

## Review Article

# The Bad, the Good, and the Ugly about Oxidative Stress

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Alzheimer's disease (AD), Parkinson's disease (PD), and cancer (e.g., leukemia) are the most devastating disorders affecting millions of people worldwide. Except for some kind of cancers, no effective and/or definitive therapeutic treatment aimed to reduce or to retard the clinic and pathologic symptoms induced by AD and PD is presently available. Therefore, it is urgently needed to understand the molecular basis of these disorders. Since oxidative stress (OS) is an important etiologic factor of the pathologic process of AD, PD, and cancer, understanding how intracellular signaling pathways respond to OS will have a significant implication in the therapy of these diseases. Here, we propose a model of minimal completeness of cell death signaling induced by OS as a mechanistic explanation of neuronal and cancer cell demise. This mechanism might provide the basis for therapeutic design strategies. Finally, we will attempt to associate PD, cancer, and OS. This paper critically analyzes the evidence that support the "oxidative stress model" in neurodegeneration and cancer.

## 1. The Verdict: Oxygen Is Guilty, Not Guilty

Oxidative stress (OS) has become a major topic in all areas of medical knowledge. Entry of the term "oxidative stress" in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) shows that the number of publications has dramatically increased from none in the early 1970's to cover ~90,000 peer-reviewed articles in 2011 (Figure 1(a)). A similar trend is recorded for Alzheimer's disease (AD), Parkinson's disease (PD), and cancer when searched jointly with OS (Figure 1(b)). Since the discovery of the superoxide dismutase (SOD) in 1969 by McCord and Fridovich ([1], for a historical perspective see [2–4]), our understanding of the molecular defense mechanisms, which include catalase [5], glutathione peroxidase (GPx), and peroxiredoxin [6] and thioredoxin reductase [7], against diverse stress stimuli and pathogens [8] has dramatically changed (reviewed in [9, 10]). Moreover, given the phylogenetic distribution and subcellular localization of the SOD isozymes, the discovery has provided strong support for the hypothesis that the chloroplasts and mitochondria of eukaryotic cells arose from prokaryotic endosymbionts

[11]. SOD is an enzyme that catalyzes the dismutation of the superoxide radical ( $O_2^{\cdot-}$ ) very efficiently ( $k_2 \sim 2 \times 10^9 M^{-1} s^{-1}$ ) through a redox reaction of its copper centre enzyme into oxygen ( $O_2$ ) and hydrogen peroxide ( $H_2O_2$ ). Today, it is clear that decrease of enzymatic activity of the defense system or an overwhelming production of  $O_2^{\cdot-}$  and/or  $H_2O_2$  is linked to neurodegenerative disorders (e.g., familial amyotrophic lateral sclerosis [12], AD [13], PD [14], and cancer [15]). The idea that oxygen might not only be involved in the beginning of life and evolution [16–18] but also it might be a toxic molecule [19] was further popularized by Halliwell and Gutteridge in their book entitled "Free Radicals in Biology and Medicine" [20] and some important follow-up papers [21–23]. The chemistry of oxygen is well known. Basically,  $O_2$  is classified as a free radical. By definition, a free radical is an atom or group of atoms with at least one unpaired electron. Indeed, the electronic configuration of the oxygen diatom is  $[2He^4]2s^4 2p^8$  with the first ten electrons placed into  $\sigma$ ,  $\sigma^*$ ,  $\pi$ , orbitals, and two unpaired electrons each located in a different  $\pi^*$  antibonding orbital. Removal of an electron

