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Control of DNA integrity in skeletal muscle under physiological and pathological conditions

Yara Bou Saada[1] · Vlada Zakharova[1,2] · Boris Chernyak[2] · Carla Dib[1] · Gilles Carnac[3] · Svetlana Dokudovskaya[1] · Yegor S. Vassetzky[1,2,4]

Abstract Skeletal muscle is a highly oxygen-consuming tissue that ensures body support and movement, as well as nutrient and temperature regulation. DNA damage induced by reactive oxygen species is present in muscles and tends to accumulate with age. Here, we present a summary of data obtained on DNA damage and its implication in muscle homeostasis, myogenic differentiation and neuromuscular disorders. Controlled and transient DNA damage appears to be essential for muscular homeostasis and differentiation while uncontrolled and chronic DNA damage negatively affects muscle health.

Keywords DNA damage · DNA repair · Oxidative stress · Aging

Introduction

DNA damage is a part of the daily life of a living organism, and the capacity of the organism to detect and repair DNA damage ensures health and survival. DNA integrity is essential for a living cell to maintain its survival and growth. Tens of thousands of spontaneous modifications per day occur in DNA of a single human cell (for review see [1, 2]). They are mainly due to endogenous genotoxic sources related to DNA replication and repair as well as free radicals which can oxidatively damage DNA. Skeletal muscles are subjected to DNA damage by exposure to endogenous and exogenous genotoxic sources. Reactive oxygen species (ROS) are thought to be a major cause of DNA damage in skeletal muscles. ROS in muscles are generated during cellular metabolism, muscle contraction, hypoxia, inflammation and muscle regeneration. In this review, we discuss the major sources of DNA damage in skeletal muscles, the consequences of DNA damage and oxidative stress in muscle physiology and in myopathies.

Oxidative stress

Reactive oxygen species represent a group of highly reactive molecules with oxidizing properties. The incomplete reduction of O_2 generates ROS with a high oxidizing potential: the superoxide radical (O_2^-), hydrogen peroxide (H_2O_2) and the hydroxyl radical (OH^-); they are products of O_2 reduction by one, two, or three electrons, respectively. Cells constantly produce ROS; in fact, any controlled enzymatic reaction involving electron transfer can lead to electron leakage which produces ROS in the presence of O_2.

Respiratory chain of mitochondria catalyzes electron transfer to oxygen and a partial reduction of O_2; this can generate ROS [3]. Muscle contraction increases oxygen consumption. This oxygen is further reduced to H_2O [4, 5]. At the same time, from 0.15 to 5% of O_2 is converted to superoxide radical [5–7]. Thus, mitochondria are an important source of ROS in skeletal muscle. Other

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pathways also lead to generation of ROS. These pathways involve xanthine oxidase (XO) [8, 9], lipoxygenases (LOX) [6, 10] and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) [6, 8, 11].

Overproduction of ROS can occur under physiological conditions and participate in normal biological processes such as signal transduction, cellular response against infections, cell proliferation, apoptosis and stimulation of antioxidant systems (for review, see [12]). ROS produced above certain limits can damage proteins, lipids, nucleotides, RNA and DNA. To avoid intracellular accumulation of ROS and to maintain cellular homeostasis, several enzymatic [13, 14] and non-enzymatic [15–19] cellular antioxidant defense systems can be activated in a coordinated manner to prevent or reduce oxidative damage. Oxidative stress occurs when redox homeostasis is impaired in the cell; this imbalance may be due to overproduction of ROS or deficiency of the antioxidant system. Non-physiological production of ROS may be the result of cellular metabolism dysfunction or exposure to an exogenous pro-oxidative source such as ionizing radiation, ultraviolet radiation, inflammation and stimulation of the immune system. For example, stimulation of the immune system leads to local and massive production of ROS partially due to stimulation of NADPH oxidase activity in phagocytes (for review see [20]). Inflammation resulting from a chronic infection generates ROS via recruited neutrophils which produce superoxide radicals and H_2O_2 [21]. An antioxidant system deficiency, including deregulation in the synthesis of glutathione or antioxidant enzymes [22] or a decrease in the stock of antioxidant vitamins [23], leads to an increase of intracellular ROS. Excessive ROS accumulation may cause irreversible damage to cellular macromolecules and consequently lead to apoptosis [24] or carcinogenesis [25]. ROS may also oxidize and alter the pool of nucleotides, thus influencing genomic integrity (for review see [26]). Importantly, several diseases are characterized by high levels of ROS including Type 2 diabetes and Alzheimer's disease. Indeed, hyperglycemia stimulates ROS production from NADPH oxidases [27], glucose auto-oxidation [28], xanthine oxidase [29] and others. Patients suffering from Alzheimer's disease accumulate high levels of amyloid-B-peptide in their brain; this peptide interacts with copper and generates Cu^{+} from Cu^{2+} due to its Cu-reductase activity, thus producing hydrogen peroxide as a by-product [30]. Increased oxidative stress in patients' brain has been correlated with increased DNA and protein oxidation and lipid peroxidation [31]; this damage participates in the development of Alzheimer's disease.

