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Review

The Changed Transcriptome of Muscular Dystrophy and Inflammatory Myopathy: Contributions of Non-Coding RNAs to Muscle Damage and Recovery

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Abstract

In order to successfully recover from damage, skeletal muscle tissue requires proper activation of a tightly orchestrated repair program. Non-coding RNAs actively participate in this complex process of demolition and rebuilding. In this review, the contribution of dysregulated non-coding RNA expression to disease-associated pathological changes is explored in hereditary muscular dystrophies and idiopathic inflammatory myopathies. Disturbances in spatiotemporal expression of non-coding RNAs appear to be key factors in disease progression, functioning both in favor of and opposed to recovery. They regulate regeneration and survival of muscle fibers as well as codetermine the severity of tissue fibrosis and inflammation. Non-coding RNAs display individual or pleiotropic effects, and strongly influence each other's activities. The described altered expression patterns can be exploited as biomarkers for diagnosis and to evaluate therapeutic success. In addition,

common signatures of these non-coding RNAs often present in different muscle disorders point to their manipulation as an approach for potentially broader therapeutic use.

Keywords
Muscular dystrophy; inflammatory myopathies; non-coding RNAs; micro RNAs; long non-coding RNAs; muscle regeneration; myositis

1. Introduction

In humans, dysfunction of the skeletal muscle system can cause progressive weakness, loss of muscle mass, and serious disability. Functional deficits can be the result of genetic defects, toxins, or idiopathic etiology. This review will focus on hereditary muscular dystrophies and acquired inflammatory myopathies.

1.1 Muscular Dystrophies

Muscular dystrophies are a group of conditions in which muscle dysfunction is either due to defective structural proteins or to genetic mutations affecting signaling molecules and enzymes. Defects in components of the large dystrophin-associated oligomeric complex of glycoproteins cause disruption of the linkage between the subsarcolemmal cytoskeleton and the extracellular matrix, which renders muscle cells vulnerable to contraction-induced damage. In Duchenne muscular dystrophy (DMD; OMIM 300677) and the milder Becker muscular dystrophy (BMD; OMIM 300376), mutations in the *dystrophin* gene itself are responsible [1]. An expansive and heterogeneous group of dystrophies comprise the limb-girdle muscular dystrophies (LGMDs), with a variety of mutations that cause weakness and wasting of the muscles in the arms and legs, of which proximal muscles are most severely affected. LGMDs are classified based on their inheritance pattern as either type 1 (autosomal dominant) or type 2 (autosomal recessive) and by their causal mutation (A to X). The severity, age of onset, and features of LGMD vary among the many subtypes and may be inconsistent even within the same family [2]. Facioscapulohumeral muscular dystrophy (FSHD; OMIM 158900) typically presents before age 20 with weakness of the facial muscles and the stabilizers of the scapula or the dorsiflexors of the foot. Weakness is slowly progressive and of variable severity [3]. Myotonic dystrophy (MD), the most common form of muscular dystrophy that begins in adulthood, is a chronic, slowly progressive, multi-system disease with symptoms including loss of muscle strength and fatigue [4]. There are two major types of the disease. Type 1 (OMIM 160900) and type 2 (OMIM 602668) are caused by mutations in *dystrophia myotonica protein kinase* and *zinc finger protein-9*, respectively. In muscular dystrophy, repeated cycles of muscle damage and regeneration deplete the tissue of its regenerative capacity.

1.2 Inflammatory Myopathies

Idiopathic inflammatory myopathy represents a heterogeneous group of rare diseases characterized by autoimmune reactions within the skeletal muscle tissue [5]. Dermatomyositis

(DM) presents with muscle weakness in the shoulders, upper arms, hips, thighs, and neck, often alongside typical skin lesions which include Gottron's sign (red scaly papules on finger joints), heliotrope rashes, and swelling around the eyes and on the upper chest or back (V-sign). Patients' skeletal muscle biopsies display complement-mediated blood vessel destruction, perimysial inflammation, and perifascicular muscle fiber atrophy [6]. Sporadic inclusion body myositis (IBM) is a chronic, slowly progressive muscle disease. Patients develop distal asymmetric weakness affecting finger flexors and proximal lower extremity weakness of the quadriceps, which later progresses to other proximal and distal muscles. Patients are predominantly men over 50 years of age. Polymyositis (PM) is a rarer condition with female predominance, often presenting as corticoid-responsive acute or subacute symmetric proximal muscle weakness. DM and PM can be subclassified on the basis of the autoantibodies present; in anti-synthetase syndrome (ASS) for instance, antibodies directed against aminoacyl tRNA synthetases can be detected. PM and IBM biopsies are both characterized by the invasion of non-necrotic muscle fibers by auto-aggressive cytotoxic T-cells and macrophages, with inflammation building up mostly at endomysial sites [7]. Muscle fibers in IBM tissue additionally develop degenerative damage, with rimmed vacuoles and inclusions containing aggregates of ectopic proteins [8]. Immune-mediated necrotizing myopathy (IMNM) presents as acute or subacute proximal muscle weakness, displaying predominant necrosis of skeletal muscle fibers [9]. The inflammatory myopathies are generally characterized by persisting inflammatory reactions that damage the skeletal muscle tissue.