from  $O_2$  results in a superoxide cation radical ( $O_2^{\cdot+}$ ). In contrast, if a single electron is added, the product is the superoxide anion radical ( $O_2^{\cdot-}$ ). Addition of one more electron will yield the peroxide ion,  $O_2^{2-}$ , which is not a radical. Since this reaction may take place in solution, it is quite likely that this ion became protonate ( $2H^+$ ) and converted into  $H_2O_2$ . This last compound represents a potential danger. In the presence of metal ions such as iron ( $Fe^{2+}$ ) and copper ( $Cu^+$ ),  $H_2O_2$  decomposes into more reactive free radical specie, the hydroxyl radical ( $\cdot OH$ ). In sharp contrast with  $O_2^{\cdot-}$ , there is not an antioxidant system to protect cells against  $\cdot OH$ . Indeed, this last radical can provoke a whole series of radical chain reactions involving damage of lipids, proteins, and nucleic acids. Therefore, an excessive generation or accumulation of  $O_2^{\cdot-}/H_2O_2$  may lead to a biochemical phenomenon known as OS. Simply, this term refers to an atypical state in which exaggerate production of reactive species overwhelms the antioxidant defense systems of the cell [24]. Interestingly,  $O_2^{\cdot-}$  and  $H_2O_2$  are recognized to play signaling functions (reviewed in [25, 26]). However,  $H_2O_2$  best fulfills the requirements of being a second messenger, that is, its enzymatic production, along with the requirements for the oxidation of thiols by this molecule, provides the specificity for time and place that are required in signaling, whilst  $O_2^{\cdot-}$  is more likely as a precursor of  $H_2O_2$ . Although efforts have been made to explain the complexities of OS in cancer [27, 28] and neurodegeneration [29–31], several questions still remain unanswered, mainly because of two key issues. First, except for a few causative genetic mutations, the underlying pathogenic mechanism(s) of Parkinson's and Alzheimer's cases is not yet well understood. Consequently, this makes it difficult to identify potential therapeutic targets to stop their progression. Therefore, it is imperative to elucidate the precise molecular mechanism and/or identify the molecular "switches" that trigger neuronal death [32]. Clearly, identifying the precise steps/"switches" in the pathological cascade has been proven difficult since multiple death signaling pathways are often activated in response to a single stimulus. Thus, the questions what kills neurons and how do they get deteriorate in neurodegenerative diseases [33, 34] are still unresolved. Second, it is not surprising that some neuroprotective clinical trials had been completely unsatisfactory [35–38]. This last outcome is even aggravated by either technical incongruities [39], the challenging task of recruitment and retention of subjects in clinical trials (e.g., AD, [40]), limited knowledge on antioxidant bioavailability [41, 42], or that they have failed because they have not been aimed at the right target [43–45].

## 2. The Bad Touch of Oxidative Stress: Involvement in Alzheimer's and Parkinson's Disease

AD and PD are the two most common progressive neurodegenerative disorders worldwide [46, 47] affecting all ethnicities but especially some genetically isolated groups, such as the "paisa community" living in the Antioquia region

of Colombia [48–52]. AD and PD are neuropathologically characterized by abundant insoluble protein deposits (e.g.,  $A\beta_{[1-40/42]}$  and hyperphosphorylated tau in AD [53],  $\alpha$ -Synuclein in PD [54], metal deposition (e.g., iron [55–57]), specific neuronal and synaptic loss of the hippocampal pyramidal neurons (AD), and dopaminergic neurons of the *substantia nigra* (PD), probably via OS [58]. Despite the fact that both of these types of cells are vulnerable to OS, it is still unknown the complete cascade of molecular events at a single cell level responsible for neural deterioration. Consequently, no effective and/or definitive therapeutic treatment aimed at reducing or delaying clinical and pathological symptoms is currently available. Therefore, it is urgently needed to elucidate the molecular cell death signaling pathway involved in these processes to identify potential pharmacological target(s).

To get insight into these issues, we initially selected peripheral blood lymphocyte (PBL) culture as model system in AD and PD. Indeed, these cells display striking biochemical similarities to neurons (e.g., [59–63]). Lymphocytes therefore represent a remarkable nonneural cell model for understanding the molecular machinery and metabolic regulation of apoptosis associated with cell survival signaling against stressful stimuli. Apoptosis is a controlled and regulated form of programmed cell death defined by specific morphological features such as rounding-up of the cell, reduction of cellular volume, chromatin condensation (i.e., stage I nuclei morphology composed of high molecular weight DNA), nuclear fragmentation (i.e., stage II nuclei morphology composed of low molecular weight DNA, highly chromatin condensation packed in round masses), classically little or no ultrastructural modifications of cytoplasmic organelles, and plasma membrane blebbing [64]. Although morphologically similar, apoptosis can be triggered through different intrinsic or extrinsic signaling biochemical routes [65–67]. Because  $H_2O_2$  is more stable reactive oxygen specie (ROS), it can work either as a second messenger in prosurvival [68] or in prodeath intracellular signaling pathways. During the last decade, we have focused on investigating the  $H_2O_2$ -induced cell death signaling in PBLs. We have consistently shown that  $A\beta_{[25-35]}$  [69], dopamine (DA, [70]), and its related neurotoxins (e.g., 6-hydroxidopamine (6OHDA), 5,6 and 5,7-dyhydroxy-tryptamine (5,6- and -5,7-DHT, [71]), paraquat (PQ, [72]), and rotenone (ROT, [73]) induce apoptosis in lymphocytes in a concentration- and time-dependent fashion by OS mechanism involving several steps:  $O_2^{\cdot-}$  and  $H_2O_2$  generation (Figure 2, step 1, *numbers in red*), activation of the nuclear factor kappa-B (NF- $\kappa$ B, step 2)/p53 (step 3)/c-Jun N-terminal kinase (JNK, step 4)/c-Jun (step 5) transcription factors, mitochondrial depolarization (step 6), and caspase-3 activation (step 7). As a result we observed the typical nuclei morphological feature of apoptosis including chromatin condensation and fragmentation (step 8). Remarkably, this cell death subroutine can be blocked by the action of antioxidants (e.g., N-acetyl-cysteine (NAC) [69, 71], vitamin C (VC, [71]), testosterone [70],  $17\beta$ -estradiol [70, 74], cannabinoids (e.g., CP55940 and JWH-015 [72, 75]), mitochondria permeabilization transition pore inhibitor (e.g., cannabinoids

