Review

Muscular dystrophies share pathogenetic mechanisms with muscle sarcomas

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Several lines of recent evidence have opened a new debate on the mechanisms underlying the genesis of rhabdomyosarcoma, a pediatric soft tissue tumor with a widespread expression of muscle-specific markers. In particular, it is increasingly evident that the loss of skeletal muscle integrity observed in some mouse models of muscular dystrophy can favor rhabdomyosarcoma formation. This is especially true in old age. Here, we review these experimental findings and focus on the main molecular and cellular events that can dictate the tumorigenic process in dystrophic muscle, such as the loss of structural or regulatory proteins with tumor suppressor activity, the impaired DNA damage response due to oxidative stress, the chronic inflammation and the conflicting signals arising within the degenerated muscle niche.

Rhabdomyosarcoma

Soft tissue sarcomas are rare mesenchymal tumors that can develop in tissues such as fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues. Rhabdomyosarcoma (RMS) is the most common malignant childhood soft tissue sarcoma, with an incidence of approximately one individual per million people in the USA, and thus approximately 400 children are affected each year [1–3].

Histologically, RMS is defined as a small round blue cell tumor which expresses markers of myogenic differentiation, including MyoD, myogenin, and desmin. Although RMS originates from cells of the skeletal muscle lineage, it may arise in both muscular and nonmuscular tissues in disparate parts of the body. Histopathological and genetic criteria define two main histological variants, termed embryonal (ERMS) and alveolar (ARMS), and a third, less common and found in adults, defined as pleomorphic (PRMS). ERMS is characterized by a severe genomic instability, often leading to loss of imprinting (LOI) or heterozygosis (LOH) in different chromosomal loci. ARMS is instead characterized by nonrandom t(2;13)(q35;q14) and t(1;13)(p36;q14) chromosomal translocations that enable the oncogenic expression of chimeric PAX3–FOXO1 and PAX7–FOXO1 transcription factors [4,5]. Clinically, ERMS presents at an earlier age, mainly in the head and neck and retroperitoneum, and is associated with a better prognosis, whereas ARMS is more common in older children and adolescents, mainly in the trunk and extremities, and has a worse prognosis because it frequently metastasizes to other tissues [6].

The high incidence of RMS in individuals affected by some cancer-associated diseases, such as Li–Fraumeni, Costello and Gorlin syndromes [7], and the generation of various experimental animal models [8] strongly suggest that RMS onset is favored by suppression of the p53 pathway in conjunction with the aberrant gain of activity of different tyrosine–kinase receptors along the Ras axis, whereas the same genetic hits in the presence of PAX3–FOXO1 or PAX7–FOXO1 fusion gene products may result in the appearance of the ARMS histotype [9–12].

Intriguingly, several lines of evidence suggest that numerous mouse models of muscular dystrophy (MD) are particularly prone to develop sarcomas, especially RMS. In the following sections we briefly describe the main features of MDs and summarize the dystrophic animal models that are associated with RMS, before discussing the potential mechanisms underlying RMS genesis in more detail.

Dystrophic mouse models developing rhabdomyosarcoma

Skeletal muscle is the most abundant tissue in the vertebrate body and is primarily responsible for body locomotion, posture, and breathing. Muscular patterning and growth is determined by the coordinated spatial and temporal action of distinct classes of myogenic progenitors [13], particularly the satellite cells (SCs), a pool of dormant cell elements closely juxtaposed to the plasmalemma of myofibers under the basal lamina that contribute to the regenerative ability of skeletal muscle [14–19].

The complexity of the muscle architecture can be severely affected whenever one of the extracellular and intracellular elements is not properly functional. MDs

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Keywords: rhabdomyosarcoma; muscular dystrophy; muscle niche; aging; oxidative stress; inflammation.

1471-4914/$ – see front matter
 http://dx.doi.org/10.1016/j.molmed.2013.07.001

Box 1. Muscular dystrophies

The mechanical resistance of skeletal, cardiac, and smooth muscle cells is in large part due to the so-called DAG complex [148], which at the sarcolemma acts as a molecular bridge interconnecting the extracellular matrix (ECM) surrounding each myofiber with the cytoskeleton (Figure I).