1.3 Skeletal Muscle's Damage Recovery System

The skeletal muscle tissue has an impressive ability to regenerate after damage, accomplished through activation of the tissue's satellite cell pool. In unharmed muscle, these cells lie quiescent underneath the basal lamina. In response to injury, immune cells are recruited to help clear the damaged muscle fibers, and satellite cells start to proliferate and differentiate to fuse with damaged fibers and form new fibers. Muscle regeneration is a highly coordinated process that resembles embryonic muscle development. This ingenious recovery mechanism gets compromised in muscle disorders, and a multitude of non-coding RNAs appear to be implicated [10]. The non-coding RNAs are grouped based upon their length as small or long non-coding RNAs. Non-coding RNAs shorter than 200 nucleotides are termed miRNAs, and function downstream of transcription factors by repressing the target mRNA after it has been transcribed. miRNA–mRNA interactions lead to translational repression and/or mRNA destabilization. On the other hand, long non-coding RNAs (lncRNAs) can display diverse regulatory activities. They accomplish epigenetic modifications by recruiting chromatin-remodeling complexes to specific chromatin loci, act as co-factors, or modify the activity of transcriptional factors. The ability of lncRNA to identify complementary sequences also allows specific interactions with mRNA, regulating the latter's post-transcriptional processing such as capping, splicing, and editing, which influences mRNA transportation, translation, degradation, and stability. In addition, miRNAs and lncRNAs do not behave as separate entities as they can complexly regulate each other's activities.

2. Non-Coding Changes in Muscular Dystrophy and Inflammatory Myopathy

Table 1 summarizes main changes to the non-coding RNAome that have been reported in muscular dystrophy and inflammatory myopathy. For studies that carried out statistical analyses, only significant changes have been indicated.

Certain aspects of the non-coding RNA regulation in muscle disease seem to represent an adequate response instated to minimize tissue damage and optimize tissue recovery. However, other changes appear to be an inappropriate response that aggravates muscle tissue damage. The impact of regulated non-coding RNA expression on muscle fiber regeneration, survival, tissue fibrosis, and inflammation is discussed under section 2.

Table 1 Reported non-coding RNAs differentially expressed in muscular dystrophies and in idiopathic inflammatory myopathies, with upregulation (↑) and downregulation (↓) indicated.

Non-coding RNA	Molecular targets	Muscular Dystrophies	Inflammatory myopathies
miRNAS			
miR-1	*G6PD, FST, UTRN, CCND1, PAX3, PAX7*	↓ DMD [11,12] ↑ DMD [13,14,15,16] ↑ DMD, BMD, LGMD, FSHD [17] ↓ MD [18,19]	↓ DM PM IBM [20]
miR-7	*EGFR*	↓ MD [21]	↓ DM [22]
miR-10	*TIAM1*	↑ FSHD LGMD [23] ↓ MD [21]	
miR-15a	*RASSF5, MKK3, LRIG1*	↑ FSHD LGMD [23]	
miR-16	*MAP7, CDS2*	↑ FSHD LGMD [23]	
miR-17 3/5p	*ERα, SRC3*	↑ FSHD LGMD [23]	
miR-18a/b	*HSF2, SOCS5*	↑ LGMD [23]	
miR-19a	*YB1, TRIAP1*	↑ LGMD [23]	↑ PM [23]
miR-19b	*PP2A*	↑ FSHD LGMD [23]	↑ PM [23]
miR-20a/b	*SDC2, KIF26*	↑ FSHD LGMD [23]	
miR-21	*MEF2C, TPM1, TGFBR2, PTEN, SMAD7, STAT3, PPARα*	↓ DMD [24] ↑ DMD [25] LMGD [26] ↑ DMD FSHD LGMD [23]	↑ DM PM IBM [23,27]
miR-22	*HER3, MLCK2*	↑ DMD [13] ↓ DMD [23]	
miR-23	*CCNG1*	↓ DMD [24]	
miR-26a	*EZH2, SMAD1, SMAD4*	↓ DMD [23]	
miR-26b	*PTEN*	↑ LGMD [23]	
miR-27a	*PINK1, AFF1*	↑ LGMD [23]	
miR-28	*NFE2L2*	↑ LGMD [23]	