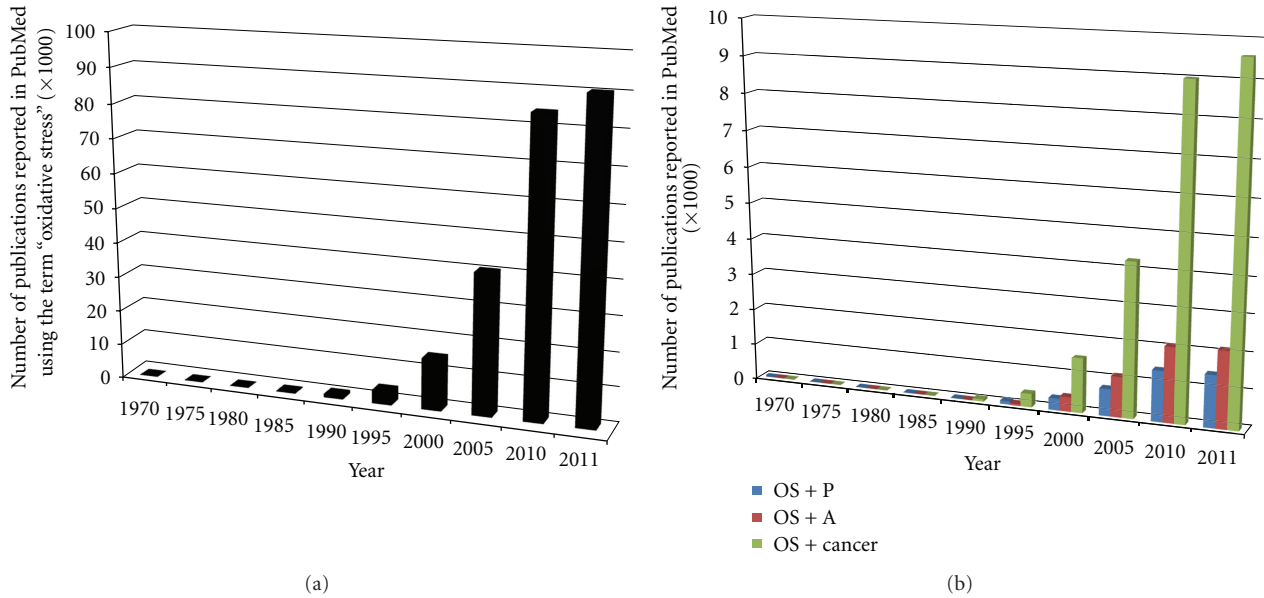


FIGURE 1: Number of articles reported in PubMed by using the term "oxidative stress" (OS) alone (a) or together (b) with the term "Parkinson" (P), "Alzheimer" (A), and "cancer".

[76]), insulin-like growth factor-1 [72, 73, 77]), high glucose [72, 73], specific pharmacological inhibitors (e.g., PDTC, pifithrin- $\alpha$ , SP600125, Ac-DEVD-cho inhibitor of NF- $\kappa$ B, p53, JNK, and caspase-3, resp.) and inhibitors of protein (e.g., cycloheximide [71]), and RNA (e.g., actinomycin D [69, 71]) synthesis. These findings may be explained by the following assumptions.  $H_2O_2$  might indirectly activate NF- $\kappa$ B through phosphorylation of the  $I\kappa B\alpha$  (i.e., the inhibitor of the complex NF- $\kappa$ B or p50/p62) either by the spleen tyrosine kinase protein (Syk, step 9, *number in blue*) at tyrosine 42 [78, 79] or at serine 32 and 36 via SH2 (Src homology 2)-containing inositol phosphatase-1 (SHIP-1, step 10)/ $I\kappa B$ -kinase (IKK) complex pathway [80]. Alternatively,  $H_2O_2$  might activate NF- $\kappa$ B through activation of the IKK complex by mitogen-activated protein kinase/ERK kinase kinase-1 (MEKK1, step 11, [81]). Once the  $I\kappa B$  is phosphorylated, the release of active NF- $\kappa$ B dimer (p50/p63) translocates into the nucleus and transcribes several antiapoptotic genes (e.g., Bcl-2, cIAP-1-2, and Bcl-xL) (step 12) and proapoptotic genes, amongst them the p53 [82]. At this point, a vicious cycle is established wherein p53 plays a critical role by balancing the cell to a death decision because of its many actions. First, p53 transcribes proapoptotic genes such as Bax (step 13), which in turn might contribute to the permeabilization of the outer mitochondrial membrane by antagonizing antiapoptotic proteins (e.g., Bcl-2, cIAP-1-2, and Bcl-xL). Second, p53 not only induces prooxidant genes (e.g., p53-induced gene-3 (PIG3), proline oxidase (PO), step 14), which generate more  $H_2O_2$  but also represses the transcription of antioxidant genes (e.g., NAD(P)H: quinone oxidoreductase-1) [83]. Elevated stress stimuli (i.e.,  $H_2O_2$  production, step 1) and further activation of NF- $\kappa$ B induce upregulation of proapoptotic genes (e.g., p53), which in

