

## Review Article

# Oxidative Stress and Mitochondrial Dysfunction across Broad-Ranging Pathologies: Toward Mitochondria-Targeted Clinical Strategies

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Beyond the disorders recognized as mitochondrial diseases, abnormalities in function and/or ultrastructure of mitochondria have been reported in several unrelated pathologies. These encompass ageing, malformations, and a number of genetic or acquired diseases, as diabetes and cardiologic, haematologic, organ-specific (e.g., eye or liver), neurologic and psychiatric, autoimmune, and dermatologic disorders. The mechanistic grounds for **mitochondrial dysfunction (MDF)** along with the occurrence of **oxidative stress (OS)** have been investigated within the pathogenesis of individual disorders or in groups of interrelated disorders. We attempt to review broad-ranging pathologies that involve mitochondrial-specific deficiencies or rely on cytosol-derived prooxidant states or on autoimmune-induced mitochondrial damage. The established knowledge in these subjects warrants studies aimed at elucidating several open questions that are highlighted in the present review. **The relevance of OS and MDF in different pathologies may establish the grounds for chemoprevention trials aimed at compensating OS/MDF by means of antioxidants and mitochondrial nutrients.**

## 1. Introduction

Mitochondria have long been recognized as the main site of bioenergetic pathways [1, 2]. After the early investigations on OS in 1980s, implications for an involvement of mitochondria in OS were found in early 1990s [3, 4], which associated MDF with OS in the pathogenesis of some diseases, such as mitochondrial myopathies (progressive external ophthalmoplegia) and Parkinson's disease [5, 6]. Those early studies opened multiple research avenues toward growing and currently

thriving investigations in a number of diseases, or disease groups, pertaining different medical disciplines. Beyond the focus on individual pathologies, or limited groups of diseases sharing molecular or clinical affinities, the present review is aimed at attempting a survey of OS/MDF across a broader range of different disorders that have been investigated for the occurrence of OS/MDF as pathogenetic mechanisms either directly or concomitant with other inborn or exogenous causes of disease.

## 2. Mitochondrial Diseases

A number of studies led to identifying a set of different disorders affecting mitochondrial function and/or structure that are collectively termed mitochondrial diseases (MDs) [7]. As shown in Table 1, primary mitochondrial diseases (PMDs) are caused by mitochondrial DNA (mtDNA) defects, while secondary mitochondrial diseases (SMDs) are caused by defects of nuclear genes encoding mitochondrial (or mitochondria-related) proteins [8]. In both cases, MDs have been associated with different deficiencies in mitochondrial functions and evidence has been reported for prooxidant states as clinical and/or molecular OS hallmarks [9–34]. Endogenous MDF in PMDs has been shown to affect oxidative phosphorylation (OXPHOS) activities in PMDs (Complex I, III, and/or IV), as in mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS) [15–19], Kearns-Sayre syndrome [23], chronic progressive external ophthalmoplegia (CPEO) [24, 25], and Pearson syndrome [26, 27]. An overall OXPHOS inhibition has also been observed in SMDs, as Alpers-Huttenlocher syndrome, along with polymerase  $\gamma$  mutations [28–31]. Implications for OS in these disorders have been reported in terms of COQ2 gene defect, encoding for OH-benzoate polyprenyltransferase catalyzing a major step in coenzyme Q10 synthesis. As a result, lower-than-normal CoQ10 levels were observed in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), a SMD and CoQ10 deficiency syndrome, a rare condition that causes MDF and includes a variety of clinical presentations as encephalomyopathy, ataxia, and renal failure [32, 33]. Protective effects of either CoQ10 or of other antioxidants were detected in Leber's hereditary optic neuropathy (LHON) [9–11], Leigh syndrome [12], neuropathy, ataxia, retinitis pigmentosa and ptosis (NARP) [14], MELAS [18, 19], and maternally inherited diabetes mellitus and deafness (MIDD) [22].

Altogether, MDs are recognized to involve the respiratory chain, both controlled by nuclear DNA and mtDNA. Mendelian mitochondrial defects can affect subunits of respiratory chain complexes, mitochondrial assembly proteins, mtDNA translation, phospholipid composition of the inner mitochondrial membrane, or mitochondrial dynamics or involve mtDNA maintenance, combining features of mendelian and mitochondrial genetics [34].

Beyond MDs, a broad and growing number of disorders have been investigated for the implications of OS in their respective pathogenetic mechanisms with concurrent involvement of MDF. Unlike strictly termed MDs, in most cases the available implications of MDF are indirect, relying on surrogate indicators, such as decreased levels of mitochondrial cofactors, or altered mitochondrial membrane potential ( $\Delta\Psi$ ), or increased lactate/pyruvate ratio, or secondary mitochondrial damage as, for example, due to iron overload or to antimitochondrial autoantibodies. Even so, the range of MDF covers an extensive number of disorders that associate OS/MDF in their pathogenetic mechanisms, as reported previously for several disorders or groups of interrelated disorders and discussed below in the present review.

## 3. Genetic Diseases

A number of genetic diseases (GDs) have been investigated for the implications of OS/MDF in their pathogenesis, as summarized in Table 2 [35–101]. The broad range of GDs investigated in this context includes a set of cancer-prone and/or ageing-related disorders and a number of GDs affecting various tissues and organs, including CNS, blood, and muscles.

**3.1. Cancer-Prone and/or Early Ageing Diseases.** These GDs are characterized by an enhanced risk of malignancies that are often more prevalent in a given disorder (e.g., myeloid leukaemias in Fanconi anaemia, FA), and many of these GDs exhibit propension to early ageing, which either affects the whole organism (progerias, e.g., Werner syndrome, WS) or is confined to given tissues, such as bone marrow impairment or neurodegeneration. A huge body of literature, omitted in the present review, associates this disease group with deficiencies in DNA repair, and the majority of research efforts—and most of funding resources—have been deployed to investigate these GDs within the theorem of DNA repair deficiency, in view of planning gene therapy protocols.

In the case of Down syndrome (DS), the trisomic condition has been viewed beyond any effort of genetic engineering, and any therapeutic approach has been mostly confined to psychological and physical rehabilitation.

The involvement of OS in this disease group has been reported since early studies in 1980s finding redox abnormalities in cells from patients with DS [53], ataxia-telangiectasia (AT) [39], or FA [54]. As for mitochondrial abnormalities, a substantial body of literature has accrued for the implications of MDF in this group of diseases (see below); thus the occurrence of OS and MDF has been documented in cellular, molecular, and animal studies and by *in vivo* evidence from human patients.

**3.1.1. Ataxia-Telangiectasia.** An established body of literature relates AT pathogenesis both with OS since 1983 [39] and with MDF. Evidence was provided for excess ROS production and oxidative DNA damage, and for mitochondrial abnormalities including ultrastructure aberrations, decreased  $\Delta\Psi$  and mitophagy, and increased expression of respiratory enzymes in AT cells [35–39].

**3.1.2. Bloom Syndrome.** Early studies suggested the occurrence of OS in Bloom syndrome (BS) [40, 41]. We have previously reported excess oxidative DNA damage (8-hydroxy-2-deoxyguanosine, 8-OHdG) in WBC from BS patients, with an unexpected decrease in glutathione disulfide: glutathione (GSSG:GSH) ratio [42]. No reports were found to be evaluated regarding any MDF in BS phenotype, and this subject warrants *ad hoc* investigations.

**3.1.3. Cockayne Syndrome.** Cockayne syndrome (CS) phenotype displays a set of OS hallmarks, such as excess reactive oxygen species (ROS) production and DNA oxidative damage, along with decreased 8-oxoguanine DNA glycosylase-1 (OGG1) expression [43, 44]. Mitochondrial abnormalities

TABLE 1: Mitochondrial dysfunction (MDF) and/or oxidative stress (OS) in some selected mitochondrial diseases.

	MDF/OS endpoints	References
<b>Primary mitochondrial DNA-related diseases</b>		
Leber's hereditary optic neuropathy (LHON)	mtDNA point mutations; Idebenone- and EPI-743-induced protection	[9–11]
Leigh syndrome, subacute necrotizing encephalomyelopathy	mtDNA point mutations; EPI-743-induced protection	[12]
Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP)	↓ ATP synthase activity, ↑ ROS; ↑ p66Shc phosphorylation; antioxidants-induced protection	[13, 14]
Mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS)	mtDNA Point Mutations; ↓ Complex I, III And IV, ↑ Free radicals in CSF, CoQ10-induced protection	[15–19]
Myoclonic epilepsy with ragged red fibers (MERRF)	mtDNA point mutations; ↓ ATP, ↑ Matrix metallo-proteinase 1; ↑ ROS, ↑ carbonylated mt proteins	[20, 21]
Maternally inherited diabetes mellitus and deafness (MIDD)	mtDNA point mutations; CoQ10-induced protection	[22]
Kearns-Sayre syndrome (KSS)	mtDNA deletions; ↑ Myoglobin and antioxidant enzymes mtDNA deletions with cyt-c oxidase-deficient cells and loss of mitochondrial respiratory chain subunits	[23]
Chronic progressive external ophthalmoplegia (CPEO)	mtDNA deletions and point mutations; ↓ Complex I and IV; ↑ OS biomarkers; tetracycline-induced antioxidant protection	[24, 25]
Pearson syndrome	mtDNA deletions; ↓ OXPHOS, iron overload	[26, 27]
<b>Secondary mitochondrial DNA-related diseases</b>		
Alpers-Huttenlocher Syndrome	Pol $\gamma$ mutations; ↓ OXPHOS; mtDNA deletions/depletion	[28–31]
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Thymidine phosphorylase mutation; mtDNA deletions ↓ CoQ10 levels	[32, 33]

TABLE 2: Genetic diseases displaying OS/MDF hallmarks.