Most MDs depend on the loss of expression or function of members of the DAG complex, leading to diseases that hamper a patient's mobility and vary enormously in terms of severity, age of onset, selective muscle involvement, and inheritance pattern. Furthermore, dystrophic patients frequently develop cardiomyopathies because the expression of various structural sarcomeric and nonsarcomeric proteins overlaps in skeletal and cardiac muscle tissues. Although advances in genetic and stem cell based therapeutic approaches have fueled hopes for effective therapies [149], corticosteroid administration still remains the only effective treatment available to counteract inflammation in MDs.

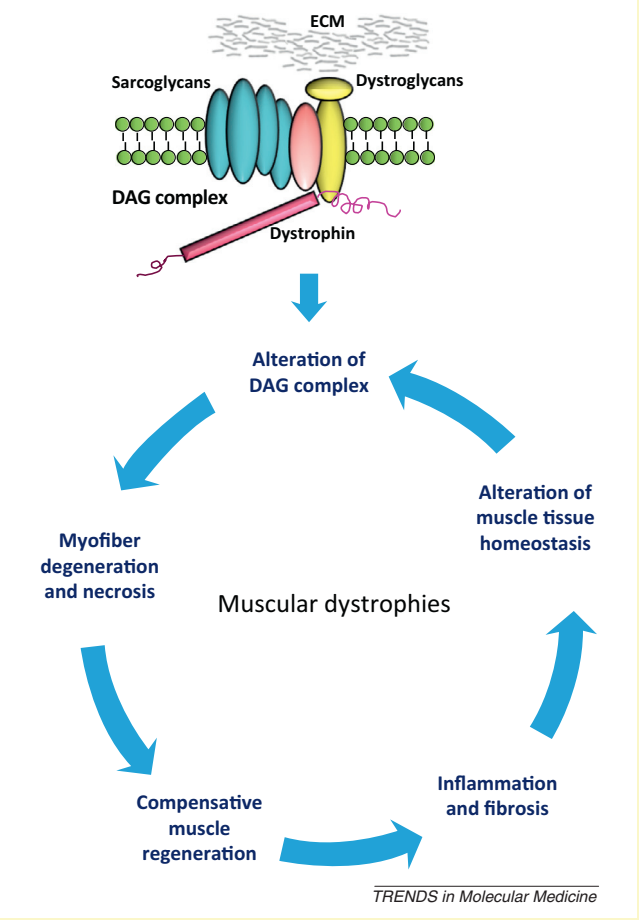

Figure I. Common features of muscular dystrophies. Following alteration of the DAG complex, the skeletal muscle undergoes a progressive necrotic degeneration followed by repeated cycles of muscle regeneration that prolonged over time consistently deplete the pool of satellite cells, ultimately impairing its regenerative ability. Dystrophic muscle is also characterized by the presence of chronic inflammation mainly represented by macrophage infiltration, and the occurrence of fibrotic and adipose areas that are responsible for muscle weakness and worsen the clinical outcome, especially by impairing the function of diaphragm muscle.

(Box 1) are clinically and molecularly heterogeneous genetic disorders caused by mutations in genes encoding a wide variety of proteins, such as extracellular matrix proteins, transmembrane and membrane-associated proteins, cytoplasmic enzymes, and nuclear matrix proteins, and are characterized by primary degeneration of skeletal muscle [20,21]. Despite this heterogeneity, MDs commonly share a variety of clinical characteristics although to different extents depending on the severity of the disease, including myofiber degeneration (necrosis) and regeneration, inflammation, and fibrosis (see Figure I in Box 1).

Over the past years, a rare occurrence of RMS in human patients affected by MDs has been reported [22,23], and more recently the analysis of MD mouse models has helped decipher that a permissive environment for sarcomas establishes within the dystrophic muscle niche, especially in aged mice (Table 1), as summarized below.

mdx mice lack functional dystrophin thus reproducing Duchenne muscular dystrophy (DMD). In comparison to human DMD, *mdx* mice exhibit a milder nonprogressive phenotype characterized by significant muscle regeneration [24–26]. The occurrence of RMS has particularly been observed in aged *mdx* mice [27,28], and tumor formation was associated with the presence of *P53* mutations [28]. Consistently, double mutant *P53/Mdx* mice are more prone to develop RMS [28].

The α-sarcoglycan (α*SGCA*) gene encodes a transmembrane glycoprotein stabilizing the dystrophin-associated glycoprotein (DAG) complex and is involved in autosomal recessive limb-girdle muscular dystrophy type 2D (LGMD2D) [29]. As seen in *mdx* mice, α*SGCA*-deficient mice are prone to develop ERMS in the presence of mutated, cancer-related forms of p53 [28], confirming that disruption of the p53 pathway cooperates in the formation of RMS.