turn amplify the initial  $H_2O_2$ -induced cell death signal. Formation of the mitochondrial permeabilization transition pore allows the release of apoptogenic proteins (by a not fully established mechanism, step 15 [84, 85]) such as the apoptosis-inducer factor (AIF, [86]) responsible for causing DNA fragmentation and chromatin condensation (i.e., stage I nuclei morphology) and cytochrome C, which together with Apaf 1, dATP, and procaspase-9 (i.e., the apoptosome) elicits caspase-3 protease activation [87]. This protease is essential for the fragmentation and morphological changes associated with apoptosis [88]. Indeed, caspase-3 activates the endonuclease DNA fragmentation factor 40 (DFF40) or caspase-activated DNase (CAD) by cutting the nuclease's inhibitor DFF45/ICAD [89]. Finally, DFF40/CAD causes nuclear chromatin fragmentation (i.e., stage II nuclei morphology), typical of apoptosis [90]. Interestingly, the apoptosis signal-regulating kinase (ASK1; step 16, [91]) and MEKK1 (step 11, [92]) phosphorylate MKK4/MAPK kinase (step 17). MEKK1 kinase therefore represents a cross-talk between the JNK and NF- $\kappa$ B pathway. Indeed, MEKK1 kinase phosphorylates IKK and MKK4. This last kinase phosphorylates JNK/stress apoptosis protein kinase (SAPK [93], step 4), which in turn phosphorylates the c-Jun transcription factor [94], also involved in transcription of death signaling [95]. Interestingly, it has also been shown that JNK1/2 cooperates in the activation of p53 apoptotic pathway [96, step 3]. Alternatively, high concentration of metal ions (e.g.,  $Fe^{2+}$ ;  $Cu^+$ ,  $Mn^{2+}$ ) alone or in combination with  $H_2O_2$  are able to directly induce mitochondria damage and apoptotic morphology by caspase-3-dependent mechanism [70, 97]. In conclusion, NF- $\kappa$ B, p53, c-Jun and caspase-3 activation, and mitochondrial depolarization are crucial events in mediating cell death by apoptosis.