miR-29	*COLs, ELN, Akt3 YY1, Mfap5, ASB2, FBN, PDGFR*	↓ DMD [11,12,23,24] ↓ mdx [28] ↓ MD [18,29] ↑ FSHD [23]	
miR-30	*MTDH12, SMAD1, CCNE2, CELSR3, EGFR, MDM2, TIMP3*	↓ DMD [12,23]	
miR-31	*MYF5*	↑ DMD [11,30] BMD [31]	
miR-33	*CPT1, HADH, SIRT6, AMPKα1, PPARα*	↓ MD [18]	
miR-34a	*HMGB1, SIRT1, MMP2*	↑ DMD FSHD LGMD [23]	↑ DM PM IBM [23]
miR-92	*PTEN*	↓ DMD[23]	
miR-93	*VEGF, IL8*	↑ FSHD LGMD [23]	
miR-95	*SGPP1*	↓ DMD [23]	
miR-99a	*IGF1R, mTOR*	↑ FSHD LGMD [23]	
miR-99b	*mTOR*	↑ FSHD LGMD [23]	↑ DM PM [23]
miR-100	*SMARCA5*	↑ FSHD LGMD [23]	
miR-101	*CREB1*	↓ DMD [23]	
miR-103	*PTGS2, CCNE1*	↑ FSHD LGMD [23]	↑ IBM [23]
miR-106	*MMP2, ETS1*	↑ FSHD LGMD [23]	
miR-107	*NF1, EP1*	↑ FSHD LGMD [23]	↑ IBM [23]
miR-125a	*TNFAIP3*	↑ FSHD LGMD [23]	↑ IBM [23]
miR-126	*EGFL7*	↑ FSHD LGMD [23]	↓ DM [32]
miR-127	*BCL6*	↑ DMD [23]	↑ PM [23]
miR-128	*MAFG*	↑ DMD [13]	
miR-130a	*SMAD4*	↑ DMD FSHD LGMD [23]	↑ DM PM [23]
miR-130b	*PTEN*	↑ FSHD LGMD [23]	↑ PM [23]
miR-132	*AChE*	↑ FSHD LGMD [23]	↑ DM PM [23]
miR-133	*MAML1, MEF2C, COLs*	↓ DMD [12] ↑ DMD [14,15,16] ↑ DMD BMD [17]	↓ DM PM IBM [20]
miR-134	*ITGB1, FBM1*	↑ DMD LGMD [23]	
miR-135a	*JAK2, MAML1, MEF2C*	↓ DMD [11]	
miR-140	*SOX4, PDL1*	↑ FSHD LGMD [23]	
miR-142	*SOCS1*	↑ mdx [33] ↑ LGMD [23]	
miR-143	*AR2B*	↑ FSHD LGMD [23]	↑ PM IBM [23]
miR-145	*MUC1*	↑ FSHD LGMD [23]	↑ IBM [23]
miR-146a	*Camk2D, PPP3R2*	↑ FSHD LGMD [23]	↑ PM IBM [23]
miR-146b	*IRF6*	↑ BMD [31] ↑ mdx [33] ↑ DMD BMD FSHD LGMD [23]	↑ DM PM IBM [20,23,27] ↑ DM PM [34]
miR-148a	*HER3*	↑ DMD LGMD [23]	↑ DM [23]
miR-148b		↑ LGMD [23]	
miR-149	*Oct-2*	↑ DMD [13]	
miR-150	*Notch3*	↑ FSHD [23]	↑ IBM [23]

miR-151	*TWIST1*	↑ FSHD LGMD [23]	
miR-152	*WNT1, MMP3*	↑ FSHD LGMD [23]	
miR-154		↑ DMD FSHD LGMD [23]	↑ DM PM [23]
miR-155	*MEF2A, SOCS1, TSPAN13, LRP1B*	↑ mdx [33,35] ↑ DMD FSHD LGMD [23]	↑ DM PM IBM [20,23,27]
miR-181 a/b	*SRCIN1, HOXA11*	↑ LGMD [23]	
miR-181d	*CRY2, FBXL3*	↑ DMD [23]	
miR-186	*AKAP12, FOXK1, HIF1α*	↑ LGMD [23]	
miR-191	*EGFR1, NFκB*	↑ LGMD [23]	↑ PM [23]
miR-192	*DLG5, ALCAM*	↑ FSHD LGMD [23]	
miR-193b	*ERα, IGFBP5*	↓ DMD [23]	
miR-195	*EGFR*	↑ FSHD LGMD [23]	↑ IBM [23]
miR-197	*PMAIP1*	↓ DMD LGMD [23]	↓ IBM [23]
miR-199a	*FZD4, JAG1, WNT2, CAV1, DYRK1A*	↑ DMD FSHD LGMD [23] ↑ mdx [36]	↑ DM PM [23]
miR-206	*Pax3, Pax7; Notch3; IGFBP5, FST, UTRN, CNND1*	↑ DMD [11,13,15,16] ↑ DMD, BMD [14,17] ↑ MD [37]	↓ DM PM IBM [20] ↓ DM [38] ↑ PM [23]
miR-208b	*CDKN1A*	↑ DMD [15]	
miR-210	*HIF1α*	↑ DMD FSHD LGMD [23]	↑ DM PM [23]
miR-214	*TRAF, EZH2, N-ras, CTGF*	↑ DMD FSHD LGMD [23]	↑ DM PM IBM [23]
miR-221	*SNTB1, Kip1, TSPAN13*	↑ DMD BMD FSHD LGMD [23]	↑ DM PM IBM [23]
miR-222	*MyoD*	↑ DMD FSHD LGMD [23]	↑ DM PM IBM [23]
miR-223	*TNFR1, DR6*	↑ DMD [11] ↑ BMD [31] ↑ LGMD [23]	↑ DM IBM [23] ↓ DM [39]
miR-224	*HOXD10, SMAD4*	↑ LGMD [23]	
miR-279	*Notch*	↑ FSHD LGMD [23]	
miR-299 3p	*SHOC2*	↑ DMD [23]	
miR-299 5p	*SHOC2*	↑ DMD LGMD [23]	↑ DM [23]
miR-301	*NFRF*	↑ LGMD [23]	
miR-320	*SOX4*	↑ LGMD [23]	↑ PM IBM [23]
miR-331	*RALA, ELF1*	↓ DMD [23]	
miR-324	*NFκB*	↑ mdx [33] ↑ LGMD [23]	↑ PM [23]
miR-335	*ICAM1*	↑ DMD [11] ↑ MD [18] ↑ DMD FSHD LGMD [23]	↑ DM [23]
miR-342	*DNMT1*		↑ PM [23]
miR-361	*STAT6, SH2B1*	↓ DMD [23]	
miR-362	*GADD45α*	↑ LGMD [23]	↑ DM PM [23]
miR-369 5p	*TNFα*	↑ DMD FSHD [23]	↑ DM [23]