Genetic diseases	OS/MDF-related Endpoints	References
<b>Cancer-prone and/or early ageing diseases</b>		
Ataxia-telangiectasia	↑ ROS production; abnormal mt structure; ↓ ΔΨ; ↑ mt enzymes; ↓ mitophagy	[35–39]
Bloom syndrome	↑ ROS production; antioxidant sensitive; ↑ WBC 8-OHdG	[40–42]
Cockayne syndrome	↓ OGG1; ↑ ROS production; ↑ DNA oxidative damage; ↑ mitophagy defective CSA and CSB localize to mt → ↓ interaction with mt OGG1	[43–46]
Down syndrome	↑ ROS production; affected mt structure; defective Complex I activity; ↓ CoQ10 lymphocyte and platelet levels; sensitive to CoQ10	[47–52]
Fanconi anaemia	↑ ROS production; ↑ 8-OHdG; ↓ GSH:GSSG; ↑ methylglyoxal; antioxidant sensitive; redox functions of FANC proteins; downregulation of antioxidant, chelating and stress proteins; ↓ ATP; ↓ ΔΨ; ↓ Prdx3; abnormal mt structure	[54–60]
Hutchinson-Gilford syndrome	↑ ROS production; ↑ SOD-2 transcript; ↓ ATP content; ↓ caspase-like proteasome activity; NAC sensitive	[61, 62]
Nijmegen breakage syndrome	PARP hyperactivation and ↑ ROS production; ↓ mt p53 translocation	[63, 64]
Rothmund-Thomson syndrome	RECQL4 response to OS; RECQL4 interaction with PARP-1 and p53	[65–67]
Werner Syndrome	WRN regulates HIF-1 activation inducing mt ROS; ↑ OS; abnormal mt structure	[68–72]
Xeroderma pigmentosum	↓ repair of cyclo-dA; ↑ lipid peroxidation and protein glycation; ↓ CoQ serum levels; defective mt gene transcripts for 16 S rRNA, ATPase 6L and lactate dehydrogenase	[73–77]
<b>Neurological and muscle genetic diseases</b>		
Adrenoleukodystrophy	↑ mtDNA oxidation and impaired OXPHOS; ↓ complex V; ↓ GSH; ↑ GSSG ↓ total antioxidant defenses in symptomatic but not in asymptomatic patients; mitochondrial inner membrane potential dissipation; ↓ ATP ATP/ADP ratio; abnormal mt ultrastructure; dysregulated Fe metabolism	[78–82]
Duchenne Muscular Dystrophy	↑ protein thiol oxidation; ↑ lipofuscin; ↑ 4-hydroxynonenal; ↑ total hydroperoxides; uncoupled OXPHOS; ↓ maximal ATP synthesis; ↓ γ-glutamyl cysteine ligase and GSH	[83–85]
Friedreich Ataxia	↓ complex I, II and III; ↓ aconitase; ↓ CoQ10 and Vit E; ↓ Fe-S cluster biosynthesis; mt Fe overload and cellular Fe dysregulation; ↑ sensitivity to OS	[86–88]
Huntington's Disease	CoQ10-induced ↓ brain protein carbonyls; ↑ NADPH oxidase (NOX) activity in human HD brains; CoQ10 + creatine exert additive neuroprotective effects in HD mice and rats	[89–92]
<b>Other Genetic Diseases</b>		
Hyperhomocysteinaemia	↑ MDA levels and carbonyl formation; ↓ sulfhydryl groups and total antioxidant status; ↓ ΔΨ; release of cytochrome-c; ↑ mt matrix metalloproteinase	[93–95]
Sickle Cell Disease	↑ ROS production; ↑ advanced glycation end products (AGEs); ↓ GSH Iron-laden mt in WBC	[96–98]
Thalassaemia	Non-transferrin-bound iron (NTBI) → damage to mitochondria, lysosomes, lipid membranes, proteins, and DNA; ↑ WBC 8-OHdG; ↓ ΔΨ; ↓ carnitine	[99–101]

consisted of excess mitophagy [45], and Kamenisch and Berneburg found that defective CSA and CSB proteins localize to mitochondria, by decreasing interaction with mitochondrial OGG1 [46].

**3.1.4. Down Syndrome.** Down syndrome (DS) represents one of the best documented GDs for the established implications of both OS and MDF in DS phenotype, both *in vitro* and *in vivo*, namely, human trisomy 21 patients and murine DS models, such as trisomy 16 [47–52]. Since the pioneering studies dating back to 1980s [53], DS phenotype has been associated with **Cu,Zn-superoxide dismutase (SOD-1)** overexpression. Thus the ratio SOD-1 to catalase (CAT) plus glutathione peroxidase (GPx) is increased; hence more hydrogen peroxide is generated by SOD-1 than CAT and GPx can catabolize, giving rise to an OS positive feedback. Valenti et al. [50, 51] investigated skin fibroblasts from DS patients, finding excess ROS production along with a deficiency in Complex I activity with the involvement of the cAMP/PKA signalling pathway [50]. This group also reported that epigallocatechin-3-gallate prevents OXPHOS deficit while promotes mitochondrial biogenesis in DS fibroblasts [51]. Other authors reported on MDF in DS, affecting Krebs cycle activities, CoQ10 deficiency and mitochondrial ultrastructure in human DS cells and in human patients [48, 49], and in trisomy 16 mice [52].

**3.1.5. Fanconi Anaemia.** Fanconi anaemia (FA) has been associated with redox imbalances since early studies including, among others, the pioneering report by Joenje et al. [54]. Thereafter, a growing body of literature has established a number of mechanistic implications of OS in the functions of several proteins encoded by FA genes, as well as by *in vitro* and animal studies, and in blood cells and biological fluids from FA patients (reviewed in [55, 56]). Three independent studies of MDF in FA cell lines of different genetic subtypes provided evidence for abnormal ultrastructure and function of mitochondria in FA cells [57–59]. Our recent report on bone marrow cell transcripts from FA patients revealed downregulation of genes involved in mitochondrial functions, antioxidant activities, heat shock proteins, and chelating proteins [60]. Thus, the role in the FA phenotype of OS/MDF may be considered well established and awaits consequent interventions in clinical management, in view of preventing or delaying disease progression.

**3.1.6. Hutchinson-Gilford Syndrome.** Hutchinson-Gilford syndrome (HGS) is a progeria displaying excess ROS production, and increased mRNA levels and protein content for mitochondrial Mn superoxide dismutase (SOD-2), along with a drop in the ATP (50%) content of HGS fibroblasts *versus* controls. Moreover, HGS cells showed defective caspase-like proteasome activity, and DNA damage was prevented by N-acetyl cysteine [61, 62].

**3.1.7. Nijmegen Breakage Syndrome.** Nijmegen breakage syndrome (NBS) features oxidative DNA damage resulting in mitochondrial p53 accumulation and resistance to apoptosis, and in poly (ADP-ribose) polymerase (PARP) hyperactivation resulting in NAD<sup>+</sup> depletion [63, 64]. Krenzlin et al.

attributed the “extremely high incidence of malignancy among NBS patients to the combination of a primary double-strand break repair deficiency with secondary oxidative DNA damage” [64].

**3.1.8. Rothmund-Thomson Syndrome.** Rothmund-Thomson syndrome (RTS) gene product RECQL4 localizes to the nucleolus in response to OS. RTS fibroblasts exhibit increased OS-related p38 MAP kinase; thus cell lifespan and growth rate are increased by p38 MAP kinase inhibitor [65, 66]. Moreover, RECQL4 was found to localize to mitochondria, and the loss of RECQL4 alters mitochondrial bioenergetics as mitochondrial reserve capacity was depressed after RECQL4 knockdown [67].

**3.1.9. Werner Syndrome.** Werner syndrome (WS), also termed “adult progeria” due to its late phenotypic onset, has been extensively investigated for its relationships with OS [68–70], and we reported the multiple involvements of the defective WRN protein both in DNA stability and in redox balance [70]. Mitochondrial ultrastructure anomalies were found in cells from the WS mouse model, Wrn helicase mutant mice (Wrn<sup>Dhel/Dhel</sup>) [68, 71]. Alterations in OS endpoints were detected in blood cells and biological fluids from WS patients to the highest extent compared to patients with other OS-related diseases and *versus* healthy donors [72].