Loss of function of dysferlin, a transmembrane protein involved in repairing the sarcolemma after muscle damage, results in two types of MD, Miyoshi myopathy and LGMD2B [30,31]. Two different *dysferlin*-deficient mouse strains (A/J and C57BL/10) have been characterized and shown to develop PRMS and mixed rhabdomyosarcomas, fibrosarcomas and liposarcomas, respectively, especially later in life [32,33]. Significantly, the simultaneous loss of dystrophin and dysferlin in double mutant mice increases the incidence of RMS [32,34].

LGMD2A is caused by mutations in the *Capn3* gene [35], encoding the muscle-specific calcium-activated neutral protease calpain-3 involved in muscle remodeling [36]. *Capn3*-deficient mice are affected by a mild progressive MD [37] and develop muscle-derived RMS [32]. The simultaneous loss of dystrophin and calpain-3 in double mutant mice significantly augments the frequency of RMS [32].

Finally, the *Large* gene encodes a putative glycosyltransferase involved in the glycosylation of dystroglycan, and its deletion in homozygous mutant mice is responsible for a severe myodystrophy (myd), considered as a form of secondary dystroglycanopathy [38–40]. Despite their considerably shortened lifespan, myd mice have been found to develop RMS, although rarely [32].

How can muscular dystrophy favor rhabdomyosarcoma genesis?

To understand the basis of sarcoma susceptibility in dystrophic muscle, it is helpful to review the main, tightly interconnected events that predispose tumor formation (Figure 1): (i) the loss of structural or regulatory proteins with tumor suppressor activity; (ii) the impaired response

Table 1. Models of dystrophic mice exhibiting development of sarcomas

Mouse models	Protein (function)	Homologous human disease (severity in mouse)	Mouse lifespan	Tumor spectrum	Refs
Single mutant mouse models					
Mdx	Dystrophin (mechanical resistance of muscle fibers)	DMD (mild)	>1 year	Mixed sarcomas	[27,28,32]
Sgca$^{-/-}$	α-Sarcoglycan (stabilization of the DAG complex)	LGMD2D (moderate)	>1 year	ERMS	[28]
Dysf AJ *Dysf*$^{-/-}$ C57BL/10	Dysferlin (repair of the sarcolemma after muscle damage)	LGMD2B (mild)	>1 year	Mixed sarcomas	[32,33]
Capn3^{tm1Jsb}	Calpain-3 (muscle remodeling)	LGMD2A (mild)	>1 year	Mixed sarcomas	[32]
Large	Large (glycosylation of dystroglycan)	Myd (moderate)	<1 year	Mixed sarcomas	[32]
Double mutant mouse models					
Mdx/*P53*$^{-/-}$	Dystrophin/ P53			ERMS	[28]
Mdx/*Dysf*$^{-/-}$	Dystrophin/ Dysferlin			ERMS PRMS	[32,34]
Mdx/*Capn3*$^{-/-}$	Dystrophin/ Calpain 3			Mixed sarcomas	[32]

Abbreviations: DMD, Duchenne muscular dystrophy; LGMD2A, LGMD2B, LGMD2D, limb-girdle muscular dystrophy type 2A, 2B, 2D; Myd, myodystrophy, a secondary form of dystroglycanopathy.

to DNA damage; (iii) the conflicting signals arising within the muscular niche of aged MD mice; and (iv) chronic inflammation.

Loss of structural or regulatory proteins with tumor suppressor activity

Reduction in protein levels of members belonging to the DAG complex is not only responsible for skeletal muscle damage observed in MDs but is also associated with several types of cancer, suggesting that a functional DAG complex may act as a tumor suppressor [41,42].

In this regard, the inactivation of dystrophin in human melanoma cell lines is associated with enhanced migration and invasiveness, whereas its re-expression restores a senescent cell phenotype [43]. Utrophin, the highly related autosomal paralog of dystrophin, is downregulated or mutated in several human tumors such as breast cancer, neuroblastomas, and malignant melanomas, and its overexpression in breast cancer cells inhibits tumor cell growth *in vitro* and *in vivo* [44].