Oxidative stress and muscle homeostasis

Reactive oxygen species production is a prominent event during muscle contraction. ROS affect the function and health of skeletal muscle. ROS are generated in multiple compartments within the muscle cell; mitochondria, sarcoplasmic reticulum, and transverse tubular sarcolemma (for review, see [6]). However, the source of ROS may also be external to the muscle cells; e.g., phagocytic cells may produce ROS after muscle injury. ROS were consudered to be toxic toxic to the muscle tissue. Now it appears that low concentrations of ROS participate in the physiological regulation of muscle. Indeed, ROS participate and trigger signaling pathways causing either "positive" responses such as muscle adaptation or "negative" responses including cell damage and death. This duality given to ROS is mainly dependent on their concentration and on time of exposure, but also on the efficiency of the antioxidant system and the capacity to repair cellular DNA.

Physiological roles of ROS in skeletal muscles

During moderate exercise, ROS act as signaling molecules and activate several signaling pathways including NF-κB (nuclear factor-κB) and AP-1 pathways, which directly stimulate the expression of several antioxidants genes such as *SOD* and *GPX* [32]. In addition, ROS stimulate expression of IGF-1 (insulin-like growth factor 1), a growth factor crucial for muscle growth [33]. Also, ROS appear to be essential for the muscle strength [34, 35]. This physiological response to ROS production reflects muscle adaptation to physical exercise. ROS released by phagocytic cells recruited to a damaged muscle site are important for the regeneration of muscle fibers [36].

ROS also influence the morphology, function and biogenesis of mitochondria [37, 38], an essential organelle for energy metabolism and muscle function. In fact, ROS produced above the physiological level, e.g., following a physical training, activate signaling pathways [39, 40]. This leads to expression of nuclear genes encoding mitochondrial proteins, genes necessary for the activation of transcription and replication of both mitochondrial DNA [41], and genes involved in mitochondrial (Mn-SOD) and cytosolic (CAT and GPX) antioxidant defense.

Muscle growth is a costly process restricted to optimal nutrient and energy availability. The central regulator of the eukaryotic cell growth and response to the variety of signals, including nutrients and oxygen, is the highly conserved mammalian target of rapamycin complex 1 (mTORC1) [42]. Mammalian TORC1 is a critical signaling complex that regulates muscle mass. For example, in mice,

muscle-specific loss of mTORC1 reduces muscle mass and oxidative function and leads to early death [43]. The reduction of muscle weight is a common effect in cancer patients, especially those that are treated with mTORC1 inhibitors, rapamycin and rapalogs. At the same time, rapamycin has been shown to consistently increase the lifespan in many model organisms. In particular, a significant decrease in the amount and function of muscle mitochondria was detected upon life-long high protein diet in mice which was reverted by chronic treatment with rapamycin [44].