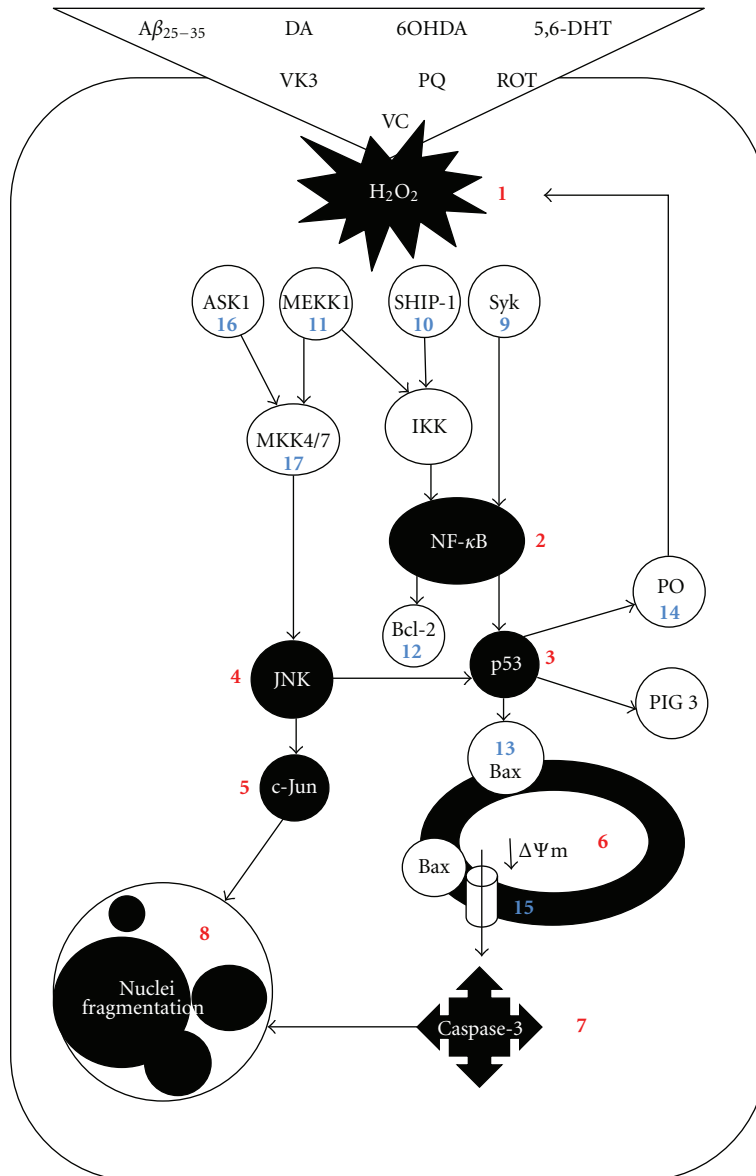


FIGURE 2: Proposed model of minimal completeness of cell death signaling induced by oxidative stress as a mechanistic explanation of neuronal and cancer cell demise. The neurotoxins  $A\beta_{25-35}$ , dopamine (DA) and its related neurotoxins (6OHDA, 5,6- and 5,7-DHT), paraquat (PQ), and rotenone (ROT) trigger a cell death subroutine in lymphocytes, a well-established model of AD and PD. This mechanism is characterized by  $O_2^-/H_2O_2$  generation (step 1, numbers in red), activation of the transcription factors NF- $\kappa$ B (step 2), p53 (step 3), and c-Jun (step 5), activation of the JNK kinase (step 4), mitochondrial depolarization (step 6), caspase-3 activation (step 7), and nuclei chromatin condensation/fragmentation (step 8). These findings may be explained by the following assumptions.  $H_2O_2$  might indirectly activate NF- $\kappa$ B through phosphorylation of its inhibitor I $\kappa$ B $\alpha$  either by Syk (step 9, numbers in blue) or via SHIP-1 (step 10)/IKK complex pathway.  $H_2O_2$  might also activate NF- $\kappa$ B through activation of the IKK complex by the MEKK1 protein (step 11). Once NF- $\kappa$ B is activated, it translocates into the nucleus and transcribes several antiapoptotic genes (step 12) and proapoptotic genes, amongst them the p53 (step 3). At this point, a vicious cycle is established. First, p53 transcribes proapoptotic genes such as Bax (step 13), contributing to the permeabilization of the outer mitochondrial membrane by antagonizing antiapoptotic proteins. Second, Bax induces prooxidant genes (e.g., p53-induced gene-3 (PIG3), proline oxidase (PO), step 14), which generate more  $H_2O_2$  (step 1) and represses the transcription of antioxidant genes.  $H_2O_2$  overproduction and further activation of NF- $\kappa$ B induce upregulation of proapoptotic genes (e.g., p53), which in turn amplify the initial  $H_2O_2$ -induced cell death signal (step 2–8). Mitochondrial damage allows the release of apoptogenic proteins (step 15) responsible for the formation of apoptosome and activation of caspase-3 protease. This protease in turn activates the endonucleases DFF40/CAD, by cutting the nuclease's inhibitor DFF45/ICAD. Finally, DFF40/CAD causes nuclear chromatin fragmentation, typical of apoptosis. Alternatively, ASK1 (step 16) and MEKK1 (step 11) phosphorylate MKK4/MAPK kinase (step 17). MEKK1 kinase also phosphorylates IKK. This last kinase phosphorylates JNK1/2/SAPK (step 4), which in turn phosphorylates c-Jun, also involved in death signaling. Noticeably, vitamin C (VC) and vitamin K3 (VK3) alone or in combination induce apoptosis in Jurkat and K562 cells by a similar mechanism as described. This mechanism might provide the basis for therapeutic design strategies in AD, PD, and cancer (leukemia).