Reduced expression or absence of α-dystroglycan has been reported in human breast, prostate, and colon cancers [41,45–47], and functional restoration of α-dystroglycan in breast cancer cells is sufficient to reduce their tumorigenic potential *in vivo* [46]. Interestingly, reduced α-dystroglycan expression has also been found in several pediatric sarcomas, including ARMS and ERMS [48], supporting a link between *SGCA* deregulation and RMS occurrence. In several highly metastatic epithelial cell lines derived from breast, cervical, and lung cancers, α-dystroglycan has been found correctly expressed but lacking laminin-binding activity due to defective expression of *LARGE* [49]. Ectopic expression of *LARGE*, which is required to synthesize laminin-binding glycans, enhanced cell adhesion and reduced cell migration *in vitro* in those cancer cells [49]. Consistently, the epigenetic silencing of *LARGE* has been shown to result in the onset of sarcomas in the CMD1D animal model [32,48], indicating that defective α-dystroglycan glycosylation is important in the occurrence of sarcomas. In this context, other genes required for the glycosylation of α-dystroglycan, such as fukutin and fukutin-related protein (FKRP), that have been associated with several muscle pathologies such as Fukuyama congenital muscular dystrophy (FCMD), LGMD2I, MDC1C, Walker–Warburg syndrome (WWS), and muscle eye brain (MEB) disease [50,51], might predispose to tumorigenesis. For example, fukutin silencing has been reported to increase the proliferation of epithelial cancer cells by activating c-jun-dependent signaling [52].

Finally, two splice variants of calpain-3, the absence of which is responsible for LGMD2A, have been found downregulated in metastatic and apoptosis-resistant melanoma cells [53], whereas overactivation of calpain-3 has been reported in cattle urothelial tumor cells [54].

The hypothesized role of some DAG complex proteins as tumor suppressors may reside in their ability to affect microtubule dynamics and stability, and thus cell proliferation and migration. Indeed, dystrophin behaves as a microtubule-associated protein (MAP) by interacting with microtubules in skeletal muscle cells [55], and dysferlin interacts with α-tubulin and microtubules [56], preventing microtubule depolymerization by controlling the levels of α-tubulin acetylation in myoblasts [57].

Impaired response to DNA damage

It has been shown that the dystrophin gene localizes within a common fragile site (CFS) and has reduced expression in cultured brain tumors [58], suggesting that instability of genes adjacent to CFSs could be simultaneously associated with multiple human diseases [59]. Actually, several