**3.1.10. Xeroderma Pigmentosum.** Xeroderma pigmentosum (XP) displays several OS features, including defective repair of DNA oxidative damage (8,5'-*(S)*-cyclo-2'-deoxyadenosine), while lipid peroxidation and protein glycation are increased in cells and brains from XP patients, along with reduced expression of SOD [73]. Mitochondrial abnormalities were exhibited in terms of defective mitochondrial gene transcripts for 16 S rRNA, ATPase 6L, and lactate dehydrogenase; moreover, lower-than-normal CoQ10 levels were observed in serum from XP patients [74–77].

## 3.2. Neurological and Muscle Diseases

**3.2.1. Adrenoleukodystrophy.** This genetic disease is characterized by progressive neurologic motor impairment and displays a set of OS-related defects. OS markers include decrease in GSH:GSSH ratio, excess lipid oxidation, and decrease in total antioxidant defenses in symptomatic but not in asymptomatic patients [78–80]. MDF was found to include impairment in OXPHOS activities and a decrease in Complex V, along with decreased ATP levels; moreover, mitochondrial inner membrane potential dissipation was reported [81]. A recent report found OXPHOS disruption and mitochondrial depletion in ABCD1 null mouse, a mouse model for adrenomyeloneuropathy [82].

**3.2.2. Duchenne Muscular Dystrophy.** Duchenne muscular dystrophy (DMD) displays a set of OS hallmarks in terms of increased protein thiol oxidation, lipofuscin, 4-hydroxynonenal (4-HNE), and total hydroperoxides, with decreased GSH, in cells and biological fluids from DMD

patients [83, 84]. A concomitant MDF was suggested by impaired OXPHOS activities and decrease in ATP synthesis in the mdx mouse model for DMD [85].

**3.2.3. Friedreich Ataxia.** Friedreich ataxia displays a number of MDF features, including decreased Complex I, II, and III, aconitase, and CoQ10 levels, with mitochondrial Fe overload [86, 87]. A concomitant OS condition was shown by decreased vitamin E levels, Fe dysregulation, and hypersensitivity to OS [88].

**3.2.4. Huntington's Disease.** Huntington's disease (HD) displays excess levels of brain protein carbonyls that are decreased by CoQ10 administration [89]. Moreover, CoQ10 and creatine exert additive neuroprotective effects in HD mice and rats. Evidence for MDF was provided by finding excess NADPH oxidase (NOX) activity in human HD brains, parallel with synaptosome fractions from cortex and striatum of HD (140Q/140Q) mice, suggesting that increased NOX2 activity at lipid rafts is an early and major source of OS and cell death in HD (140Q/140Q) neurons [89–92].

### 3.3. Other Genetic Diseases

**3.3.1. Hyperhomocysteinaemia.** The set of dysmetabolic defects in hyperhomocysteinaemia (HHC) both include MDF and OS [93–95]. Evidence for MDF was provided by decreased  $\Delta\Psi$ , release of cytochrome-c and by increase in mitochondrial matrix metalloproteinase [93, 94]. Implications of OS in HHC phenotype were shown by a decrease in sulfhydryl groups and total antioxidant status in plasma from HHC patients [95].

**3.3.2. Sickle Cell Disease.** Sickle cell disease (SCD) is mainly characterized by sickle erythrocyte haemolysis resulting in excess free Fe release that, as such, triggers OS. Thus, excess ROS production and advanced glycation end products (AGEs) were observed, with a concomitant GSH decrease [96, 97]. An early paper reported on Fe-laden mitochondria in sickled reticulocytes from SCD patients [98], and that early observation warrants further up-to-date investigations.

**3.3.3. Thalassaemia.** Thalassaemic patients showed oxidative damage to lipid membranes, proteins, and DNA (WBC 8-OHdG) [99]. Mitochondrial damage was found to be induced by non-transferrin-bound Fe, resulting in decreased  $\Delta\Psi$  [100]. The observation of lower-than-normal levels of l-carnitine also might be related to MDF [101].

## 4. Ageing and Ageing-Related Degenerative Disorders

**4.1. Ageing.** Ageing is not regarded as a disease per se; however several diseases have been associated with ageing, as summarized in Table 3. Extensive and multi-decade-long literature relates ageing to OS and MDF. As a brief selection of this vast body of evidence, OS and **nitrosative stress (NS)** hallmarks were shown by excess age-related oxidative DNA damage, decreased GSH : GSSG ratio, **increased inducible**

**NOS (iNOS) expression**, and Fe accumulation [102–104]. A major focus on age-related MDF has resulted in an established body of evidence including, among others, MDF related to decrease in both OXPHOS activities (Complexes I and IV) and Krebs cycle (downregulated pyruvate dehydrogenase along with overexpressed pyruvate kinase and lactate dehydrogenase). Moreover, Prdx3 overoxidation and mtDNA damage were reported [105–107].

**4.2. Cardiovascular Diseases.** Also cardiovascular diseases (CVDs) have been broadly investigated—since early studies—for the implications of OS/MDF in their pathogenesis. Double-edged physiopathological roles for ROS and reactive nitrogen species (RNS) are recognized, both as mediators of cardiovascular functions and as effectors of cardiovascular tissue damage [108, 109]. Among the best recognized OS/NS hallmarks, excess lipid and protein oxidation, altered NADPH regulation, and peroxynitrite formation have been reported [108, 109]. Well-established implications of MDF are available for CVDs, including reports on mitochondrial aberrations, SOD-2 upregulation, and mtDNA mutations in atherosclerotic plaques [110–113].

**4.3. Metabolic Syndrome.** Extensive evidence for OS/MDF implications in metabolic syndrome has been accumulating in recent years [114–119]. Evidence for OS-related changes was provided by excess TBARS and plasma 8-isoprostanes, along with decrease in total antioxidative activity and in serum vitamins C and E. An involvement for MDF in these disorders was found by downregulated Complex I, NADPH oxidase, and in SIRT3, leading to excess mitochondrial protein acetylation; also observed was a decreased mtDNA copy number and dysregulated carnitine palmitoyltransferase [114–119].

**4.4. Osteoarthritis.** Osteoarthritis (OA) features a number of OS hallmarks, as **decreased total antioxidant capacity**, thiol levels, catalase activity, and prolidase activity, along with **increased total peroxides and lipid peroxides, and myeloperoxidase overexpression** [120]. Evidence for MDF in OA patients was shown by downregulated SOD-2 and Complexes I, II, and III, and by mitochondrial genome dysregulation, with 17 upregulated and 9 downregulated genes [121–124].

**4.5. Diabetes.** Type 2 diabetes has been extensively investigated for its pathogenetic implications of OS/MDF. Diabetic patients displayed excess oxidation of proteins, lipids, and DNA, that is, increased levels of 15-F2t-iso-prostaglandin and 4-HNE, as products of lipid oxidation, and advanced oxidation protein products, advanced glycation end products (AGEs), excess oxidative DNA damage (8-OHdG), upregulated NADPH oxidase, Trx and HSP70, and decreased GSH : GSSG ratio [125–128]. Downregulation of Complex I and/or IV, and of SOD-2 point to MDF occurrence in diabetic patients [129–133]. It should be recalled that Type 2 diabetes occurs as a secondary clinical feature in some OS/MDF-related pathologies, such as the mitochondrial disease, MELAS [17], and genetic diseases, as Fanconi anaemia [55] and Werner syndrome [71].

TABLE 3: Ageing and ageing-related degenerative disorders displaying OS/MDF hallmarks.

Diseases	OS/MDF hallmarks	References
Ageing	Age-related ↑ oxidative DNA damage and ↓ GSH : GSSG ratio; ↑ Fe accumulation; impaired mt function related to ↓ complex I and IV; overoxidized Prdx3; mtDNA damage ↓ pyruvate dehydrogenase; ↑ pyruvate kinase and lactate dehydrogenase	[102–107]
Cardiovascular diseases	lipid and protein oxidation; NADPH oxidase dysregulation; ↑ peroxynitrite; mt damage and dysfunction; endothelial dysfunction, with ↓ NO bioactivity; ↑ SOD-2 and mtDNA mutations in atherosclerotic plaques	[108–113]
Metabolic syndrome	↑ plasma 8-isoprostanes; ↓ total antioxidant capacity; ↓ serum Vit C and E; ↑ TBARS; ↓ complex I; ↑ NADPH oxidase; downregulated SIRT3 leading to ↑ mt protein acetylation; Nod-like receptor protein 3 (NLRP3) activation; ↓ mtDNA copy number; ↓ paraoxonase-1; dysregulated carnitine palmitoyltransferase	[114–119]
Osteoarthritis	↓ total antioxidant capacity, thiol levels, catalase activity and prolidase activities; ↑ total peroxides and lipid peroxides, ↑ myeloperoxidase; mt genome dysregulation (17 up- and 9 downregulated mt genes); ↓ complexes I, II and III; ↑↓ SOD-2	[120–124]
Type 2 diabetes mellitus	↑ 15-F2t-IsoP and AOPP; ↑ HNE, Trx and HSP70; ↓ GSH:GSSG; ↑ 8-OHdG and protein carbonyls in saliva; ↑ NADPH oxidase; ↓ complex I and/or IV; ↑ SOD-2 and TrxR3 in platelets; ↑ NO and S-nitrosylation	[125–133]

## 5. Neurologic and Neuropsychiatric Diseases

The relevance and implications of MDF and OS has been investigated in a number of CNS-related diseases, as summarized Table 4. Disease-specific abnormalities in terms of OS/MDF are highlighted below.