miR-376a	*Ago2, CDK2*	↑ DMD LGMD [23]	
miR-376c	*CCND1*	↑ DMD FSHD LGMD [23]	↑ DM [23]
miR-378	*MyoR, CASP9, PDK1*	↑ DMD [13] ↓ DMD BMD [40]	↓ DM PM IBM [20]
miR-379	*IL18*	↑ DMD FSHD LGMD [23]	↑ DM PM [23]
miR-381	*LRP1B*	↑ DMD LGMD [23,41]	↑ DM IBM [23]
miR-382	*GOLM1, MMP10*	↑ DMD LGMD [23]	↑ DM PM [23]
miR-409 3p	*RSU1, STAG2*	↑ DMD [23]	↑ DM [23]
miR-423	*RFVT3*	↓ DMD [23]	
miR-432	*KEAP1*	↑ DMD LGMD [23]	↑ DM PM IBM [27]
miR-452	*WWP1*	↑ DMD LGMD [23]	↑ DM [23]
miR-455	*ROCK2*	↑ mdx [33] LGMD [23]	
miR-483	*Notch3, MAPK3*	↑ DMD [13]	
miR-485 3p	*PGC1α*	↑ LGMD [23]	
miR-485 5p	*PGC1α*	↑ DMD [23]	
miR-486	*ICAM1, PAX3, PAX7, PTEN, DOCK3*	↓ DMD [23] mdx [42]	
miR-487b	*IRS1*	↑ DMD LGMD [23]	↑ DM [23]
miR-491	*WNT3a*	↑ LGMD [23]	
miR-493 3p	*TSPAN1, WNT3a*	↑ DMD [23]	
miR-495	*PBX3*	↑ DMD LGMD [23]	↑ DM [23]
miR-497	*IKKβ*	↑ mdx [33] ↑ FSHD LGMD [23]	↑ PM [23]
miR-499	*SOX6*	↑ DMD [11] ↑ DMD, BMD [15]	
miR-500	*LRP1B*	↑ LGMD [23]	↑ PM [23]
miR-501	*GAN*	↑ LGMD [23]	↑ DM PM [23]
miR-502	*SET*	↑ LGMD [23]	
miR-510	*PRDX1*	↓ LGMD [23]	
miR-517	*Pyk2*	↑ FSHD [23]	
miR-518a	*NFκB*	↑ DMD LGMD [23]	
miR-518c	*PTEN, TP53*	↑ LGMD [23]	
miR-542 5p	*BMP7*	↑ LGMD [23]	
miR-562	*HGFR*	↑ LGMD [23]	
miR-652	*Lgl1*	↑ mdx [33]	
miR-693		↓ LGMD [23]	
miR-2537		↑ DMD LGMD [23]	↑ DM [23]
miR-2837		↑ LGMD [23]	
miR-4442			↑ DM PM [43]
miR-4983		↑ DMD LGMD [23]	↑ DM PM [23]
miR-5021		↑ DMD LGMD [23]	
miR-7058		↑ FSHD [23]	
miR-7070		↑ LGMD [23]	
miR-7075		↓ DMD [23]	

miR-7083		↑ LGMD [23]	
miR-7089		↓ LGMD [23]	
miR-7105		↑ FSHD [23]	
miR-10617		↓ LGMD [23]	
miR-11040		↓ DMD LGMD [23]	↓ DM IBM [23]
miR-13145		↑ DMD FSHD LGMD [23]	↑ DM [23]
miR-13156		↓ DMD [23]	
miR-13190		↑ LGMD [23]	
miR-13205		↑ LGMD [23]	
miR-13232		↑ FSHD LGMD [23]	↑ DM [23]
miR-13258		↑ DMD LGMD [23]	↑ PM [23]
miR-13268		↑ FSHD LGMD [23]	↑ PM [23]
Let-7b/c/e/i		↑ FSHD LGMD [23]	
Let-7g		↑ LGMD [23]	
lncRNAs			
H19	*let-7*		↑ ASS IBM [44]
Linc- MD1	*MAML1, MEF2C*	↓ DMD [45]	
Lnc-MyoD	*IMP2*		↑ ASS IBM [44]
MALAT-1	*MYBL2, MyoD*		↑ ASS IBM [44]