Among many functions exerted by mTORC1, one of the most complex ones involves regulation of mitochondrial homeostasis. mTORC1 is essential for mitochondrial biogenesis, phosphorylation of mitochondrial proteins and regulation of selective degradation of mitochondria by autophagy and mitophagy [45]. Under favorable conditions, mTORC1 stimulates mitochondrial biogenesis via transcriptional regulation of a number of mitochondrial genes. Remarkably, mTORC1 activity is induced by low level of ROS, while high ROS levels lead to its inhibition [46]. ROS probably activate mTORC1 via oxidation of cysteine groups either in the mTORC1 complex itself [47] or in some of its upstream regulators [48]. In addition, one of mTORC1 upstream regulators, Sestrin 2, has an antioxidant function that suppresses ROS [49]. Sestrin 2 may function as a direct scavenger for ROS [50] and is also involved in the regulation of mitochondria respiration [51]. Overall, the inactivation of mTORC1 by ROS represents a feedback mechanism, since it leads to reduction of mitochondria via mitophagy and thus prevents further increases in ROS formation. Taken together, these findings demonstrate that skeletal muscle adaptation to ROS production is important for the energy metabolism and mitochondrial biogenesis (Fig. 1).

Pathological effects of oxidative stress on skeletal muscles

Oxidative stress is a major contributor to aging. Indeed, ROS can affect skeletal muscles health and aging; they can reduce the efficiency of myogenic differentiation. An excess in ROS production alters mitochondria necessary for the myogenic differentiation [52]. Besides oxidative damage to mitochondrial DNA, ROS can also cause mitochondrial fragmentation and alteration of mitochondrial permeability facilitating the release of cytochrome *c*, which triggers apoptosis (for review see [53]). Oxidative stress can also promote autophagy by stimulating the maturation of autophagosomes [54], as well as mitophagy [55]. Interestingly, mitochondrial ROS can change the fate of muscle precursor cells (satellite cells) by promoting their transdifferentiation into adipocytes [56]. This may contribute to muscle aging.

ROS can also affect muscle regeneration. Besides the flow of ROS produced by skeletal muscle cells in response to various internal and external stimuli, ROS can be generated by non-muscle cells. Indeed, ROS produced by inflammatory cells after a muscle injury followed by a local inflammation are involved in the regeneration and repair of the damaged muscle. In contrast, a constitutive presence of ROS maintained by neutrophils develops into a pathological state which promotes muscle injury by damaging myoblasts and myotubes and by slowing muscle regeneration [36]. During inflammation, ROS generated as a result of the TNFα inflammatory cytokine action may prevent the formation of β-catenin-E-cadherin complexes in the vicinity of the cell membrane, thereby altering interactions between the cell and the extracellular matrix and between cells, thus inhibiting the formation of myotubes [57, 58].

ROS accumulation causes muscle atrophy and muscle weakness. In fact, aged muscles produce more ROS and

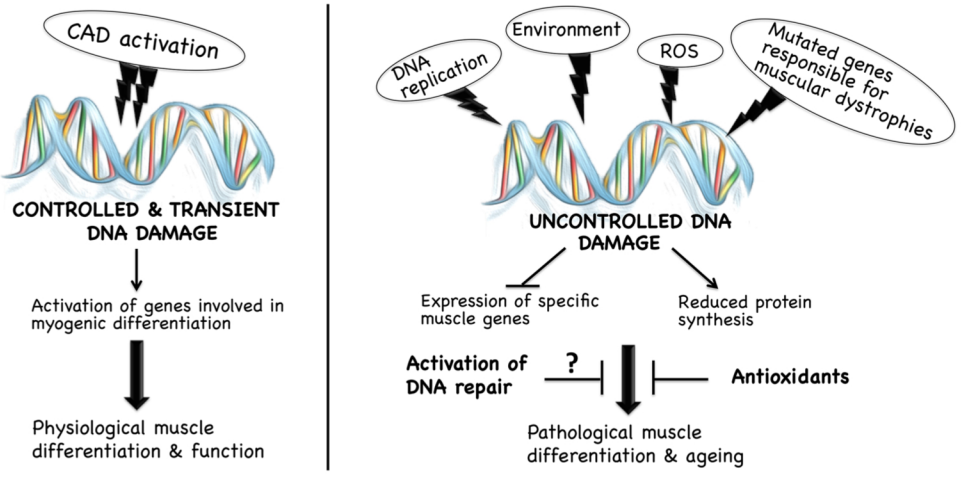

Fig. 1 Physiological and pathological roles of ROS and DNA damage in muscle

accumulate oxidative damage [59, 60]. Muscle inactivity, most commonly seen in elderly people, causes local ROS production which might lead to muscle atrophy [61, 62]. In old muscles, antioxidant muscle adaptation to ROS production is diminished [63]. In addition, the accumulation of iron with age accelerates the production of ROS [64]. Therefore, muscles become more susceptible to ROS with aging, which leads to an increased level of lipid oxidative degradation, protein oxidation and oxidative damage of DNA. A strong ROS production is accompanied by muscle fatigue and a decrease in muscle strength [35, 65].