### 5.1. Neurologic Diseases

**5.1.1. Alzheimer's Disease.** Alzheimer's disease (AD) is characterized by  $\beta$ -amyloid deposition as a major neuropathological hallmark, which is related to a complement of OS-related alterations, such as oxidative damage to DNA, RNA, proteins, and lipids in synapses. Moreover, CoQ10 and MitoQ decrease OS endpoints and Fe metabolism in AD cells [134–136]. Concomitant MDF relates to OXPHOS alterations, that is, loss of Complex IV, and Complex V is oxidatively damaged and functionally altered. Mitochondria-associated ER membranes were found to be significantly increased in AD cells [134–139]. A recent paper reported on the 4-HNE-induced oxidation of lipoic acid that, in turn, affects lipoamide dehydrogenase, whose expression is significantly decreased in brains from human AD patients and from AD mice [138]. Zarrouk et al. [140] reported lipid alterations in AD patients that related to peroxisomal dysfunctions, via a cortical accumulation of saturated very long chain fatty acids (VLCFA), substrates for peroxisomal  $\beta$ -oxidation. This study investigated the effects at the mitochondrial level of VLCFAs that were tested on human neuronal SK-NB-E cells and found an inhibition of cell growth and mitochondrial dysfunctions that were observed by cell counting with trypan blue, MTT assay, and measurement of  $\Delta\psi$ . VLCFA-treated-cells displayed stimulation of OS, along with lower levels of mitochondrial Complexes III and IV, changes of the cytoplasmic distribution of mitochondria, presence of large mitochondria, and enhancement of the mitochondrial mass [140]. The key involvement of peroxisomes in AD was reported by Kou et al. [141] in human postmortem brains; the patients were grouped into three cohorts of increasing severity (stages I-II, III-IV, and V-VI, resp.), based on the neuropathological Braak staging for AD on one hemisphere. Lipid analyses of cortical regions from the other hemisphere revealed accumulation of C22:0 and VLCFA, C24:0 and C26:0, all substrates for peroxisomal  $\beta$ -oxidation, in cases with stages V-VI pathology compared with those modestly affected (stages I-II). Confocal laser microscopy demonstrated a loss of peroxisomes in neuronal processes with abnormally phosphorylated tau protein, implicating impaired trafficking as the cause of altered peroxisomal distribution. These findings pointed to peroxisome-related alterations in AD, which may contribute to the progression of AD pathology [141].

**5.1.2. Amyotrophic Lateral Sclerosis.** Amyotrophic lateral sclerosis (ALS) features a set of OS/MDF hallmarks. Familial ALS accounts for approximately 10% of cases and is associated with mutations of the gene encoding SOD-1 [142–144]. Abnormalities were found in endoplasmic reticulum proteins, with modifications of the Golgi network [143, 144].

Moreover, a decrease was reported in WBC glutathione peroxidase, SOD-1 and NADPH oxidase, and dysregulated Fe metabolism. MDF was detected in terms of decreased Complex I and ATP/ADP ratio and abnormal mitochondrial ultrastructure [144–146].

**5.1.3. Epilepsy.** Epilepsy features NF $\kappa$ B-induced upregulation of NOS II gene expression with NO-,  $\cdot\text{O}_2^-$ , and ONOO $^-$ -dependent decrease of Complex I activity and increased Complex-III-dependent  $\cdot\text{O}_2^-$  production of epileptic brain mitochondria; seizure-related ROS formation and a **protective effect of acetyl-L-carnitine** indicate concomitant OS in epilepsy [147–150]. Decrease of lipoic acid synthetase suggests inhibition of Krebs cycle along with defective mitochondrial energy metabolism [149].

**5.1.4. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.** Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) both display OS and MDF hallmarks. Patients with ME/CFS showed excess urinary 8-OHdG, plasma lipid peroxides and serum oxidized LDL and decreased vitamin C, along with decreased vitamin E and HSP70. Mitochondria from ME/CFS patients displayed lower-than-normal CoQ10 levels, whereas ATP production was increased, and Complexes I, III, and IV activities were overexpressed [151–156].

**5.1.5. Multiple Sclerosis.** Multiple sclerosis displays a number of OS hallmarks, such as increased WBC luminol-dependent chemiluminescence, carbonyl protein and MDA, nitric oxide metabolites, and total antioxidant capacity [157, 158]. Melatonin induced increased SOD and GPx and decreased MDA levels. The occurrence of MDF was shown by decreased OXPHOS activity and by mtDNA deletions and reduced PGC-1 $\alpha$ , a transcriptional coactivator and master regulator of mitochondrial function [158–160].

**5.1.6. Parkinson's Disease.** A pioneering report by Di Monte et al. in 1992 suggested a link between the observation of decreased GSH levels in Parkinson's disease and MDF [6]. More recent studies have found a number of altered OS-related endpoints, namely, excess plasma F2-isoprostanes, hydroxyeicosatetraenoic acid products, cholesterol oxidation products, neuroprostanes, phospholipase A2 and platelet activating factor-acetylhydrolase activities, urinary 8-OHdG, and dysregulated Fe metabolism [161, 162]. Evidence for MDF was provided by observations of decreased Complex V and CoQ10 levels, enhanced oxidation of cysteine residues within Complex I, and excess lactate [163–165].

### 5.2. Psychiatric Diseases

**5.2.1. Autistic Spectrum Disorders.** Autistic spectrum disorders (ASD) include a group of paediatric and adolescent diseases that display a number of OS and MDF hallmarks. Extensive evidence for OS and NS in cells and biological fluids from ASD patients was reported by several independent studies, including decreased GSH : GSSG ratio in WBC and

TABLE 4: Neurologic and neuropsychiatric diseases displaying OS/MDF hallmarks.

Diseases	OS/MDF hallmarks	References
A. neurologic diseases		
Alzheimer's Disease	Aberrations in OXPHOS and Krebs cycle; altered mt-associated endoplasmic reticulum membranes as related to amyloid precursor protein; dysregulated Fe metabolism; HNE- induced oxidation of lipoic acid; ↓ lipoamide dehydrogenase in brain of AD patients and of AD mice; ↓ Complexes III and IV; ↑ mitochondrial mass	[134–141]
Amyotrophic lateral sclerosis	protein misfolding at endoplasmic reticulum (ER); altered Golgi network; oxidative damage to ER proteins; ↓ WBC glutathione peroxidase; ↓ SOD-1 related to disease progression; ↓ NADPH oxidase; ↓ complex I and ATP/ADP ratio; abnormal mt ultrastructure	[142–146]
Epilepsy	↑ NOS II with NO <sup>-</sup> , <sup>•</sup> O <sub>2</sub> <sup>-</sup> and ONOO <sup>-</sup> dependent ↓ complex I activity; ↑ complex III-dependent <sup>•</sup> O <sub>2</sub> <sup>-</sup> production of brain mitochondria; ↓ lipoic acid synthetase	[147–150]
Myalgic encephalomyelitis/ /chronic fatigue syndrome	↑ urinary 8-OHdG; ↑ TBARS; ↓ Vit C; ↓ HSP70; ↑ plasma peroxides and oxidized LDL; ↓ CoQ10; ↑ ATP production; ↑ complex I, III and IV	[151–156]
Multiple sclerosis	↑ lipid hydroperoxide, carbonyl protein, and NO metabolites; ↓ total radical-trapping antioxidant parameter; Melatonin-induced ↑ SOD and ↑ GPx, and ↓ MDA; ↓ OXPHOS activity; mtDNA deletions	[157–160]
Parkinson's disease	↑ lipid peroxides; ↑ urinary 8-OHdG; ↑ plasma F(2)-IsoPs, HETEs, 7beta-and 27-hydroxycholesterol, 7-ketocholesterol, F(4)-NPs; dysregulated Fe metabolism ↓ CoQ10, and ↓ complex V; ↑↓ cysteine oxidation within complex I; ↑ lactate	[6, 161–165]
B. psychiatric diseases		
Autistic spectrum disorders	↓ GSH/GSSG in WBC; ↑ 4-hydroxynonenal in plasma and RBC membranes; ↑ 3-nitrotyrosine and 8-OHdG; downregulated OXPHOS (↓ complex I, III, IV and V); ↓ aconitase; ↑ mtDNA deletions, GC → AT transitions, and GC → TA transitions	[166–172]
Bipolar disorder	↓ attachment of hexokinase 1 to outer mt membrane; ↓ GSH/GSSG; ↓ CAT expression;	[173–175]
Major depression	altered IL-6, IL-10, and IL-6/IL-10 ratio versus F2-isoprostanes; ↑ protein carbonylation and glutathione reductase expression; ↑ SOD, CAT and PER ↑ PMNs apoptosis (cytochrome c release); ↓ complex I subunits	[176–179]
Obsessive-compulsive disorder	↑ MDA/TBARS; ↑ SOD; ↓ GSH/GSSG; prevailing CC (Ala/Ala) SOD-2 genotype	[180–182]
Schizophrenia	↑ lipid peroxidation, damage to proteins, and DNA; ↓ antioxidant levels (CoQ10, Vit E, GSH and melatonin); autoimmune responses; ↑ TBARS, IL-6 and PCC levels; ↓ TRX levels; ↓ plasma total antioxidant status	[183–187]