Over the years, not only *in vitro* (e.g., [98–107]) or *in situ* (e.g., [55, 108–115]) but also *in vivo* studies have validated the findings highlighted in Figure 2, step 1–8. Of note, McLellan et al. [116] have shown directly that a subset of amyloid plaques (e.g., dense core plaques) produce ROS, that is,  $H_2O_2$ , in animal Alzheimer's models (e.g., Tg2576 APP overexpressing transgenic mice) and in human postmortem Alzheimer tissue. Wang et al. [117] found that  $A\beta_{[1-42]}$  injection in Sprague-Dawley male rats increased JNK and NF- $\kappa$ B protein levels in brain. This effect was prevented by hydrogen-rich saline implicating OS. Likewise, Mogi et al. [118, 119] showed significant increase in the levels of p53, NF- $\kappa$ B, and caspase-3 reflecting apoptosis in the Parkinsonian brain. In agreement with these human brain data, Liang et al. [120] have shown that NF- $\kappa$ B activation contributes to 6-OHDA OS-induced degeneration of dopaminergic neurons through a NF- $\kappa$ B-dependent p53-signaling pathway in rat model of PD. Interestingly, Li et al. [121] have shown that bilobalide (an active component of *Ginkgo biloba*) and the peptide inhibitor of NF- $\kappa$ B, SN50 inhibit 6-OHDA-induced activation of NF- $\kappa$ B and loss of dopaminergic neurons in rat *substantia nigra*. Muñoz et al. [122] have shown that systemic administration of NAC protects dopaminergic neurons against 6-OHDA-induced degeneration in rats. Remarkably, Braithwaite et al. [123] have shown that SP600125 inhibition of JNK provides neuroprotection in a Tg2576/PS<sup>m146L</sup> transgenic mice model of AD. To establish *in vivo* relevance of our *in vitro* findings, we showed that SP600125 increased the survival and locomotor activity of *Drosophila melanogaster* (*D. melanogaster* [124]), used as a valid model of PD [125, 126], against acute exposure to PQ [127]. Furthermore, the cannabinoid CP55,940 prolongs survival and improves locomotor activity in *Drosophila* against acute exposure to PQ [124]. We also demonstrated that pure polyphenols such as gallic acid (GA), ferulic acid (FA), caffeic acid (CA), coumaric acid (CouA), propyl gallate (PG), epicatechin (EC), epigallocatechin (EGC), and epigallocatechin gallate (EGCG) protect, rescue, and, most importantly, restore the impaired movement activity (i.e., climbing capability) induced by PQ in the fly [128]. Remarkably, PG and EGCG protected and maintained movement abilities in flies cotreated with PQ and iron [128]. Recently, Ortega-Arellano et al. [129] have demonstrated that chronic polyphenols prolong life span and restore locomotor activity of *D. melanogaster* chronically exposed to PQ compared to flies treated with PQ alone. These observations support the notion that polyphenols might be potential therapeutic compounds in the treatment of PD [130, 131]. Moreover, Bonilla-Ramirez et al., [132] have found that desferrioxamine (DFO), ethylenediaminetetraacetic acid (EGTA), and D-penicillamine chelators were able to protect but not rescue *D. melanogaster* against acute or chronic metal intoxication. Taken together, *in vitro* and *in vivo* data suggest that antioxidants (e.g., NAC [133]), polyphenols, cannabinoids, metal chelators [134], mitochondrial targeted antioxidant compounds [135, 136], pharmacological inhibition of NF- $\kappa$ B [137, 138], p53 [139, 140], JNK [141], and caspase-3 may be of therapeutic value in AD and PD.

