phosphorylate and transactivate other transcription factors such as p53 and c-Myc (Johnson and Nakamura 2007), with respect to conducting apoptosis (Fuchs et al. 1998; Dhanasekaran and Reddy 2008). For instance, JNK2 phosphorylates p53 at Ser-6, and this event stabilizes the levels of p53 by inhibiting its ubiquitin-mediated degradation of p53 (Fig. 4) (Oleinik et al. 2007). In addition, this phosphorylation is also important for p73 (a member of the p53 family)-mediated apoptosis (Jones et al. 2007). Expression of some proapoptotic genes, for example Bax (Bcl2-associated X protein) and PUMA (p53-upregulated modulator of apoptosis), depends on p53 and p73 (Dhanasekaran and Reddy 2008).

Involvement of oxidative stress in various environmental drug- and toxin-induced organ pathophysiology and diabetes

Most of the environmental toxins such as arsenic (As), cadmium (Cd), chromium (Cr), iron (Fe), lead (Pb), mercury (Hg), copper (Cu), vanadium (V), and cobalt (Co) cause multiorgan damage via oxidative stress. Fe, Cu, Cr, V, and Co undergo redox cycling reactions for the formation of free radicals. On the other hand, redox-inactive metals such as Hg, Cd and Pb produce free radicals in an indirect way by the depletion of major antioxidants particularly glutathione and other antioxidant enzymes (Valko et al. 2005). Common mechanisms involving Fenton generation of the superoxide and hydroxyl radical appear to be involved for Fe, Cu, Cr, V, and Co.

$$M^{(n+1)+} + O_2^{\cdot -} \rightarrow M^{n+} + O_2 \,(\text{where, M} = \text{metal})$$
$$2O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + O_2$$
$$M^{n+} + H_2O_2 \rightarrow M^{(n+1)+} + OH^{\cdot} + OH^- \,(\text{Fenton reaction})$$

Fenton reactions are mainly associated with peroxisomes, microsomes, and mitochondria (Valko et al. 2005). In addition to the Fenton reaction, hydroxyl radical and hydrogen peroxide combine to form superoxide.

$$OH^{\cdot} + H_2O_2 \rightarrow H_2O + O_2^{\cdot -} + H^+$$

Superoxide is not very reactive and unable to attack DNA. However, it undergoes Fenton reaction, leading to the production of extremely reactive hydroxyl radicals which can damage any biomolecule.

It has been proposed that arsenic (As) binds directly to critical thiols as well as produces hydrogen peroxide (Valko et al. 2005).

$$H_3AsO_3 + H_2O + O_2 \rightarrow H_3AsO_3 + H_2O_2$$

Das et al. (2010a) demonstrate a pivotal role of mitochondria in hepatocytes death via apoptosis. It has also been shown that ROS generated during $NaAsO_2$ exposure induce apoptosis via PKCδ-JNK-dependent pathway in hepatocytes (Das et al. 2010a). Besides, $NaAsO_2$ exposure also induces testicular (Das et al. 2009b), cardiovascular (Ghosh et al. 2009) as well as renal toxicity (Roy et al. 2009) predominantly via ROS production and induces mitochondria-dependent apoptosis via NFκB-MAPKs-dependent pathways. Copper nano structure has also been reported to induce oxidative stress and toxicity in hepatic (Manna et al. 2012) and renal tissue (Sarkar et al. 2011) via mitochondria-dependent pathways. Bhattacharyya et al. (2012) show that iron induces hepatocytes death via MAPK activation and mitochondria-dependent apoptotic pathway.

The redox-inactive metals such as Hg, Cd, and Pb can make stable covalent bonds with the sulfhydryl groups of proteins (Ercal et al. 2001). Among these, Hg^{2+} and arsenites (As^{3+}) have strong affinities for GSH, thereby reducing the intracellular GSH content. However, Hg^{2+}, Cd^{2+}, and As^{3+} can also produce hydrogen peroxide and other free radicals in an indirect way, which further depletes intracellular GSH level via oxidation (Ercal et al. 2001).