excess lipid peroxidation (4-HNE) in plasma and in RBC membranes [166–168]. Moreover, increased protein and DNA damage (3-nitrotyrosine, 3-NT, and 8-OHdG) was reported in frozen samples from necroptic cerebellum and temporal cortex of individuals with ASD [169]. The occurrence of both MDF in ASD patients includes downregulation of genes involved in electron transport chain (decreased Complex I, III, IV, and V) and in Krebs cycle (decreased aconitase expression), Mitochondrial DNA damage was reported, in terms of OS-mediated mtDNA deletions and transitions, namely, GC → AT and GC → TA [170–172]. Altogether, the established evidence for OS/NS/MDF in ASD patients sets realistic grounds for clinical interventions aimed at counteracting these metabolic imbalances in ASD patients.

5.2.2. **Bipolar Disorder.** Evidence for OS in bipolar disorder (BD) has been provided in terms of lipid peroxidation and reduced  $\text{Na}^+ - \text{K}^+$ -ATPase activity, which can be counteracted by lithium treatment [173]. Moreover, decreased plasma levels of total glutathione and GSH, together with lower catalase expression, increased protein carbonyls, 4-HNE, and 3-NT were found in BD patients [174, 175]. Mitochondrial abnormalities in BD patients displayed decreased attachment of hexokinase I to outer mitochondrial membrane and decreased Complex I levels [175].

5.2.3. **Major Depression.** Major depression (MD) has been reported to be associated with OS and with inflammation endpoints, namely, excess levels of IL-6, IL-10, and IL-6/IL-10 ratio *versus* F2-isoprostanes, along with increased protein carbonylation and expression of GR, GPx, SOD, and CAT [176–178]. A study of postmortem prefrontal and parieto-occipital cortices of MD patients revealed downregulated mRNA and protein levels of Complex I subunits (NDUFV1, NDUFV2, and NADUFS1) [179].

5.2.4. **Obsessive-Compulsive Disorder.** Obsessive-compulsive disorder (OCD) features some OS hallmarks, as excess MDA/TBARS and SOD-1, along with decreased GSH : GSSG ratio [180, 181]. A study reported on a shift in mitochondrial SOD-2 genetic subtype, with increased prevalence of the TBARS-related CC (Ala/Ala) genotype *versus* CT (Ala/Val) genotype in OCD patients that was significantly lower than in healthy donors [182].

5.2.5. **Schizophrenia.** An extensive body of evidence points to the occurrence of OS, NS, and proinflammatory condition in schizophrenia (SZ) [183]. In particular excess lipid peroxidation, damage to proteins and DNA, decreased plasma total antioxidant status, and antioxidant levels (Trx, CoQ10, Vit. E, GSH, and melatonin) were observed in SZ patients, along with autoimmune responses, as excess IL-6 and PCC levels [184–186]. An involvement of MDF in SZ pathogenesis is shown by a recent report on a significant decrease in Complex I activity both *versus* health donors and *versus* BD patients [186] and suggested by the abovementioned decrease in CoQ10 levels [187].

## 6. Cancer

A huge body of literature—of over 12,000 MedLine citations—associates malignancies of several organs and tissues with OS/MDF. While recognizing the outstanding differences in the pathogenesis of different malignancies; however general remarks to the involvement of OS/MDF in carcinogenesis may be provided, as reviewed recently [188, 189]. An OS condition produces irregular cell membrane borders as a result of lipid peroxidation, breaks, and considerable DNA damage, resulting in mutations and eventually cancer, via oncogene activation or tumour suppressor gene inactivation. These mutations may initiate carcinogenesis. Once initiated cellular transformation, cancer cells display an increased anaerobic glycolysis enabling to support neoplastic proliferation (Warburg effect) [190]. During cancer promotion, hypoxic condition prevents pyruvate, produced by anaerobic glycolysis, to be converted into Acetyl-CoA and to enter into Krebs cycle (MDF). The accumulated pyruvate is disposed through an alternative pathway which leads to the formation of lactate, which decreases microenvironmental pH. In this phase, therefore, glycolysis is not affected by hypoxia and continues producing pyruvate and reaction intermediates useful to the pentose phosphate pathway that lead to the ultimate synthesis of purine and pyrimidine bases, essential to cellular high replicative activity. Thus, Krebs cycle is affected by hypoxia and stops. During cancer progression, acid microenvironment promotes tumour angiogenesis. The restored oxygen supply activates aerobic glycolysis but the cells continue to produce lactic acid even in presence of oxygen and MDF endures. Further microenvironmental acidification was related to the metastatic phenomenon [189].

Brief examples of some selected malignancies will be cited herein, as shown in Table 5. Though relevant, literature on the involvement of OS/MDF in preneoplastic lesions (e.g., leukoplakia) or cancer-predisposing diseases (e.g., hepatitis C) is not cited here.

6.1. **Bladder Cancer.** Evidence for OS and NS hallmarks in bladder cancer was provided by excess oxidative DNA damage (8-OHdG), 3-NT, and by peroxiredoxin 4 (Prdx4) upregulation that were associated with poor prognosis [191, 192]. An involvement of MDF in bladder cancer was reported by finding excess mtDNA mutations (G8697A, G14905A, C15452A, and A15607G) [193] and altered mitochondrial expression profile of proteins involved in OXPHOS, glycolysis/gluconeogenesis, and Krebs cycle [194].

6.2. **Breast Cancer.** Extensive studies have focused on the involvement of OS/MDF in breast cancer pathogenesis [195–197]. Among OS endpoints, excess 8-OHdG and protein carbonyl were reported, along with upregulated total SOD, SOD-1, and EC-SOD in plasma and breast tumours. Moreover, BRCA1 mutations were found to cause OS in tumour microenvironment [198, 199]. Implications for MDF in breast cancer include upregulation of >95 gene transcripts associated with mitochondrial biogenesis and/or translation.

TABLE 5: Neoplastic disorders displaying OS/MDF hallmarks.

Malignancies	OS/MDF hallmarks	References
Bladder cancer	↑ 8-OHdG, 3-NT, and Prdx4 associated with a poor prognosis; ↓ serum levels of Vit C and E, SOD and GPx, and serum antioxidant capacity; ↑ mtDNA mutations; altered mitochondrial protein expression profile (OXPHOS, glycolysis/ /gluconeogenesis, Krebs cycle)	[191–194]
Breast cancer	↑ 8-OH-dG and protein carbonyl; ↑ total SOD, SOD-1, and EC-SOD in plasma and breast tumours; BRCA1 mutations cause OS in tumour microenvironment; ↑ >95 gene transcripts associated with mt biogenesis and/or mt translation; mt location of phosphorylated BRCA1; progression-related ↓ CoQ10 levels; ↓ SOD-2	[195–201]
Cervical cancer	↑ lipid peroxidation; ↑ GPx; ↓ SOD; ↓ CAT; null GSTM1 and GSTT1 polymorphisms associated with ↑ risk of cervical neoplasia; ↑ Prdx3	[202–208]
Colorectal cancer	↑ 8-OHdG; ↑ SOD, GR and GPx; ↓ GST; U-shaped association between the relative mtDNA copy number and risk of colorectal cancer	[209–211]
Endometrial cancer	↑ tumour specific mtDNA mutations; ↓ complex I; ↑ mtDNA level; ↑ mitochondrial biogenesis; ↑ SOD-2; ↑ CAT; ↑ Prx3	[212–214]
Gastric cancer	↑ 8-OHdG; ↓ hOGG1; ↑ SOD-2; <i>H. pylori</i> -induced mtDNA mutations and decrease of mtDNA content	[215–217]
Hepatocellular carcinoma growth	↑ 8-OHdG and 4-HNE associated with microvessel density, vascular endothelial Factor, and Akt activity; d-ROM, α-fetoprotein, and fasting plasma associated with HCC recurrence; survival rate related to ↑ SOD-2 and Trx; ↑ mtDNA 9-bp polymorphism	[218–221]
Lung cancer	↑ MDA; ↑ aldehydes in exhaled breath; ↑ 8-OHdG; polymorphism of OGG1 Ser326Cys; ↑ thymidine glycol in ever-smokers; ↓ CAT and carbonic anhydrase; ↓ AOC in never-smokers than in ever-smokers; ↑ HO-1 expression; ↓ CoQ10; mt HSP90s associates with worse clinical outcome; ↓ mtDNA; ↑ ΔΨ <sub>m</sub>	[222–228]
Melanoma	↑ 8OHdG associated with a poor prognosis; ↑ NOS1 polymorphism (rs2682826); ↑ TNF-α enhancing action of tumour-associated macrophages; ↑ OXPHOS	[229–232]
Myeloid leukaemias	↑ MDA; ↓ thiol plasma levels; ↑ PC, TBARS and LOOH; ↓ ferric reducing ability of plasma (FRAP); GSTP1 Ile105Val polymorphism associated with CML; ↑ CAT; ↑ Trx; ↑ adenosine deaminase and xanthine oxidase; ↓ PRDX4 expression in APL; disease-related 2- to 50-fold ↑ amplification of mtDNA; survival advantage in patients with SOD-2 T versus C polymorphism; ↓ mt-encoded genes and ↑ mtDNA copy number	[233–241]
Oral cancer	↑ MDA and NO; ↑ AGEs; ↓ CAT ↓ SOD in tissue, while ↑ SOD in erythrocytes; somatic mutation of D-loop of mtDNA was associated with better survival	[242–246]
Thyroid oncocyctic carcinoma	disruptive mtDNA mutations in complex I and III; ↓ complex I; ↓ respiration; ↓ ATP synthesis; ↑ ROS; ↓ mitochondrial biogenesis	[247, 248]