To sum up, oxidative stress can severely affect myogenic differentiation and muscle regeneration by altering satellite cells proliferation, cell fusion and differentiation. It thus alters the morphology and function of skeletal muscle and accelerates muscle aging. ROS have been described to be involved in the pathophysiology of several muscle diseases, including DMD [120–122], myotonic dystrophy [123], LGMD dystrophy [124], FSHD [80] and sarcopenia [125]; antioxidants have been suggested as a treatment of muscle disease in dystrophic mouse models [126, 127] (discussed in the "Antioxidants in treatment of neuromuscular disorders" section).

Oxidative DNA damage

DNA damage plays a major role in mutagenesis, carcinogenesis, and aging. It may be either endogenous (i.e., due to respiration and cell metabolism) or exogenous. Several types of oxidative DNA damage are caused by ROS: simple DNA lesions (oxidized bases, abasic sites, etc.) and complex DNA lesions such as OCDL (non-DSB oxidative clustered bi-stranded DNA lesions) (for review, see [52]).

8-Hydroxy-2′-deoxyguanosine (8-OH-dG) is the most abundant and most studied oxidative modification of DNA [53]. The 8-OH-dG is generated following guanosine hydroxylation and pairs preferably with adenine. When 8-OH-dGs are not eliminated, they can generate GC → TA transversions during DNA replication [54]. 8-OH-dG lesions are repaired primarily by the base excision repair (BER) pathway; this releases the base and creates an abasic site (AP site, for apurinic/apyrimidinic site) [55, 56].

ROS can also generate apurinic/apyrimidinic sites by capturing the hydrogen of deoxyriboses. Unrepaired AP sites can lead to the cleavage of the sugar-phosphate bond of the DNA backbone and cause DNA single-strand breaks (SSB) [57]. AP sites are frequently induced in the genome (50,000–200,000 injuries per mammalian cell) [58, 59]. However, in the presence of ROS their amount is largely increased [60] and their persistence causes deleterious effects. Indeed, AP sites may be transformed into SSB. Several SSBs close to each other on both strands of DNA can form double-strand breaks (DSBs). This effect is frequently caused by ionizing radiation (for review see [57]). DSBs are mutagenic when repaired by non-homologous end joining and have the potential to induce chromosomal translocations (reviewed in [61]. AP sites are also mutagenic due to the preferential incorporation of adenine on the opposite strand of the DNA during replication. To ensure the complementarity of bases, the AP site is thus replaced by a thymine nucleotide [62] (for review, see [63]).

DNA damage response

DNA damage response (DDR) is distinct, complex and functionally intertwined pathways for maintaining genome integrity. These pathways include coordinated process for the detection of DNA damage, the accumulation of DNA repair factors at the site of damage, and finally the physical repair of DNA damage. Each DNA repair mechanism is specific for one or more types of DNA damage [64]. Two major DNA damage detection pathways, ATM (Ataxia Telangiectasia Mutated) and ATR (ATM-related), are interconnected and regulate each other in response to different stimuli and different types of DNA damage (reviewed in [65]). These DDR pathways lead to a temporary cell cycle arrest, thus coordinating DNA repair. When DNA damage is excessive, apoptosis is triggered upon excessive DNA damage [66]. When lesions affect DNA bases and do not alter the double helix structure of DNA, such as 8-OH-dG, AP sites and SSB, they are repaired via the BER pathway [56]. DNA mismatches induced by 8-oxo-dG and AP sites are repaired by the mismatch repair (MMR) (for review see [67]). Two DDR pathways are responsible for DSB repair: the homologous recombination (HR) pathway that requires sister chromatid as a DNA template [68] and is thus considered as an error-free repair mechanism, and the non-homologous end joining (NHEJ) pathway, an error-prone repair process that can generate insertions or deletions [69].