Pal et al. (2012) have shown that mercury induces oxidative stress and mitochondria-dependent apoptosis in hepatocytes via NFκB-MAPKs-dependent signaling pathways. Pal et al. (2011) and Ghosh et al. (2010a) show that cadmium induces oxidative stress and apoptosis via both extrinsic and intrinsic pathways in hepatocytes. They also show that cadmium triggers apoptotic cell death via NFκB-MAPKs-dependent signaling pathways. It has also been proposed that Cd can replace Fe and Cu in various cytoplasmic and membrane proteins (e.g., apoferritin, ferritin), thus increasing the amount of Cu and Fe ions which produce oxidative stress via Fenton reactions (Casalino et al. 1997). Pb can also induce free radical production via interaction with oxyhemoglobin and δ-aminolevunilinic acid pathways (Ercal et al. 2001). Pal et al. (2013) show the involvement of oxidative stress in Pb-induced hepatic pathophysiology, which ultimately results in mitochondria-dependent apoptosis via NFκB-MAPKs-dependent signaling pathways.

A number of drugs have been used for the treatment for a variety of diseases. However, clinical uses of most of these drugs are greatly limited by their serious adverse effects which may ultimately lead to different organ failure via oxidative stress. Overdose of acetaminophen, one of the most commonly used analgesic and antipyretic drugs, causes acute liver poisoning via oxidative stress (Ghosh and Sil 2007). At therapeutic doses, acetaminophen is primarily bioactivated in the liver, by cytochrome P450 s to the reactive metabolite N-acetyl-p-benzoquinone imine which is primarily detoxified by conjugation with GSH. However, at higher doses of acetaminophen, conjugation leads to the critical depletion of GSH causing acute oxidative stress and cellular necrosis. Besides, acetaminophen overdose can also decrease the activities of the key antioxidant enzymes. ROS can further activate JNK MAPK which induces hepatocytes via phosphorylation of Bcl-xL and Bcl-2 (Das et al. 2010c; Ghosh et al. 2010b, Ghosh and Sil 2009). In addition, acetaminophen overdose induces nephrotoxicity via ROS formation as a result of depleted GSH and decreased antioxidant enzyme activities (Das et al. 2010b; Ghosh et al. 2010c).

Besides, doxorubicin, one of the most effective chemotherapeutic drugs, also causes cardio- and testicular toxicity via oxidative stress and cellular apoptosis. During metabolism, the quinone moiety of doxorubicin undergoes a redox cycling reaction and produces superoxide radical, which in turn produces H_2O_2 and (·OH) and induces oxidative stress. In addition, doxorubicin also decreases intracellular GSH and antioxidant enzyme activities (Pal and Sil 2012; Das et al. 2011). Das et al. (2011) and Ghosh et al. (2010a, b, c, d, 2011a, b) clearly show that doxorubicin impaired cardiac cell survival through the activation of p53 and JNK-p38, which led to NF-κB activation via the IKK pathway and mitochondria-dependent cell apoptosis. Doxorubicin can also stimulate testicular apoptosis via the activation of MAPKs and p53-dependent signaling pathways (Das et al. 2012d).

Similarly exposure of nonsteroidal anti-inflammatory drugs such as nimesulide in overdose induces severe hepatotoxicity. The hepatotoxic mechanism of nimesulide is mediated mainly via ROS production. The stress condition is becoming more aggravated when GSH pool is depleted. Nimesulide has also been found to reduce the activities and expression of the antioxidant enzymes (Singh et al. 2012; Chatterjee et al. 2006; Chatterjee and Sil 2006, 2007). ROS can ultimately induce hepatocytes death via caspase-dependent apoptotic pathways (Singh et al. 2012).

Diabetes mellitus, the most common metabolic disease, is an important health problem worldwide. The serious long-term disorders related to diabetes apart from hyperglycemia

and hyperlipidemia are cardiovascular complications, diabetic nephropathy, and retinopathy (Baynes and Thorpe 1999; Ceriello 2000; Yim et al. 2007). Hyperglycemia-induced oxidative stress contributes to the development and progression of diabetes and related pathogenesis. Under diabetic/hyperglycemic condition, oxidative stress occurs via multiple mechanisms. Persistent hyperglycemia causes disruption of the mitochondrial electron transport chain and produces superoxide anions (Nishikawa et al. 2000). Under diabetic condition, increased oxidative glucose metabolism increases mitochondrial production of superoxide, which further produces (·OH) and H_2O_2. Hyperglycemia can also increase oxidative stress via the enhanced activity of polyol/sorbitol pathway (Ciuchi et al. 1996), auto-oxidation of glucose (Wolff and Dean 1987), nonenzymatic glycation of proteins (Mullarkey et al. 1990), glycated protein-induced activation of NADPH oxidase (Zhang et al. 2006a, b), hexosamine flux (Wold et al. 2005), and free fatty acids (Evans et al. 2002).