Moreover, phosphorylated BRCA1 was found to locate to mitochondria, and disease progression-related decreased CoQ10 levels and SOD-2 expression were reported [199–201].

**6.3. Cervical Cancer.** Cervical cancer features excess lipid peroxidation, with overexpressed GPx and decreased SOD and CAT expression [202–206]. Null mutations in GSTM1 and GSTT1 polymorphisms were associated with excess risk of cervical neoplasia [207]. Mitochondrial Prdx3 was found to be overexpressed in high-risk patients [208].

**6.4. Colorectal Cancer.** Colorectal cancer (CrC) is characterized by excess oxidative DNA damage (8-OHdG) that was correlated to CD80 mRNA mucosal levels; SOD, GR, and GPx overexpression was observed, with GST inhibition [209, 210]. The relative mtDNA copy number showed a U-shaped association *versus* CrC risk [211].

**6.5. Endometrial Cancer.** Endometrial cancer (EC) features OS-related anomalies by decreased SOD and CAT expression, along with increased lipid hydroperoxides and glutathione reductase (GR) [212]. In type I EC the occurrence of pathogenic tumour specific mtDNA mutations as well as a reduction of assembled Complex I in tumour samples were found associated with an activation of antioxidant enzymes and with an increase of mitochondrial biogenesis. Tissue from EC showed doubling citrate synthase activity, the mitochondrial DNA content, and the TFAM level [213, 214].

**6.6. Gastric Cancer.** Gastric cancer features excess 8-OHdG levels and decreased expression of 8-oxoguanine glycosylase (OGG-1) [215, 216]. An involvement of MDF in gastric cancer was suggested by SOD-2 overexpression and by the recent report that found *H. pylori*-induced mtDNA mutations and a decrease of mtDNA content [215, 217].

**6.7. Hepatocellular Carcinoma.** Hepatocellular carcinoma (HCC) has been investigated extensively for its pathogenetic implications of OS/MDF, also related to other nonneoplastic or preneoplastic liver disorders [218–221]. Among OS-related hallmarks, HCC was found to display excess 8-OHdG and 4-HNE associated with microvessel density, vascular endothelial growth factor, and Akt activity; moreover, d-ROM,  $\alpha$ -fetoprotein, and fasting plasma were associated with HCC recurrence [218, 219]. Implications of MDF were reported by the association of mitochondrial SOD-2 and Trx *versus* patients' survival rate and by excess mtDNA 9-bp deletion polymorphism in HCC patients [220, 221].

**6.8. Lung Cancer.** A number of studies provided extensive evidence for the involvement of OS and MDF in lung cancer (LC) [222–228]. The altered OS endpoint found in LC included excess aldehyde levels, both in plasma MDA and in exhaled breath, and with decreased serum antioxidant capacity. Oxidative DNA damage was both reported as excess levels of 8-OHdG and of thymidine glycol in ever-smokers. A recent meta-analysis confirmed a strong association between a variant OGG1 Ser326Cys and the risk of developing lung cancer, stressing the role of oxidative DNA damage repair in

this clinical setting [223, 227]. Moreover, haeme oxygenase-1 (HO-1) was found overexpressed, while CAT and carbonic anhydrase were downregulated [223–225]. An involvement of MDF in LC was associated with decrease in mtDNA and lower-than-normal CoQ10 levels; moreover, mt HSP90s was associated with worse clinical outcome; mitochondria were found to display increased  $\Delta\Psi$  [226–228].

**6.9. Melanoma.** An increased oxidative DNA damage (8-OHdG) was found in melanoma patients' cells that was associated with a poor prognosis, with increased NOS1 polymorphism (rs2682826) and increased TNF- $\alpha$  levels enhancing the action of tumour-associated macrophages [229–231]. Mitochondria from metastatic melanoma cells displayed increased expression of OXPHOS activities *versus* nonneoplastic melanocytes [232].

**6.10. Myeloid Leukaemias.** Blood cell malignancies have been extensively investigated for the pathogenetic implications of OS/MDF; however most of this literature appears to be focused on myeloid leukaemias (ML); thus the literature in this subject regarding lymphoid leukaemias is omitted. A number of studies have provided substantial evidence for OS hallmarks in ML, including excess lipid peroxides (measured as MDA, TBARS, and LOOH) and protein carbonyls and decreased thiol plasma levels and ferric reducing ability of plasma (FRAP); moreover, increased expression of CAT, Trx, adenosine deaminase, and xanthine oxidase, along with decreased Prdx4 were reported, and GSTP1 Ile105Val polymorphism was associated with ML [233–238]. Anomalies in mitochondrial structure and function in ML included a disease-related 2- to 50-fold increased amplification of mtDNA, survival advantage in patients with SOD-2 T *versus* C polymorphism (in codon 16 of the mitochondrial targeting sequence of SOD-2), and a decrease in mitochondrial-encoded genes against an increased mtDNA copy number [239–241].

**6.11. Oral Cancer.** Oral cancer displays both OS and NS hallmarks, with excess MDA and NO levels, and AGEs levels. Decreased CAT and SOD expression was found in OC tissue, while SOD expression was enhanced in erythrocytes [242–245]. As an indicator of MDF, somatic mutation of D-loop of mtDNA was associated with better survival [246].

**6.12. Thyroid Oncocytic Carcinoma.** Thyroid oncocytic carcinoma (TOC) is characterized by mitochondrial hyperplasia and harbours high loads of disruptive mtDNA mutations, the large majority in respiratory Complex I genes. The analysis of a TOC cell line (XTC.UC1) displayed a complete loss of Complex I, a reduced rate of respiration and ATP synthesis driven by Complex I substrates, and an increase of ROS production [247, 248].

## 7. Autoimmune Diseases

This class of diseases (Table 6) is characterized by a number of OS-related hallmarks; as for MDF, most of abnormalities may be ascribed to antimitochondrial autoantibodies (AMA).

TABLE 6: Autoimmune diseases displaying OS/MDF hallmarks.