DNA replication and transcription are also affected by DNA damage. Indeed, if replication bypasses DNA lesions, it can generate mutations and can, therefore, initiate carcinogenesis. If transcription is blocked by DNA damage, it causes senescence or apoptosis, thus accelerating cellular aging [1]. Thus, excessive ROS production, antioxidant deficiency or inefficient DNA damage detection or repair affect the level of oxidative modifications of DNA and, therefore, modulate the frequency of mutations and possibly cancer incidence [63, 70].

DNA damage, myogenic differentiation and muscle function

DNA damage, as well as oxidative stress, affects myogenic differentiation of skeletal muscle cells. Several studies have demonstrated the transient presence of DNA breaks in the process of myogenic differentiation in vitro and during muscle regeneration in vivo [71, 72]. Indeed, in skeletal muscle cells, the activation of the caspase-activated DNase (CAD) by caspase 3 during early stages of the myogenic differentiation results in controlled DNA cleavage and transient strand breaks formation. These controlled events are described as crucial to the myogenic differentiation progress, activating and targeting particular genes, e.g., by inducing DNA damage in the promoter of P21 cell cycle regulatory factor [73]. Coordinated DNA strand breaks are then rapidly repaired by the temporary caspase-triggered base excision repair pathway, as demonstrated by transient accumulation of XRCC1 repair foci in early myogenic differentiation [74]. Thus, as with the ROS, the transient and controlled DNA damage turns out to be "beneficial" for the muscle cells. For example, high doses of antioxidants which significantly reduced DNA damage also inhibited cell differentiation [75]. However, the excess and/or constitutive presence of ROS negatively affects both myogenic differentiation and muscle function.

In post-mitotic differentiated cells which no longer replicate their genetic material, DNA repair mechanisms are generally attenuated and this leads to accumulation of DNA damage during and after myogenic differentiation. However, DNA repair remains active for genes highly expressed in differentiated cells, such as genes encoding structural proteins and functional enzymes, thereby protecting the integrity of these genes and the function of their products [76, 77].

DNA damage accumulated in myoblasts after genotoxic treatment inhibits the expression of specific muscle genes (myogenin and *MHC*) and blocks the formation of myotubes [78]. This "differentiation checkpoint" induced by DNA damage corresponded to the cell cycle arrest of myoblasts in G1 or in G2 phases. However, the myogenic differentiation checkpoint is reversible since withdrawal of the genotoxic agent leads to restoration of myogenic differentiation in vitro. This differentiation checkpoint delays global gene reprogramming associated with myogenic differentiation to allow DNA repair and most likely protects against the accumulation of DNA damage in differentiated myotubes, which can compromise genomic integrity of muscle fibers. Thus, the presence of DNA damage in muscle satellite cells may affect their capacity to regenerate damaged muscles. On the other hand, the presence of sustained DNA damage from prolonged and repeated exposure of myoblasts undergoing differentiation to genotoxic agents such as ionizing radiation led to the formation of giant multinucleated myotubes with distorted phenotype [78]. Thus, phenotypically abnormal myotubes may arise from the bypass of the differentiation checkpoint which can compromise muscle remodeling and function.

DNA damage and chromosomal aberrations were observed in the skeletal muscle tissue and primary myoblast cultures from patients with muscular dystrophies, such as facioscapulohumeral dystrophy (FSHD), Duchenne muscular dystrophy (DMD) and limb girdle muscular dystrophy (LGMD), resulting in the accumulation of γH2AX foci, a marker of DNA double-strand breaks [79–82].

DNA damage directly contributes to aging by repressing gene expression, or indirectly by inducing apoptosis or cellular senescence [83, 84]. Oxidative DNA damage seems to be the major type of DNA damage which appears with/during aging [85, 86]. Accumulation of oxidative damage in nuclear and mitochondrial DNA was observed in aged skeletal muscles of mice, rats and humans [87–89]. Oxidative DNA damage blocks transcription and reduces protein synthesis and degradation; an attenuated synthesis of key proteins such as actin and myosin weakens the muscle function and strength [90, 91].