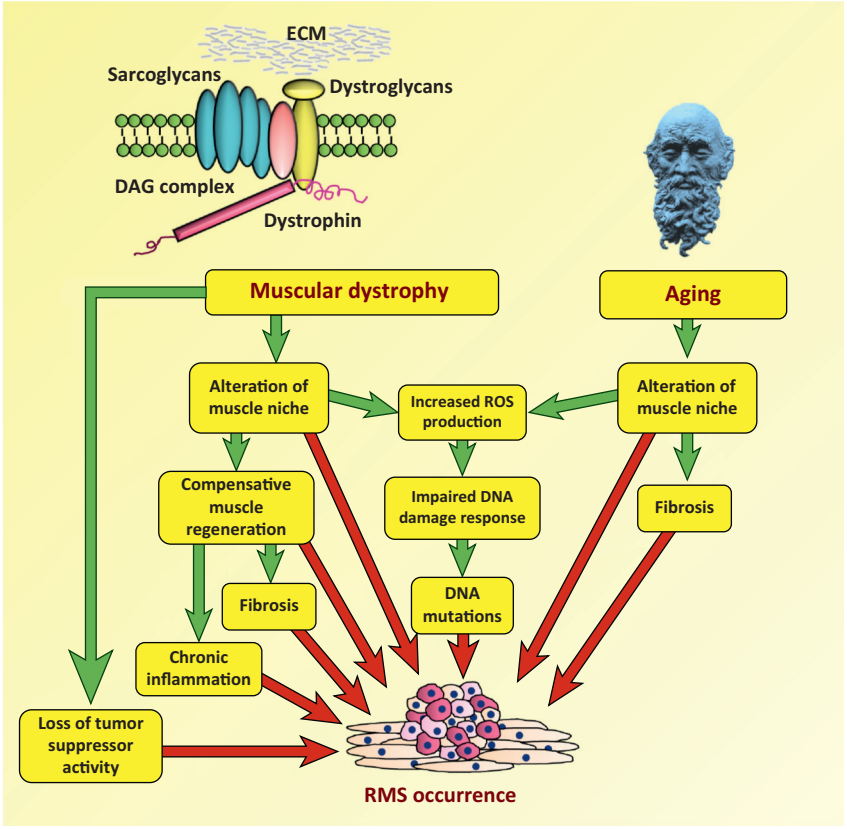

Figure 1. Aged muscular dystrophy skeletal muscles share a subset of pathological characteristics that may provide the molecular and cellular basis of RMS susceptibility. In particular, the accumulation of ROS, which characterizes both dystrophic and aged muscles, may have a major role in favoring RMS formation due to both the accumulation of DNA mutations and the simultaneous impairment of the DNA damage response system. In concomitance, the profound alteration of the muscular niche experienced by both muscular dystrophy and aged muscle can drive out several cell progenitors hosting the muscle niche from their original fate, eventually allowing cancer formation. Abbreviations: ECM, extracellular matrix; RMS, rhabdomyosarcoma; ROS, reactive oxygen species.

independent lines of evidence suggest that the etiology of MDs can share some molecular mechanisms with cancer. In this regard, the specific genomic alterations detected in the sarcomas described in the various aforementioned MD mouse lines, ranging from loss of tumor suppressors (Cdkn2a, Nf1) and amplification of oncogenes (Met, Jun) to recurrent duplications of whole chromosomes (8 and 15) and aneuploidy [32], typically result from unrepaired DNA double-strand breaks (DSBs) that occur during early events in cancer development [60,61]. In accordance, a marked activation of the major canonical DNA damage response pathway, that is, the ataxia telangiectasia mutated (ATM) kinase and its downstream target histone γ-H2AX [62–64], was observed in murine dystrophic muscle prior to tumor formation and in different prepathologic muscle from human DMD, LGMD2A, -2B, and -2I [32]. Consistently, impaired DNA repair has been found in Emery–Dreifuss muscular dystrophy and a number of different diseases collectively called laminopathies, because the mutations in the genes that encode lamins and emerin (a lamin-associated protein) affect the structural integrity of nuclear lamina, replication, and gene transcription, which are intimately associated with the DNA damage repair system [65,66].

Several studies have documented the key role of oxidative stress and abnormal production of reactive oxygen species (ROS) in the pathophysiology of MDs [67,68] and other muscular pathologies, such as sporadic inclusion body myositis (s-IBM) [69]. Indeed, antioxidant treatments have been shown to counteract myocyte injury in *mdx* mice [70]. In particular, ROS formation appears to be a causative event rather than a consequence of muscle degeneration [71], and increased ROS can cause failure to repair DSBs, leading to genomic instability, tumorigenesis, and age-related diseases [72]. In addition, increased ROS levels can interfere with the activity of the ATM kinase in orchestrating the signaling cascades that initiate the DNA damage response [73], therefore leading to the misrepair of DSBs. These results suggest that genomic instability observed in dystrophic muscle could likely be associated with oxidative stress. Interestingly, the accumulation of unrepairable DNA damage in fibroblasts from patients with Hutchinson–Gilford progeria syndrome, a rare disease caused by mutations of lamin A and characterized by accelerated aging [74], has been linked to ROS generation and is prevented by treatment with the antioxidant, *N*-acetylcysteine [75].

The first indication of age-related alterations in DSB repair is the exponential increase in the incidence of cancer with aging [76], because cancer is associated with genome rearrangements and LOH. DNA repair itself can be subjected to age-related changes as decline of DNA repair

efficiency and fidelity leads to more mutations, and further exacerbates age-related functional decline [77]. Because the occurrence of sarcomas is mostly detectable in aged dystrophic mice, it is likely that increased oxidative stress in dystrophic muscle concurs to DNA damage prior to MD onset and further dampens its repair, thereby allowing the accumulation of mutations and breakpoints that predispose RMS formation. Finally, it is worth noting that RMS has been associated with constitutional mismatch repair deficiency syndrome [78] and that altered gene expression of several members belonging to the DNA repair system has been reported in RMS [79].

Conflicting signals arising within the dystrophic and aged muscle niche

The muscular niche is the microenvironment in which a number of myogenic and nonmyogenic progenitors reside in a systemic milieu that provides trophic support [80–83].