Diseases	OS/MDF hallmarks	References
Antiphospholipid Syndrome	↑ Serum amyloid A, C-reactive protein, and 8-isoprostane and prostaglandin E2 ↑ peroxide production, nuclear abundance of Nrf2, ↓ antioxidant enzymatic activity; ↓ intracellular GSH; altered $\Delta\Psi$ ; beneficial effects of CoQ10 supplementation	[249, 250]
Pemphigus Vulgaris	↑ MDA; ↓ antioxidants (Vit. A and E); ↓↑ CAT and ↓ GSH-Px; autoantibodies against desmosomal, mitochondrial, and other keratinocyte self-antigens	[251–254]
Primary Biliary Cirrhosis	↓ Antioxidant vitamins (A, C and E); ↓ GST, ↑ HOCl associated with eosinophil peroxidase; ↑ IgG against LOOH; serum and saliva antimitochondrial autoantibodies against E2 subunits of 2-oxoacid dehydrogenase enzymes (pyruvate dehydrogenase, 2-oxo-acid dehydrogenase, and 2-oxo-glutarate dehydrogenase)	[255–258]
Psoriasis	↑ MDA, 8-OHdG, LOOH and NOx; ↓ CAT, SOD, GSH-Px, GSH and total antioxidant status; release of mitochondrial cytochrome c; ↑ CYP4F8 mRNA	[259–263]
Rheumatoid Arthritis	↑ LOOH; ↑ MPO, ↑ $\cdot\text{O}_2^-$ and $\cdot\text{OH}$ in neutrophils from peripheral blood and synovial infiltrate; ↓ CAT, SOD, GSH-Px, GSH; TNF- $\alpha$ -associated ER stress; ↑ AGE-IgG; chemokine (MCP-1/CCL2, RANTES/CCL5)-associated ROS; mtDNA mutations positively correlated with macroscopic synovitis	[264–269]
Sjögren's Syndrome	↑ protein carbonyl and AGEs; ↑ 4-HNE; ↑ TNF- $\alpha$ , MPO and nitrotyrosine; ↑ 8-OHdG and hexanoyl-lysine; ↑ Trx; ↑ LDH and mitochondrial GOT; antimitochondrial autoantibodies in patients' saliva	[270–274]
Systemic Lupus Erythematosus	↓ CAT, SOD, GSH-Px, GSH; ↑ chemokine-associated ROS; ↓ ATP; ↑ $\Delta\Psi$ ; persistent mt hyperpolarization abnormal expression of mt pyruvate dehydrogenase complex	[264, 275, 276]
Systemic Sclerosis	↑ MDA, dityrosines and carbonyls; ↓ uric acid and total antioxidants status in saliva; ↓ GSH; ↓ SOD; ↑ GPx; plasma antimitochondrial autoantibodies	[277–280]
Vitiligo	↑ 4-HNE; ↓ cardiolipin; ↓ GSH; ↓ MPO; ↓ GST and CAT; ↑ GSTM1 null and GSTM1/GSTM1 double-null type; altered OXPHOS lipid-dependent subunits	[281–283]

Thus, most of the observed MDF endpoints are secondary to AMA-induced damage.

**7.1. Antiphospholipid Syndrome.** Antiphospholipid syndrome (APS) features a set of OS- and inflammation-related altered endpoints, including excess serum amyloid A, C-reactive protein, 8-isoprostane and prostaglandin E<sub>2</sub>, increased peroxide production, nuclear abundance of Nrf2, and decreased antioxidant enzymatic activity and intracellular GSH [249]. Mitochondria from APS patient cells displayed altered  $\Delta\Psi$ ; moreover, beneficial effects of CoQ10 supplementation were observed, by improving the preservation of mitochondrial ultrastructure [250].

**7.2. Pemphigus Vulgaris.** Pemphigus vulgaris displays OS-related alterations including excess lipid peroxidation (MDA), decreased antioxidant levels (Vit. A and E), and altered expression of CAT and GPx [251–253]. Autoantibodies against mitochondrial, desmosomal, and other keratinocyte self-antigens were reported [253, 254].

**7.3. Primary Biliary Cirrhosis.** Patients with primary biliary cirrhosis (PBC) display decreased levels of antioxidant vitamins (A, C and E), excess HOCl release associated with eosinophil peroxidase, and decreased GST expression [255–257]. The autoimmune condition in PBC was found to show IgG production against lipid peroxides and serum and saliva AMA against E<sub>2</sub> subunits of 2-oxoacid dehydrogenase enzymes (pyruvate dehydrogenase complex, 2-oxo-acid dehydrogenase, and 2-oxo-glutarate dehydrogenase) pointing to autoimmune onset of MDF [258].

**7.4. Psoriasis.** This disorder features a number of OS- and NS-related hallmarks including excess lipid peroxidation (MDA and LOOH), oxidative DNA damage (8-OHdG), and nitrogen oxides (NO<sub>x</sub>) levels, with decreased total antioxidant status and GSH levels. Decreased expression of CAT, SOD, and GPx was observed [259–261]. Moreover, mitochondrial damage could be inferred by release of mitochondrial cytochrome c and by upregulated CYP4F8 mRNA [262, 263].

**7.5. Rheumatoid Arthritis.** Rheumatoid arthritis was found to display excess lipid peroxide levels, along with increased expression of myeloperoxidase and excess ROS production in neutrophils from peripheral blood and synovial infiltrate. This finding was related to downregulation of CAT, SOD, and GPx and decreased GSH levels, along with TNF- $\alpha$ -associated ER stress. Immune imbalance included excess AGE-IgG and chemokine (MCP-1/CCL2, RANTES/CCL5)-associated ROS [264–268]. Mitochondrial damage was reported as mtDNA mutations that were positively correlated with macroscopic synovitis [269].

**7.6. Sjögren's Syndrome.** A number of OS- and NS-related hallmarks characterize Sjögren's syndrome (SS) patients, including excess protein carbonyls and AGEs, 4-HNE, TNF- $\alpha$ , MPO, and 3-NT; moreover, excess 8-OHdG and hexanoyllysine were found in SS patients. Excess expression of Trx,

LDH and mitochondrial GOT were found in these patients [270–273]. An autoimmune-based MDF was reported by finding antimitochondrial autoantibodies in SS patients' saliva [274].

**7.7. Systemic Lupus Erythematosus.** Systemic lupus erythematosus patients display a set of OS hallmarks, such as decreased CAT, SOD, and GPx expression, with decreased GSH levels, and excess chemokine-associated ROS production [275, 276]. Defective mitochondrial function was related to lower-than-normal ATP levels, increased  $\Delta\Psi$ , and persistent mitochondrial hyperpolarization [264, 276].

**7.8. Systemic Sclerosis.** Patients with systemic sclerosis (SSc) display some altered OS endpoints that include excess MDA, dityrosines, and carbonyls, with lower-than-normal uric acid levels, GSH, and total antioxidants status in saliva. Decreased SOD expression was accompanied by increased GPx expression [277–279], and mitochondrial damage was associated with high-sensitivity C-reactive protein and AMA in SSc patients [280].

**7.9. Vitiligo.** Vitiligo patients feature a set of OS-related hallmarks, such as excess 4-HNE with decreased cardiolipin and GSH levels. A decreased expression of MPO, GST, and CAT was reported, and GST polymorphism displayed excess GSTM1 null and GSTT1/GSTM1 double-null type [281, 282]. An involvement of MDF in vitiligo was suggested by altered OXPHOS lipid-dependent subunits [283].

## 8. Miscellaneous Pathologies

Two disorders and a pathologic condition that could not be ascribed to the above disease classifications are discussed for their pathogenetic implications of OS/MDF in Table 7.

**8.1. Cataract.** Patients with cataract display excess lipid peroxidation (TBARS) with decreased thiol levels and ferric reducing/antioxidant power; moreover, an increase in dehydroascorbate/ascorbate ratio was observed [284, 285]. A study of polymorphisms of SOD-1, CAT, and GPx genes in cataract patients found that G/G genotype of the SOD-1 (251A/G polymorphism) was associated with an increased risk of cataract [286]. Several reviews discuss the roles of mitochondria in cataract pathogenesis [287], and a H<sub>2</sub>O<sub>2</sub>-specific induction of mitochondrial Prdx3 in the eye lens was observed [288].

**8.2. Fibromyalgia.** Fibromyalgia (FM) is characterized by excess lipid peroxidation and TNF- $\alpha$  levels, with loss of total antioxidant capacity [289–291]. A line of studies by Cordero and his colleagues has focused on MDF in FM, reporting on decreased  $\Delta\Psi$  and CoQ10 levels, along with excess mt <sup>•</sup>O<sub>2</sub><sup>-</sup> production and excess mitophagy [291–293].

**8.3. Malformations.** When mechanistic aetiology is available, malformations may occur as a result of exposures to xenobiotics before or during pregnancy (reviewed in [294]), or some organ-specific malformations may be ascribed to

TABLE 7: Miscellaneous pathologies displaying OS/MDF hallmarks.

Diseases/conditions	OS/MDF hallmarks	References
Cataract	↑ TBARS; ↓ thiols; ↓ ferric reducing/antioxidant power; ↑ dehydroascorbate/ascorbate; ↑ G/G genotype of SOD-1—251A/G polymorphism; H <sub>2</sub> O <sub>2</sub> -specific induction of Prdx3 in the eye lens	[284–288]
Fibromyalgia	↑ lipid peroxidation; ↓ total antioxidant capacity; ↑ TNF- $\alpha$ ; ↓ $\Delta\Psi$ ; ↓ CoQ10; ↑ mt $\cdot\text{O}_2^-$ ; excess mitophagy	[289–293]
Malformations	OS and MDF in teratogenic action; thalidomide causes embryonic DNA oxidation in susceptible but not resistant species; GSH depletion, or inhibition of GPx or GR; ↓ mt NADH oxidase in teratogen-sensitive embryonic tissues; ethanol upregulates NOX regulatory subunits and increases NOX expression; ↓ complex I and IV and ATP synthase in fetal alcohol syndrome	[294–300]

endogenous mechanisms in the phenotype of some genetic diseases, as for example, Fanconi anaemia (reviewed in [55]). Whether teratogenic outcomes derive from exogenous or endogenous factors, a vast body of literature has focused on OS- and MDF-related pathogenetic mechanisms. The induction of developmental defects and malformations has been associated with OS and MDF in teratogenic action [295]. Thalidomide was reported to cause embryonic DNA oxidation in susceptible yet not in resistant species, which was associated with GSH depletion, or inhibition of GPx or GR, and with decreased mitochondrial NADH oxidase in teratogen-sensitive embryonic tissues [296, 297]. Ethanol was reported to upregulate NOX regulatory subunits and increases NOX expression [298]. An involvement of MDF in developmental anomalies was suggested by alterations of mitochondrial respiration [299] and by reduced activities of respiratory chain Complexes I and IV and ATP synthase in a murine model of fetal alcohol syndrome [300].