Mitochondrial DNA damage in aging and disease

Accumulation of mitochondrial DNA (mtDNA) damage in muscles leads to sarcopenia, an age-related health problem that results in the loss of skeletal muscle function and mass (up to 50% by age 80) [92]. Mitochondrial DNA damage occurs at a higher level than nuclear DNA damage [93], due to a high rate of ROS production in mitochondria, the absence of histones which protect DNA molecule from damage and the absence of some types of DNA repair in mitochondria. Oxidative damage contributes to accumulation of mtDNA deletions and in particular of a "common deletion" or mtDNA4977 which occurs between two 13 bp direct repeats that are separated by 4977 bp. The levels of mtDNA4977 were at least 100-fold higher in human skeletal and cardiac muscles from aged subjects [92, 94]. Both the number and variety of mtDNA rearrangements increased dramatically with age [95]. This correlated with mtDNA oxidative damage and a decline in mitochondrial ATP production in skeletal muscles [88, 96].

As multiple copies of the mtDNA exist in the mitochondrial reticulum, both wild-type and mutant mtDNA coexist in a state of heteroplasmy. Thus, almost no effect of mutation is observed until mutant mtDNA reaches a certain

fraction (a so-called "phenotypic threshold"). This threshold can be attained only after expansion of the mutation which appears in a single mtDNA molecule. This process called "clonal expansion" can occur without selection due to random genetic drift and nonselective increase of mtDNA replication which keeps the number of wild-type mtDNA copies constant [97]. Studies of clonal expansions of mtDNA mutations are particularly important for understanding age-related changes in skeletal muscles. Histological analysis using specific staining for the active mitochondrial cytochrome *c* oxidase (COX) revealed rare distinctive COX-deficient fibers containing a large proportion of mutant mtDNA (typically with deletions) [98, 99]. Each COX-deficient fiber contained one type of deletion while other deficient fibers contained different deletions, which clearly confirmed their clonal nature and indicated that expanded mutations caused most if not all of the observed COX defects. The proportion of COX-deficient fibers was typically less than 0.1% in young human muscles and increased $\sim$10 times with age. At least in some cases, COX deficiency was followed by complete degeneration of the fiber via apoptosis and necrosis [99–101].

The age-related defects in mtDNA could be recapitulated in vivo in mice with a genetic modification of a proofreading exonuclease activity of mitochondrial polymerase gamma (*polG*) resulting in an error-prone "mutator" enzyme. The "mutator" (homozygous $Polg^{mut/mut}$ knock-in) mice generates $10–20 \times 10^{-4}$ mutations per base pair of mtDNA; this is accompanied by multiple symptoms of premature aging, including dilated cardiomyopathy, thymic involution, testicular atrophy, sarcopenia, etc. [102, 103]. No signs of oxidative stress were detected in these studies; however, recent studies using more sensitive ROS assays have demonstrated oxidative stress in various tissues of the mutator mice [104]. Mitochondrial hydrogen peroxide level was similar in young "mutator" and control mice, but increased with age in "mutator" mice while remaining unchanged in the control. Furthermore, transgenic overexpression of mitochondria-targeted catalase has been shown to partially attenuate cardiomyopathy in the "mutator" mice [105]. Recently, it was shown that the mitochondria-targeted antioxidant 10-(6′-plastoquinonyl) decyltriphenylphosphonium (SkQ1) [106] diminished the expression of the oxidative stress markers, delayed development of aging-related pathologies and prolonged the lifespan of the "mutator" mice. All these findings suggest a link between prolonged accumulation of mtDNA mutations, ROS production and premature muscular aging.

DNA damage in neuromuscular disorders

The accumulation of γH2AX foci, a DNA double-strand breaks marker, and the appearance of aneusomia with age was observed in muscle tissue and primary myoblast cultures from patients with DMD and LGMD type 2B (LGMD2B). DNA damage was also detected in the non-affected muscles of a DMD fetus and young DMD patients and was, therefore, considered to be an early event in this pathology [81]. In addition, disruption of genes responsible for muscular dystrophies (dystrophin gene for DMD, dysferlin gene for LGMD) in murine models was accompanied by DNA damage, γH2AX foci accumulation, genetic instability characterized by duplications and amplifications of oncogenes, activation of the DNA damage response pathway, and an increased susceptibility to develop sarcoma [81].