### 3. The Good Touch of Oxidative Stress: A Perspective for Cancer Cell Death

Oxidative stress has two opposite outcomes in cancer cells: on one side, OS has been associated to initiation, promotion, progression, and maintenance of tumor cell phenotypes [26, 27]. Specifically,  $H_2O_2$  stimulates proliferation, migration, and adhesion of these cells [142–144]. However, the causative relationship of ROS increase, and oncogene activation remains unclear. On the other side, OS has been associated with antitumorogenic actions, senescence, and apoptosis [145, 146]. Strikingly, NF- $\kappa$ B has been found to play pro- and antiapoptotic roles, which might depend on the type of cell [147–151], intracellular level of ROS, induced or constitutive expression of NF- $\kappa$ B, quantity of cellular antioxidant defenses, and absence or presence of growth factors or metabolic sources (e.g., glucose). Therefore, NF- $\kappa$ B constitutes a critical molecule in cell survival/death decision. Based on our previous experience with OS mechanism and cell death, we hypothesize that cancer and neurodegeneration processes share common cellular foundations. In contrast to the unsatisfactory results of the antioxidant therapy in AD [152, 153] and PD [154], generation of ROS to kill cancer cells is currently not only an idea but has already been effective as treatment in cancer patients (e.g., procarbazine, doxorubicin, and arsenic). We reasoned that the OS mechanism depicted in the Figure 2 might be operative in both neurodegeneration and cancer processes but with opposite therapeutic approaches: while it might be used to destroy malignant cells, it might also be stopped with antioxidants or signals to retard or delay neural cell death. Concerning the former consideration, we found that low-dose (10  $\mu$ M) vitamin K3 (VK3, also known as menadione or 2-Methyl-1,4-naphthoquinone) or high-dose (10 mM) vitamin C (VC, also known as ascorbate,  $AscH^-$ ) alone or in combination induced apoptosis in Jurkat (model of acute lymphoblastic T-cell leukemia [155]) and K562 (model of myelogenous leukaemia cells) cells by OS mechanism [156]. This data provided, for the first time, *in vitro* evidence supporting a causative role for OS in VK3- and VC-induced apoptosis in Jurkat and K562 cells in a domino-like mechanism similar to the mechanism identified in lymphocytes and neuronal cells under OS (Figure 2). The VC/VK3 observations can be explained because the synthetic VK3 can be reduced via one- or two-electron transfer by intracellular reductases or by VC. The two electron reductions of VK3 to hydroquinone VK3 ( $VK3QH_2$ ) can slowly autoxidise to reform VK3. The single-electron reduction of the VK3 by  $VC^-$  ( $AscH^-$ ) gives semiquinone anion radical ( $VK3Q^{\cdot-}$ ), which in turn reduces  $O_2$  to  $O_2^{\cdot-}$  and regenerates the VK3. Consequently, redox cycling of VK3 can ensue and produce large amounts of  $O_2^{\cdot-}$ , which can dismutate via SOD to form  $H_2O_2$  and  $O_2$ . As mentioned,  $H_2O_2$  can take part in metal-catalyzed reactions to form more toxic species of active oxygen such as  $\cdot OH$ . Therefore, if the single-electron reduction pathway predominates and the rate of redox cycling of VK3 exceeds the capacity of the detoxifying enzymes (e.g., catalase, GPx, and SOD), OS occurs, ultimately triggering a specific subroutine of cell death signaling (Figure 2 and

[156]). Altogether these data suggest that VK3 and VC or any molecule capable of producing excessive amount of  $O_2^-/H_2O_2$  can be useful in the treatment of leukemia (e.g., arsenic [157], taxol [158]).

#### 4. **Dangerous Liaisons: Oxidative Stress as Central Aspect for Neurodegeneration and Cancer**

Up-to-date, >200 pathogenic mutations distributed in 3 (*Aβ amyloid precursor protein (APP)*, *presenilin-1 (PSEN1)*, *presenilin-2 (PSEN2)*), and 6 genes (*α-Synuclein (SNCA)*, *Leucine-rich repeat kinase 2 (LRRK2)*, *PARKIN*, *PTEN-induced putative kinase 1 (PINK1)*, *DJ-1*, and *P-type ATPase 13A2 (ATP13A2)*) have been conclusively shown to cause familial Alzheimer and Parkinsonism, respectively (<http://www.molgen.ua.ac.be>, reviewed in [159, 160]). Interestingly, mutations in those genes are directly related to OS and mitochondrial alterations [161, 162]. Specifically, Vinish et al. [163] have found increase in malondialdehyde content and SOD activity in peripheral blood parameters in PD patients with *PARKIN* mutations in comparison to controls. Ramsey and Giasson [164] found that the p.E163K DJ-1 mutant loses the ability to protect against OS while demonstrating a reduced redistribution towards mitochondria. Moreover, Ren et al. [165] have shown that DJ-1 protects cells against UVB-induced cell death dependent on its oxidation and its association with mitochondrial Bcl-X(L). Heo et al. [166] have shown that the p.G2019S mutation in *LRRK2* generates  $H_2O_2$  and induces neurotoxicity via its kinase activity. Last, the Butterfield's group has shown that mutation in *APP* and *PSEN1* (e.g., *APP<sup>NLH</sup>/PS-1<sup>P264L</sup>* mice) induces brain OS [167, 168]. Taken together, these data support the notion that environmental and genetic pathways converge in the pathogenesis of AD [169] and PD [170–172]. It is interesting to note that iron accumulation is linked with the brain pathology in AD [55] and familial PD [56, 57]. These observations suggest that iron might play a toxic role in the pathophysiology of both neurologic disorders [173, 174], most probably linked to a common molecular mechanism of cell death via generation of intermediate ROS and mitochondrial damage [97, 175, 176]. Therefore, it is not unusual that PD patients develop dementia [164, 177, 178] concomitantly with AD pathology [179]. Moreover, recent data suggest that exposition to ethacrynic acid, a compound that induces cellular glutathione (GSH) depletion therefore causing OS, increases presenilin-1 protein levels in human neuroblastoma SH-SY5Y cells [180]. Furthermore, the  $\gamma$ -secretase protein complex mediates OS-induced expression of  $\beta$ -site APP cleaving enzyme I (BACE1) resulting in excessive  $A\beta$  production in AD [181]. Remarkably, extensive analysis of the effects and interactions of the AD [182, 183] and PD [184, 185] pathogenic genes in *D. melanogaster* has shown that mutations in *parkin* [186, 187], *pink-1* [188], *α-synuclein* [189], *Lrrk* [190] genes, or overexpression of normal *α-synuclein* [189] cause death of dopaminergic neurons in *Drosophila* probably via OS [166, 191–195]. Accordingly, it has been shown that DJ-1 and *parkin* are