## 9. Discussion

“Free radical theories” have been proposed for ageing since 1956 by Harman [301, 302] and subsequently for some high impact disorders as cardiovascular diseases [303], diabetes [304], and neurodegenerative diseases [6, 305–307]. Almost sixty years after Harman’s hypothesis, many individual disorders—or groups of interrelated disorders—have been investigated for the implications of OS in their respective pathogenetic mechanisms. An important step in this research line was provided by the recognition, in 1990s, of the direct association of MDF with OS [3–5].

In spite of the outstanding information accumulated in these decades, one may notice that the database is usually confined to each medical discipline and, to the best of our knowledge, a comprehensive and interdisciplinary view is still missing or partial. Moreover, the clinical management of several OS/MDF-related disorders often disregards this information, by failing to adopt therapeutic or chemopreventive means targeted to compensate OS/MDF.

Among the OS-related endpoints, the most commonly observed abnormalities across broad-ranging disorders were

found by means of (a) oxidation products of biomolecules, including lipid peroxidation products, DNA hydroxyl adducts, advanced glycation end-products, and protein carbonyls; (b) abnormal expression or regulation of antioxidant activities, namely, SOD, CAT and glutathione-related activities (GR, GPx, GST), (c) glutathione levels and GSH:GSSG ratio, and (d) defects in iron metabolism.

Definitely less investigated than OS, the NS-related endpoints, as 3-nitrotyrosine and NO bioactivity, have been reported to be associated with other redox-related anomalies in some diseases, such as diabetes [127, 128], bladder cancer [191], autism [169], schizophrenia [183], and Sjögren’s syndrome [271]. Albeit relatively unexplored, the subject of nitrosative damage deserves higher attention in further studies, as NS-related endpoints might provide precious insights in the pathogenesis of several OS/MDF-related disorders.

Almost invariably, MDF hallmarks were detected in OS-related disorders in the evaluated literature, thus providing an overall pattern of an OS/MDF association, as expected on the grounds of a MDF-related onset of OS [3]. The most frequently observed changes in MDF, and in mitochondrial ultrastructure, included (a) changes in one or more activities of the electron transport chain, OXPHOS, that is, Complexes I to V; (b) decreased expression of Krebs cycle-associated activities; (c) defects in mitochondrial SOD-2 and/or Prdx3 expression; (d) mtDNA deletions, decreased mtDNA copy numbers and mitophagy [307]; (e) decreased levels of CoQ10 and/or of ATP; (f) changes in lactate/pyruvate ratio; and (g) changes in mitochondrial membrane potential ( $\Delta\Psi$ ). Alterations in OXPHOS activities were most commonly reported across a broad range of disorders displaying MDF hallmarks. Relatively few studies reported on changes in Krebs cycle-related activities, such as pyruvate dehydrogenase and pyruvate kinase in ageing [105], lipamide dehydrogenase in Alzheimer’s disease [138], liponic acid synthetase in epilepsy [149], and aconitase in Friedreich ataxia [87]. Another relevant biomarker of MDF, SOD-2 expression, was reported to be increased in gastric cancer [215] and hepatocellular carcinoma [220]; SOD-2 activity was found increased in atherosclerosis [111], type 2 diabetes mellitus [131], and upregulated SOD-2 transcripts in Hutchinson-Gilford syndrome

[61]. Altogether, the observed overexpression or upregulation of SOD-2 may suggest a homeostatic response in mitochondrial redox balance. The mitochondrial peroxidases, Prdx3 and Prdx4, were found to display expression changes in bladder cancer that related to disease prognosis [191], and Prdx3 upregulation was associated with increased cervical cancer risk [208]; H<sub>2</sub>O<sub>2</sub>-induced Prdx3 overexpression was observed in the eye lens in cataractogenesis [288]. Prdx4 was downregulated in acute promyelocytic leukemia [237] and Prdx3 overoxidation was reported in ageing [105]; moreover, Prdx3 was found to be downregulated in cells from Fanconi anaemia (FA-G) [57]. Unlike SOD-2, mitochondrial peroxidases show different patterns of up- or downregulation in different disorders; however their pathogenetic roles deserve being elucidated in forthcoming studies of other OS/MDF-related disorders.

As another possibly sensitive endpoint in evaluating MDF, CoQ10 levels have been found lower than normal in an extensive number of disorders, including genetic diseases (Down syndrome, xeroderma pigmentosum, and Friedreich ataxia) [48, 73, 86], lung cancer [223], neurologic diseases (myalgic encephalomyelitis/chronic fatigue syndrome and Parkinson's disease) [153, 162], and fibromyalgia [291]. These data, though confined to some selected disorders, concur with the most frequent findings of deficiencies in OXPHOS-related activities in most of the diseases where MDF was reported. It should be considered that measurements of CoQ10 levels in patients with OS/MDF-related disorders should be viewed as a preliminary step in view of possible clinical interventions using CoQ10.

Unlike OXPHOS, only few studies have reported on abnormalities in Krebs cycle-related endpoints. In Alzheimer's disease, a decreased expression of lipoamide dehydrogenase was detected in brain of both AD patients, and of AD mice, along with the observation of 4-HNE-induced oxidation of  $\alpha$ -lipoic acid (ALA) [138]. Ageing was also associated with deficiencies in Krebs cycle-related endpoints, as tissue cells and skin fibroblasts of old donors displayed decreased expression of pyruvate dehydrogenase, pyruvate kinase, and lactate dehydrogenase [106]. A lipoic acid synthetase deficiency was detected in neonatal-onset epilepsy [149]. Quite surprisingly, no study was found in this review reporting on ALA levels, although analytical means for ALA measurement [308] and assay kits are available. This information gap should be filled in forthcoming studies both aimed at elucidating disease pathogenesis and in view of appropriate design for clinical trials using ALA.

Mitochondrial DNA was found to be affected by point mutations or by deletions both in primary and secondary mtDNA-related diseases (Table 1). Several other disorders, however, displayed mtDNA damage or changes, as mtDNA copy number or mitophagy [307]. A recent paper by Napoli et al. [171] reported on OS-mediated deletions mtDNA in autistic children; damaged and mutated mtDNA was detected in ageing cells [104–106]; among malignancies, breast, endometrial, gastric, hepatocellular, lung, and thyroid cancers were associated with dysregulation of mtDNA genes or of markers of mitochondrial biogenesis [199, 213, 214, 219, 228, 247, 248]; moreover, mtDNA damage was reported in

cardiovascular disorders [112] and in osteoarthritis [122–124]. Other two markers of MDF, either mitochondrial membrane potential ( $\Delta\Psi$ ) or mitochondrial ultrastructure, were found to be altered in several disorders, including Fanconi anaemia [57–59], Down syndrome (see [49, 52], reviewed in [309]), and fibromyalgia [291, 292].

Far from being confined to the classically termed mitochondrial diseases, the present information points to the association of MDF with OS and, to a limited extent, with NS across a number of diseases pertaining to broad-ranging medical disciplines. Thus, one may imagine treasuring the current knowledge of mitochondrial diseases in order to design appropriate interventions in several pathologies. In this prospect, the cofactors recognized as “mitochondrial nutrients,” as ALA, CoQ10, and L-carnitine (CARN) (or its derivatives) [310, 311] should be regarded as a prime tool in mitigating MDF and, hence, OS in several disorders; a line of ongoing clinical studies is foreseen by at least one extensive study group focused on mitochondrial diseases, on the grounds of the novel discipline termed “mitochondriology” [312, 313]. The present and growing awareness for the pathogenetic roles of OS/MDF in several disorders has prompted a number of clinical groups to undertake clinical trials testing mitochondrial nutrients aimed at counteracting OS/MDF in patients with an extensive number of diseases. The current knowledge of previous clinical trials and the prospects of study design are reported in a parallel review to the present paper [314].

## 10. Conclusion

The association of MDF with OS and, probably, NS is a widespread phenomenon encompassing a broad number of different disorders. The current knowledge of mitochondrial diseases and of other OS/MDF related diseases should prompt further investigations to elucidate the roles of OS/MDF in a number of disorders, in the prospect of rational interventions aimed at mitigating OS/MDF-related clinical progression.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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