Abbreviations: acetylcholinesterase (AChE); AF4/FMR2 family member 1 (AFF1); argonaute 2 (Ago2); A-kinase anchor protein 12 (AKAP12); protein kinase B 3 (Akt3); activated leukocyte cell adhesion molecule (ALCAM); AMP kinase subunit α (AMPKα1); autophagy-related 2B (AR2B); ankyrin repeat and SOCS box containing 2 (ASB2); antisynthetase syndrome (ASS); B-cell lymphoma 6 (BCL6); Becker muscular dystrophy (BMD); bone morphogenetic protein 7 (BMP7); calcium/calmodulin-dependent protein kinase II delta (Camk2d); caspase 9 (CASP9); caveolin 1 (CAV1); cyclin (CCN); cyclin-dependent kinase 2 (CDK2); cyclin-dependent kinase inhibitor 1A (CDKN1A); CDP-diacylglycerol synthase 2 (CDS2); cadherin EGF LAG seven-pass G-type receptor 3 (CELSR3); collagen (COL); carnitine palmitoyltransferase 1A (CPT1); cAMP responsive element binding protein 1 (CREB1); connective tissue growth factor (CTGF); cryptochrome 2 (CRY2); discs large homolog 5 (DLG5); dermatomyositis (DM); Duchenne muscular dystrophy (DMD); DNA methyltransferase 1 (DNMT1); dedicator of cytokinesis 3 (DOCK3); death receptor 6 (DR6); dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A); epidermal growth factor like-7 (EGFL7); epidermal growth factor receptor (EGFR); E74-like factor 1 (ELF1); elastin (ELN); endophilin 1 (EP1); estrogen receptor α (ERα); enhancer of zeste homologue 2 (EZH2); forkhead box M1 (FBM1); fibronectin (FBN); F-box and leucine-rich repeat protein 3 (FBXL3); forkhead box protein K1 (FOXK1); facioscapulohumeral muscular dystrophy (FSHD); follistatin (FST); frizzled 4 (FZD4); glucose-6-phosphate dehydrogenase (G6PD); growth arrest- and DNA damage-inducible gene 45α (GADD45α); gigaxonin (GAN); Golgi membrane protein 1 (GOLM1); Hydroxyacyl-Coenzyme A dehydrogenase (HADH); human epidermal growth factor receptor 3 (HE R3); Hepatocyte growth factor receptor (HGFR); hypoxia-inducible factor 1α (HIF1α); high-mobility group box 1 (HMGB1); homeobox (HOX); heat shock factor 2 (HSF2); sporadic inclusion body myositis (IBM); intercellular adhesion molecule 1 (ICAM1); insulin-like growth factor-binding protein-5 (IGFBP5); insulin-like growth factor 1 receptor (IGF1R); inhibitor κB kinase β (IKKβ); interleukin (IL); IGF2-mRNA-binding protein 2 (IMP2); interferon regulatory factor 6 (IRF6); insulin receptor substrate 1 (IRS1); integrin beta 1 (ITGB1); jagged 1 (JAG1); janus kinase (JAK); Kelch-like ECH-associated protein 1 (KEAP1); lethal giant larvae 1 (Lgl1); kinesin family member 26B (KIF26B); kinesin-like protein 1 (Kip1); lethal (Let); limb girdle muscular

dystrophy (LGMD); leucine-rich repeats and immunoglobulin-like domains 1 (LRIG1); low-density lipoprotein receptor-related protein (LRP1B); v-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog G (MAFG); metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1); mastermind-like 1 (MAML1); microtubule-associated protein 7 (MAP7); metadherin (MTDH); microfibrillar-associated protein 5 (Mfap5); mitogen-activated protein kinase (MAPK); myotonic dystrophy (MD); mouse double minute 2 homolog (MDM2); muscle differentiation 1 (MD1); mitogen-activated protein kinase kinase 3 (MKK3); matrix metalloproteinase (MMP); mammalian target of rapamycin (mTOR); Myb-related protein B2 (MYBL2); myocyte enhancer factor (MEF); myogenic differentiation D (MyoD); myogenic differentiation repressor (MyoR); myogenic factor 5 (MYF5); myosin light chain kinase 2 (MLCK2); metadherin 12 (MTDH12); mucin (MUC); nuclear factor 1 (NF1); nuclear factor (erythroid-derived 2)-like 2 (NFE2L2); nuclear factor κB (NFκB); nuclear factor κB repressing factor (NFRF); octamer-binding protein 2 (Oct-2); paired box protein (PAX); pre-B-cell leukemia homeobox 3 (PBX3); phosphoinoside-dependent protein kinase 1 (PDK1); programmed death-ligand 1 (PDL1); platelet derived growth factor receptor (PDGFR); peroxisome proliferator-activated receptor co-activator 1α (PGC1α); PTEN-induced putative kinase 1 (PINK1); polymyositis (PM); phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1); protein phosphatase 2A (PP2A); peroxisome proliferator-activated receptor (PPAR); protein phosphatase 3 regulatory subunit B beta isoform (PPP3R2); peroxiredoxin 1 (PRDX1); phosphatase and tensin homolog deleted on chromosome 10 (PTEN); prostaglandin-endoperoxide synthase 2 (PTGS2); proline-rich tyrosine kinase 2 (Pyk2); RAS Like proto-oncogene A (RALA); Ras association domain-containing protein 5 (RASSF5); riboflavin transporter 3 (RFVT3); rho-associated protein kinase 2 (ROCK2); Ras suppressor 1 (RSU1); syndecan 2 (SDC2); sphingosine-1-phosphate phosphatase 1 (SGPP1); suppressor of clear C. elegans Homolog 2 (SHOC2); SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5 (SMARCA5); sex-determining region Y-box (SOX); Src-homology2(SH2)B (SH2B1); sirtuin (SIRT); small mothers against decapentaplegic (SMAD); syntrophin B1 (SNTB1); suppressor of cytokine signaling (SOCS); steroid receptor coactivator 3 (SRC3); SRC kinase signalling inhibitor 1 (SRCIN1); stromal antigen 2 (STAG2); signal transducer and activator of transcription (STAT);; tissue inhibitor of metalloproteinases-3 (TIMP3); transforming growth factor β receptor 2 (TGFBR2); T lymphoma invasion and metastasis 1 (TIAM1)tumor necrosis factor α (TNF α); tumor necrosis factor α -induced protein 3 (TNFAIP3); tropomyosin 1 (TPM1); Tumor necrosis factor receptor associated factor (TRAF), tetraspanin (TSPAN); tumor necrosis factor receptor 1 (TNFR1); tumor protein p53 (TP53); TP53 regulated inhibitor of apoptosis 1 (TRIAP1); twist-related protein 1 (TWIST1); utrophin (UTRN); vascular endothelial growth factor (VEGF); wingless-type (WNT); WW domain containing E3 ubiquitin protein ligase 1 (WWP1); Y-box binding protein 1 (YB1); Yin Yang 1 (YY1).