Sarcomas arisen in MD mice are mainly localized to the skeletal muscle, suggesting that the cells of origin are likely to be part of the muscle niche. Two types of stem cells reside in this environment, SCs and multipotent stem cells (MPSCs) [81,84,85], the latter cell population including a variety of several progenitors displaying myogenic ability, such as mesenchymal stem cells (MSCs) [86,87], hematopoietic derived cells [88–90], interstitial space-associated cells [91,92], small vessel-associated pericytes [93,94], and mesoangioblasts [95–97]. RMS can originate from SCs, differentiating myoblasts and MSCs, in the presence of certain genetic hits, such as loss of p53, gain of the Ras pathway, and expression of PAX3–FOXO1 or PAX7–FOXO1 [9–12,98–104]. However, in light of the variety of the cell elements that make up the niche, we cannot exclude that RMS may originate from other cell types.

How can cell progenitors undertake a tumorigenic road in the dystrophic muscular niche? To address this question, we should consider that muscle stem cell potential derives from the combination of the intrinsic properties of the cell and the extrinsic cues from the environment [105–108], and therefore cancer may arise as a consequence of alterations of the intrinsic properties of cell progenitors, changes in the niche and/or the systemic milieu, or, most likely, a combination of all these factors.

As described above, cell intrinsic effects reflecting on DNA integrity have been associated with accumulation of oxidative damage in MD muscle, and also the individual age-dependent decline may turn into DNA-damaging responses [109], even in skeletal muscle [110]. Consistently, premature aging syndromes, or progeroid syndromes, are mainly caused by defects in repairing DNA, strengthening the idea that aging is accelerated by an impairment of DNA repair [111].

Within the dystrophic and aged muscle niche, the fate of the different cell progenitors, normally resulting from the combined action of paracrine signals provided by several vascular, fibroadipogenic progenitors (FAPs) [112–117], and ECM architecture [118], could be diverted to a cancerous road by miscellaneous external conflicting signals. Indeed, muscle-derived stem cells (MDSCs) can generate osteosarcoma and RMS following exposure to contradictory extracellular signals, that is, concomitant osteogenic and myogenic differentiation signals, and regardless of the occurrence of genetic changes [119]. Also, the aged muscular niche can drive SCs out of quiescence [120], and this may potentially create a permissive state for tumor formation.

A common characteristic observed during aging and in MDs is the replenishment of the muscular tissue by fibrotic and fat tissue. This occurs because the aged SCs can enter alternative differentiation programs by adopting fibroblastic and adipogenic fates [121,122], particularly in response to injury [122–126], whereas MSCs can trans-differentiate into adipocytes in DMD muscle [127,128]. These findings suggest that the increased rate of cell trans-differentiation observed in aged MD mice may be permissive for RMS and also provide a rationale for explaining the frequent occurrence of RMS in nonmuscular tissues, because recent results have shown that a deliberate activation of Sonic hedgehog signaling (Shh) in mouse adipocytes is sufficient to give rise to RMS [129].

Chronic inflammation

The inflammatory response is an early hallmark of muscle damage necessary to activate the sequence of events required for tissue repair and the recovery of muscle homeostasis [130]. A condition of chronic inflammation is found in most muscular diseases due to either a direct involvement of the immune/inflammatory system, as in the case of inflammatory myopathies, or activation of inflammatory pathways as a consequence of structural alterations in skeletal muscle tissue, as in the case of MDs. This association involves either intrinsic pathways, when inflammatory responses are triggered by oncogenes or tumor suppressor genes, or extrinsic pathways, in conditions causing nonresolving smoldering inflammation [131–133]. Notably, typical cancer-promoting pathways are activated by inflammatory cytokines classically overexpressed in dystrophic muscles, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Although high doses of TNF-α result in antitumor activity, low doses enhance cell growth and migration in several cell types, and may contribute to oncogene activation and thus to tumorigenesis [134]. IL-6, a downstream effector of oncogenic Ras [135], has proangiogenic and tumor-promoting activity in several cancer types [136–138] and shows antiapoptotic effects on normal and malignant epithelial cells through the activation of STAT3, thus increasing cell survival [136].