During hyperglycemia, glucose enters into the polyol pathway, where in the presence of NADPH, it is reduced to sorbitol by the action of aldose reductase. Then, sorbitol is re-oxidized by sorbitol dehydrogenase to fructose. At the same time, NADH is produced from NAD^+. NADPH, a cofactor in the production of GSH from GSSG, maintains the redox equilibrium between GSH and GSSG. Due to the increased activation of polyol pathway, availability of NADPH is decreased, which further causes depletion of GSH and leads to increased oxidative stress.

Besides, advanced glycation end-products (AGEs) are formed when reducing sugars such as glucose and glucose-derived dicarbonyl compounds react nonenzymatically with amino groups of proteins forming irreversible Shiff bases and more stable Amadori products. AGEs are then formed via auto-oxidation of Amadori products. AGEs bind with their receptors RAGE and produce ROS production even in the presence of intact antioxidant mechanisms. In addition, glycation can also inactivate antioxidant enzymes and impair antioxidant defense.

Another important nonmitochondrial source of ROS in the diabetic condition is increased hexosamine flux. Under hyperglycemic condition, overproduction of mitochondrial superoxide causes inhibition of GAPDH (glyceraldehyde-3-phosphate dehydrogenase) and cytochrome enzymes of the electron transport chain responsible for oxidative phosphorylation in the Krebs cycle. This leads to the accumulation of glycolytic intermediates upstream of GAPDH (Du 2000) and activates the polyol and hexosamine biosynthetic pathway. Increased hexosamine biosynthetic pathways decrease the NADPH/$NADP^+$ ratio due to the inhibition of glucose-6-phosphate dehydrogenase and induce oxidative stress by two mechanisms: decreasing the bioavailability of GSH and decreasing the enzymatic activity of catalase.

Conclusion

Arrays of stimuli make cells to commit suicide which may involve mitochondria or may follow a mitochondria-independent pathway, and researches have continuously revealed that there exists a major cross-talk between them. Decades of research have also shown that ROS plays a very important regulatory upstream factor here. Basically, different cytotoxic stimuli may impart their effects via cell surface receptors or directly by acting over mitochondria. In the first scenario, cell surface death receptors get induced and in turn enhance ROS production. In the second case, mitochondrial membrane integrity, transmembrane potential, respiratory chain, etc. get disturbed and initiate ROS production. This ROS in its downstream activates different signaling molecules. Like in mitochondria-independent mechanism, the redox-sensitive ASK1 signalosome gets activated and in turn activates the downstream effector MAPKs (e.g., JNK). JNK further activates and/or represses its downstream pro and/or antiapoptotic molecules and their regulators. Besides, in mitochondria-dependent mechanism, delicate balance between mitochondrial pro- and antiapoptotic factors (Bcl2 family proteins) gets disturbed resulting in OMM or IMM poration and subsequent release of mitochondrial apoptogenic factors which ultimately induce apoptosis in caspase-dependent or caspase-independent manner. In many aspects as mentioned above, ROS plays a central role, the main source of which is mitochondrial respiratory chain. Uncoupling, disturbance, or inhibition of this chain produces ROS.

However, in spite of numerous reports regarding diseases (e.g., diabetes, Alzheimer's, cancer, etc.) and drug- or toxin-induced pathophysiology and the obvious involvement of oxidative stress, the exact role of ROS and its cross-talks with these apoptotic pathways remain illusive till date. Further intensive research and major breakthroughs in this field of free radical biology will be very much important for proper and extensive dissecting this relationship, which may in turn open a variety of approaches to ameliorate the effect of environmental toxins and curing deadly diseases such as diabetes, Alzheimer's, and cancer.

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