2.1 Changes Linked to Muscle Fiber Regeneration

Skeletal muscle regeneration is marked by satellite cell activation and expansion, which requires regulated temporal and spatial expression of muscle-specific transcription factors termed myogenic regulatory factors (MRFs). This system allows undifferentiated muscle precursor cells to transform to fully functional multinucleate muscle fibers [46]. Transcription factors MRF4, myogenin, MyoD, and myogenic factor 5 (Myf5) cooperatively establish this phenotypic transition through their regulation of proliferation, cell cycle arrest, and regulated activation of sarcomeric and muscle-specific genes. Spatiotemporal expression of non-coding RNAs cooperates with these processes [10], with sequential non-coding RNA systems aiding progression through the

differentiation stages that transform progenitor muscle cells to fully functional terminally differentiated muscle fibers. For instance, skeletal muscle-specific miR-206 is strongly connected with muscle regeneration. miR-206 functions as a stress-induced suppressor of tissue destruction through its ability to activate compensatory mechanisms that promote the formation of new muscle fibers, an activity it accomplishes by suppressing expression of *PAX7*, *NOTCH3,* and *histone deacetylase 4*. Deletion of miR-206 delays regeneration after cardiotoxin injury in mice [47]. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) prevents differentiation of myoblasts to myotubes. Its expression is dynamically regulated during skeletal muscle differentiation. It is highly abundant in proliferating myoblasts, in which it represses *MyoD* expression. MALAT-1 recruits Suv39h1 to MyoD-binding loci, subsequently allowing formation and stabilization of the Suv39h1/HDAC1/HP1β complex and the trimethylation of Histone 3 lysine 9, leading to the repression of target genes. At the onset of differentiation, miR-181a expression is induced, causing MALAT-1 degradation through direct interactions and by the Ago2-dependent RNA-induced silencing complex machinery in the nucleus. The repressive complex destabilizes and gets replaced by the Set7-containing activating complex, allowing *MyoD* trans-activation [48]. On the other hand, lnc-MyoD is required for terminal muscle differentiation. At a certain moment, MyoD blocks proliferation to create a state permissive to differentiation, engaging lnc-MyoD to interact with IGF-2-mRNA binding protein 2, preventing it from inducing proliferative genes [49].

Reduced muscle fiber maturation can be observed in muscular dystrophies, and is associated with changes in miRNA and lncRNA expression patterns. While miR-31 is highly expressed at the early stages of differentiation of satellite cells *in vitro*, the levels in satellite cells derived from the standard DMD model, the mdx mouse, remain high, delaying muscle differentiation [30]. Muscle regeneration-associated miR-31 appears to exhibit a specific role in DMD, and miR-31 expression is more abundant in DMD biopsies than in those from healthy controls and from BMD patients. While miR-31 levels decrease during healthy muscle differentiation, levels remain high in differentiation-induced DMD myoblasts. Locked nucleic acid oligonucleotides against miR-31 are able to rescue dystrophin protein expression in human DMD myoblasts [30], indicating that the increased miR-31 observed in muscular dystrophy aggravates the pathology. Downregulation of linc-MD1 in DMD coincides with the reduced ability of myoblasts to undergo terminal differentiation [45]. Muscle recovery-associated miR-206 is strongly upregulated in regenerating muscle fibers in DMD in an attempt to restore muscle fiber damage. In this respect, ectopic miR-206 was shown to rescue deficient myogenesis in an MD1 cell model, likely by promoting MyoD expression [50]. In DM, decreased miR-206 levels have been described [20,38], which might compromise skeletal muscle regeneration.

Dystrophin is a protein required for sarcolemmal integrity and functions as an epigenetic modulator through its effects on the neuronal nitric oxide synthase/histone deacetylase 2 pathway. In muscular dystrophy, several miRNAs that inhibit *dystrophin* translation *in vitro* are upregulated, which includes miR-31, miR-146, and miR-223. For instance, miR-31 levels are increased 50-fold in muscle from mdx mice compared to the control strain [30]. Chronic activation of this system presumably accelerates disease progression, and expression of *dystrophin*-inhibiting miRNAs inversely correlates with exon skipping success in the mdx model [31]. However, this process is complexly regulated, with certain non-coding RNAs such as miR-133b and miR-206 repressing the dystrophin compensatory protein utrophin [51], while others including miR-195 and miR-758 enhance dystrophin protein expression [31].