essential for mitochondrial function and rescue *pink-1* loss of function [196, 197]. Since these genes are conserved in invertebrates (insects) and vertebrates (mammals) [198], we believe that *D. melanogaster* could provide new insights into the relationship between gene mutations, OS, and mitochondria [184]. Taken together, these data suggest that OS is at the pathobiological basis of PD and AD and that its generation and detrimental effects can be exacerbated by environmental factors and mutation in causative genes.

Surprisingly, epidemiological studies have consistently shown the cooccurrence of PD and melanoma [199, 200] and this association is strongly increased by mutations in *PARKIN*, *LRRK2*, and *α-Synuclein* (for a review, see [201]). Moreover, Veeriah et al. [202] have shown that point mutations and exon rearrangements of *PARKIN* are linked to glioblastoma multiform, colon cancer, and lung cancer. Although, the exact mechanism(s) underlying the observed cancer-PD association is not clear, it has been suggested that genes (e.g., *PARKIN*) that cause neuronal dysfunction when mutated in the germline may instead contribute to oncogenesis when altered in nonneuronal somatic cells [202]. Whether OS is involved in these malignancies needs further investigation. However, based on the assumption that cancer and neurodegeneration share some of the same genes and molecular mechanisms of OS-induced cell death, one may anticipate a positive correlation between OS, cancer and PD. Recently, Zhang et al. [203] have found that Parkin is a p53 target and Parkin contributes to the role of p53 in regulating antioxidant defense. Indeed, ectopic Parkin expression significantly reduced ROS levels in H460p53siRNA treated with or without  $H_2O_2$ . Simultaneous knockdown of p53 and Parkin results in higher intracellular ROS levels than individual knockdown of p53 and Parkin. Moreover, ectopic Parkin expression significantly increased GSH (reduced) levels, thus altering the GSH:GSSG (oxidized) ratio in human lung cancer line, H460p53siRNA. Interestingly, Parkin knockdown in H460 (control) cells and Parkin knockout in mouse embryonic fibroblast (MEF) cells significantly decreased GSH levels and the GSH:GSSG ratio. Given that Parkin has also been reported to repress p53 [204], together these data suggest that the regulation of Parkin by p53, or vice versa, could be cell type or tissue specific. Further investigation is warranted in this topic.

#### 5. **Oxidative Stress: Quo Vadis?**

In conclusion, there is enough support evidence for the role of OS in AD, PD, and cancer. Clearly, the relationships between some causative genes of Parkinson's such as *PARKIN* and *LRRK2* and cancer will challenge the medical research for designing new therapeutic approaches and the necessity to bring new proposals of unified models of disease and molecular mechanisms. In this respect, the model of minimal completeness of cell death induced by  $H_2O_2$  (see Figure 2, steps 2–8) might provide a platform to evaluate new natural or synthetic antioxidants, pharmacological agents which target the mitochondria, transcription factor(s), and/or caspase-3, or it simply might be used as a model to test other novel hypothesis (e.g., [205, 206]). In this regard,

plant polyphenols has been suggested as promising compounds for the prevention of neurodegenerative diseases and treatment of cancer (For reviews see [130, 207–209]). Yet, whether polyphenols might function as effective antioxidant compounds *in vivo* is still a controversial issue [210–213]. One of the most urgent issues is to clarify the many studies reported to show failed clinical benefit or persuasive evidence of neuroprotection [214]. Most importantly, we will need to definitely establish the molecular mechanism(s) of cell death in neurodegenerative disorders before novel treatments can be available. Undoubtedly, there are still many unresolved issues. Perhaps, studying the biology of cancer cells might provide understanding of the underlying pathogenic mechanisms of cell death in neurodegeneration and help developing new treatment strategies.

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