In addition, macrophages which represent the main component of immune cell infiltrate in dystrophic muscle have a major role in cancer-promoting inflammation. In particular, alternatively activated (M2) macrophages have been involved in tumor progression because of their ability to remodel tissues, promoting angiogenesis and suppressing adaptive immunity [139,140], and a switch of macrophages to the M2 phenotype has been observed in the late stage of the pathology in dystrophic *mdx* mice [141], thus representing an explanation for the age-related tendency towards RMS formation in this DMD experimental model.

Potential limitations of the association between MD and RMS in humans

Although aged MD mice are prone to sarcoma formation, dystrophic individuals appear to be more protected, as only a few cases have been reported thus far [22,23]. Many

factors can contribute to make this difference, including the shorter average lifespan in patients, given that the onset of RMS in mice can be clearly seen during aging. Also, corticosteroid therapy, employed to counteract inflammation in MD patients, might represent an 'obstacle' to the appearance of RMS, as MD mice are not treated with anti-inflammatory drugs. Also, we do not know if a reduction of the expression of DAG proteins may occur during aging, thus favoring RMS formation.

An emerging body of evidence indicates that there are parallelisms but also fundamental differences in how the process of tumorigenesis occurs in mice and humans [142]. One factor that is likely to have an important role at the organismal level is the significantly higher rate of cumulative DNA damage observed in mice than in humans because of the approximately seven times higher basal metabolic rate in mice compared with humans, leading to markedly increased levels of endogenous oxidants responsible for the bulk of DNA damage and accumulated mutations [143]. Indeed, mice excrete 18-fold more breakdown products of DNA that has been damaged by endogenous oxidants per kg of body weight than do humans [143]. In addition, the evolutionary development of several distinct and more efficient antineoplastic mechanisms has led to a decrease in cancer susceptibility in humans compared with mice [144].

Noteworthy, the mouse models of MD are frequently characterized by a milder nonprogressive phenotype compared with the human pathology. In this regard, it has been recently shown that longer telomeres in mice protect muscles from the exhaustion of SCs, thereby improving the regenerative ability of dystrophic muscle [145]. We may speculate that the presence of a less severe, long-lasting chronic condition, as frequently recapitulated by several mouse MD models, may result in tumor formation because of the prolonged formation of ROS affecting the genomic stability.

Concluding remarks

Several independent lines of evidence obtained from animal models suggest that sarcoma genesis may be elicited by the simultaneous presence of MD and aging (Figure 1).

On the one hand, the mutated expression of DAG complex-related genes can translate into loss of tumor suppressor activity within a deeply subverted environment, like that of degenerating, dystrophic muscle that is characterized by compensative regeneration, chronic inflammation, and fibrosis, each of which represents a tumor predisposing factor. Consistently, dystrophic muscle is characterized by a marked oxidative stress that may severely affect genomic stability, therefore explaining the accumulation of genetic aberrations recognized in MD mice prior to cancer onset. In this context, the regenerating muscular environment may greatly increase the chance of developing RMS in the presence of cancer-associated alterations, as observed during skeletal muscle regeneration in mice lacking p53 [146].

On the other hand, an aged microenvironment is less effective at maintaining the myogenic fate of muscle stem cells [147] and, instead, facilitates conversion to a fibrogenic fate through increased Wnt signaling [122]. Thus, ambiguous signals arising in an aged and dystrophic muscular niche, such as increased transforming growth factor-β (TGF-β) signaling and fibrous tissue deposition, can strongly affect the commitment of diverse cell progenitors. Remarkably, aging may additionally impair the ability to repair the genetic mutations acquired through increased oxidative stress (due to MD), especially in animals, which are evolutionarily less efficient in repairing DNA damage.

Finally, chronic smoldering inflammation that characterizes both dystrophic and aged muscle tissue can represent a key condition predisposing RMS formation.

In conclusion, we may hypothesize that the accumulation of DNA damage and the presence of confusing paracrine signals occurring in the dystrophic, aged muscular niche can likely change the commitment of numerous muscle and nonmuscle cell progenitors towards a tumorigenic fate.

Acknowledgments

This work was supported by a NEDD (Network Enabled Drug Design) grant, Regione Lombardia to E.M., Associazione Amici per il Cuore-ONLUS, Chiari (Brescia, Italy), and University of Brescia research fund (ex 60%) to A.F. and E.M., and Associazione Italiana per la Ricerca sul Cancro (Project 6021) and Association Francaise contre les Myopathies (Project 15679) to R.D., and Ministero dell'Università e della Ricerca (PRIN 2009WBFZYM_002) to G.S.

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