2.2 Changes Influencing Muscle Fiber Survival

Muscle mass is dependent upon the relative balance between muscle fiber biosynthesis and degradation; in muscle disorders the scales often tip towards the latter. Muscle atrophy develops through downregulation of protein synthesis and activation of the ATP-dependent ubiquitin–proteasome pathway. Proteins become poly-ubiquitinated, which sentences them to destruction by the proteasome. Damaged muscle fibers that are beyond repair become necrotic and are cleared by tissue-infiltrating immune cells. In addition, apoptotic cell death mechanisms contribute to muscle fiber loss in a wide spectrum of neuromuscular disorders [52].

Non-coding RNA expression is regulated in the active phase of muscle fiber necrosis and degeneration that develops at 4 to 6 weeks of age in the mdx mouse model. These processes involve linc-MD1, miR-1, and miR-133a, displaying complex expression patterns that change over time [53]. The decreased levels of miR-378 in DMD and BMD lead to increased levels of its targets phosphoinositide-dependent kinase-1 and caspase 9, which results in excessive apoptosis [40]. miR-455, an inducer of muscle wasting and atrophy, is also increased in muscular dystrophy [23,33]. For miR-21, which is associated with resistance to apoptosis [54], mixed results have been obtained in the study of muscular dystrophy, with studies reporting both up- [25, 26] and down- [24] regulation.

In regard to IBM, decreased levels of miR-206 have implications for the muscle tissue's interactions with the RNA-binding protein TAR DNA binding protein 43 (TDP-43). TDP-43 is a component of the protein aggregates present in IBM muscle fibers [55], and has been linked with neurodegeneration [56]. Reduced miR-206 levels potentially dampen TDP-43 activity, compromising its role as a maintenance factor of the autophagy system [57], which could contribute to the characteristic disturbed clearance of damaged muscle proteins in IBM muscle fibers.

2.3 Changes Linked to Muscle Tissue Fibrosis

If damaged fibers cannot be replaced by new ones, the void is filled by extracellular matrix components and fatty tissue. This is a reparative process, yet yields no functional benefit to the skeletal muscle tissue. Transforming growth factor-β, the key regulator driving fibrosis, regulates miRNA expression and steers the activation of intracellular pro-fibrotic signalling cascades. Many miRNAs are pro-fibrotic, but miR-29 in particular has surfaced as a major player. Downregulation of miRNA-29a and the resulting de-repression of its pro-fibrotic targets appears in multiple organs when they develop fibrosis.

The progressive muscle damage associated with muscular dystrophy leads to accumulated deposition of excessive fibrous connective tissue, and many have described reduction of miR-29 expression levels in muscular dystrophy [11, 12, 18, 28, 29]. In MD, decreased miR-29 leads to increased levels of the pro-fibrotic protein ankyrin repeat and suppressor of cytokine signaling box-containing 2 (ASB2) [24]. ASB2, a subunit of the E3 ubiquitin-ligase complex, is a negative regulator of muscle mass. Supplementation by intramuscular injection of miR-29 in mdx muscle downregulates the expression of fibrotic markers, including collagens 1 and 3 and vimentin [28]. In addition, miR-29 expression levels return to normal in mdx mice treated with exon skipping [12, 13].

For the pro-fibrotic mediator miR-21, mixed results have been obtained. Upregulation was observed in the DMD mdx mouse model [25] while significant downregulation in the urine of non-ambulant DMD patients was detected [24]. Treatment with antagomirs leads to improvement of the mdx disease phenotype, and vice versa, overexpression leads to more severe muscle pathology [58]. However, knocking out miR-21 in a mouse model for laminin-deficient congenital muscular dystrophy does not improve the muscular phenotype [59]. In inflammatory myopathies, increased pro-fibrotic miR-21 has been reported [23, 27].

2.4 Changes Influencing Muscle Tissue Inflammation

Muscle injury causes muscle fiber membrane damage, releasing cellular content and chemotactic factors to the extracellular space. This process induces infiltration by specific subtypes of immune cells, aimed to clear the tissue of damaged material and make room for fresh fibers. Consecutive waves of immune cells infiltrate the muscle tissue, composed first of mast cells and neutrophils followed by macrophages and T-cells. At an early stage, cytotoxic M1 macrophages remove the muscle debris generated by the trauma. Later on, T cells are recruited and monocytes differentiate to M2 macrophages. This way, the pro-inflammatory microenvironment at the muscle lesion gradually transforms to an anti-inflammatory microenvironment, allowing muscle tissue remodeling. However, in many muscle diseases, inflammation persists beyond its protective use. An expansive list of miRNAs display pro-inflammatory activities and many are implicated in chronic muscle inflammation. They are either directly regulated by the transcription factor nuclear factor κB (NFκB), or target other factors within the NFκB signaling pathway.

In muscular dystrophies, inflammation develops secondary to the primary genetic defect. Nonetheless, chronic inflammation represents an important aspect of these diseases, and immunosuppressive treatment is still the mainstay of therapy for DMD today. Pro-inflammatory miR-222 and miR-223 are expressed in the damaged muscle tissue areas, strongly correlating with inflammatory cell infiltration [11]. miR-155, a non-coding RNA that facilitates appropriate activation of macrophages by regulating transition and balance of M1 and M2 macrophage phenotypes, is upregulated in mdx muscle, illustrating the tissue's attempt to regenerate [33, 35]. However, a set of miRNAs involved in pro-inflammatory signaling gets strongly upregulated in DMD. miR-142, miR-146, miR-301, miR-324, miR-455, miR-497, and miR-652 levels are significantly increased in the mdx mouse model. Levels normalize when mice are treated with vamorolone and prednisone [33]. The resultant activities of these miRNAs, however, need to be regarded as a dynamic balance effect. For instance, miR-146a initially dampens inflammation, but exacerbates inflammation after prolonged induction [60].