A deficiency in DNA damage repair has been reported in Emery–Dreifuss muscular dystrophy, disease caused by the mutation in genes encoding emerin or lamin A/C, and in several laminopathies caused by mutations in genes encoding proteins of the nuclear lamina. Indeed, mutations in the gene encoding lamin A/C, involved in DNA repair and maintenance of genome integrity, disrupt DNA damage response and repair mechanisms, leading to genomic instability and premature aging [107–109].

The presence of DNA damage prenatally and at birth has been described in skeletal muscles of a mouse model of spinal muscular atrophy (SMA), a genetic disorder characterized by progressive limb and trunk paralysis, muscle atrophy and motor neuron degeneration. An increase in DNA fragmentation was observed few days after birth, accompanied by cell death [110].

Recently, DNA damage and oxidative stress were shown to be involved in the pathophysiology of facio-scapulo-humeral dystrophy (FSHD), one of the most common genetic myopathies characterized by a progressive and asymmetric weakening of a specific group of skeletal muscles, typically facial, shoulder girdle and upper arms muscles. FSHD is a multifactorial disease that results from the combination of genetic and epigenetic events mapped at the 4q35 locus [111]. These alterations lead to chromatin relaxation followed by overexpression of many 4q35 genes, notably *DUX4*, the major actor in FSHD pathology. FSHD myoblasts derived from patients show a distinct transcription profile; they exhibit morphological differentiation defects and are sensitive to oxidative stress. We found that constitutive presence of oxidative DNA damage in in vitro cultured FSHD myoblasts is related to *DUX4* expression and appearance of morphological defects in FSHD myotubes [80]. Moreover, we demonstrated that a

high basal level of DNA damage resulted in the accelerated saturation of DNA repair machinery in FSHD [79].

Antioxidants in treatment of neuromuscular disorders

The consequences of DNA damage in muscle satellite cells and fibers are dual: the controlled DNA damage is necessary for muscle differentiation [73, 74] while ROS-induced DNA damage may lead to degeneration and aging of differentiated muscles [78, 88, 112, 113]. DNA damage and ROS may also inhibit proliferation and differentiation of muscle satellite cells [78] (for review, see [4]). Since the most DNA damage is caused by ROS, treatment of muscle cells with antioxidants was proposed and tested. Application of antioxidants improved proliferation of muscle progenitor cells [114], myotubes formation [115], functioning of differentiated muscles [116, 117] and the capacity of muscle satellite cells to fuse and to regenerate damaged muscles [80, 91, 118]. Antioxidants also stimulated angiogenesis which can improve muscle regeneration after ischemia [119]. On the other hand, high doses of antioxidants inhibited normal muscle differentiation [75, 118]. Whether specific treatment of DNA damage in in vivo injured muscles or muscles of patients with neuromuscular dystrophies could reverse the defective phenotype remains the subject of further studies.

Conclusions

DNA damage and oxidative stress seem to be closely linked and can affect myogenic differentiation, the morphology and function of skeletal muscle. ROS are involved in the pathophysiology of several muscle diseases, including DMD [120–122], myotonic dystrophy [123], LGMD dystrophy [124], FSHD [80] and sarcopenia [125]. The beneficial effect of antioxidant treatment on muscles was observed in dystrophic mouse models [126, 127].

Oxidative stress, inefficient or altered DNA repair, chronic inflammation, overtraining, inactivity and muscle injury are major causes of DNA damage in skeletal muscles. DNA damage accumulation can induce point mutations, deletions, translocations and illegitimate recombination [128–130]. Apoptosis can protect cells from cell transformation and malignancy; thus, programmed cell death could simultaneously be a secure alternative to preserve muscle health, and a reason for muscle atrophy and muscle regeneration exhaustion.

Common characteristics of certain muscular dystrophies suggest the involvement of DNA damage and genetic instability in the pathophysiology of these diseases and their susceptibility to developing cancer (for review, see [82]). Mutations in genes responsible for muscular dystrophies can lead to DNA damage, premature aging as well as cancer development. Further studies are needed to decipher the molecular pathways linking DNA damage, muscle atrophy, muscle aging and cancer in human muscular dystrophies.

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