In inflammatory myopathies, infiltration by auto-aggressive immune cells that target muscle constituents is a primary disease mechanism. miR-146 is especially associated with inflammatory myopathies and becomes induced in immune cells and in muscle fibers [34]. miR-146a has been observed to negatively regulate the type 1 interferon pathway [61]. Marked overproduction of type 1 interferon-inducible transcripts and proteins is characteristic of DM with perifascicular atrophy [62]. The expression of several interferon-stimulated genes, such as *myxovirus resistance protein 1*, *interferon-stimulated gene 15,* and *retinoic acid-inducible gene I*, has been confirmed at the protein level in perifascicular regions and on the capillaries of the muscle biopsies [63, 64, 65].

DM patients also have high levels of circulating type 1 interferon cytokines [66, 67], and disease activity correlates with interferon-stimulated gene transcript levels in the blood [68]. Type 1 interferon pathway blockade is therefore a therapeutic route worth exploring, and strategies that are able to increase levels of miR-146 could be of benefit in DM by attenuating type 1 interferon-induced reactions.

3. Discussion

Genome transcripts that do not code for protein represent the vast majority of the mammalian transcriptome, and the time they were put aside as useless now lies long behind us. Highly deregulated expression patterns in muscular dystrophy and inflammatory myopathy contribute to disease progression. Their up- or downregulation represents the tissue's response, which can either be good or bad for the muscle tissue's integrity: an appropriate response accelerating tissue damage recovery or a misplaced response leading to increased muscle damage. Muscle non-coding RNAs are involved in many aspects relevant to muscle pathology through regulation of the muscle tissue's regenerative capacities, muscle fiber survival, and the build-up of inflammation within the skeletal muscle tissue. Many studies describe miRNA levels, but, as is obvious from table 1, the lncRNAs remain under-represented. Also, it appears that most research has focused on muscular dystrophy, and that, in comparison, other muscle diseases have not yet received due attention.

From what we know now, one can conclude that non-coding RNAs are plausible disease markers. They could represent useful diagnostic markers which could potentially replace invasive muscle biopsy. The miR-483 increase, for instance, is equally detectable in muscle tissue and in serum samples from DMD patients [13]. miRNA profiling appears a useful strategy to monitor DMD disease progression [14,69]. However, caution is warranted as dysregulation of non-coding RNAs may represent a common signature of diseased muscle. Yet, distinctive expression patterns could still be associated with individual muscle disorders. In this respect, miR-208b levels have been put forward as a potent biomarker to distinguish DMD from BMD [15]. miRNA typing could speed up differential diagnosis in patients that carry a *dystrophin* variant with yet unknown pathological repercussions. In addition, non-coding RNAs could be exploited as objective markers to evaluate therapeutic responses in clinical trials. miR-1, miR-29, and miR-149 expression levels have been described to return to normal in mdx mice successfully treated with exon skipping [12, 13].

Non-coding RNAs could be an amenable therapeutic target in muscle disease, regardless of whether the changed expression patterns are causal to the disease or merely reflecting secondary degeneration/regeneration responses of the muscle tissue. Their precise involvement would, in this respect, appear of secondary importance to their universal potential for therapeutic innovation. Many muscle disorders display common signatures of non-coding changes, allowing selection of potential targets with broader therapeutic use. Strategies for interventions targeting miRNAs are to administer oligonucleotides that inhibit miRNA activity (antagomirs) or regulate the biological function of its target genes (agomirs). Many muscle diseases remain non-treatable to this day, and subgroups of inflammatory myopathy patients are refractory to immunosuppressive treatment. For IBM in particular, no satisfactory treatment option is available at the moment. As miRNAs are important regulators of inflammatory reactions, therapeutics in the form of miRNA

mimics of antagonists would be able to control the rampant progress of inflammation in inflammatory myopathies [70]. Also, targeting non-coding RNAs could be developed as ancillary therapeutics in support of molecular therapies. In DMD, where exon skipping techniques have not lead to the hoped-for improvements, combination therapies might boost the therapeutic outcome.

4. Conclusions

The dysregulated non-coding RNA profile of muscular dystrophy and inflammatory myopathy has both beneficial and detrimental potential. Altered expression levels can represent an appropriate response accelerating tissue damage recovery, or a misplaced response leading to increased muscle damage. The ever-increasing number of reports describing the complex involvement of non-coding RNAs in muscle disease mechanisms aid us to distinguish friend from foe. In addition, studies describing the RNAome have substantially increased our knowledge of muscle disease mechanisms, and can provide us with useful biomarkers for further development for diagnostic purposes or to monitor experimental therapy effectiveness in clinical trials. Also, they represent attractive ancillary therapeutic targets.

Author Contributions

BDP developed the concept of this review, searched, summarized, and interpreted published results, and drafted and finalized the manuscript.

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Competing Interests

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