Review

Muscle Weakness in Rheumatoid Arthritis: The Role of Ca²⁺ and Free Radical Signaling

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ABSTRACT

In addition to the primary symptoms arising from inflammatory processes in the joints, muscle weakness is commonly reported by patients with rheumatoid arthritis (RA). Muscle weakness not only reduces the quality of life for the affected patients, but also dramatically increases the burden on society since patients’ work ability decreases. A 25–70% reduction in muscular strength has been observed in patients with RA when compared with age-matched healthy controls. The reduction in muscle strength is often larger than what could be explained by the reduction in muscle size in patients with RA, which indicates that intracellular (intrinsic) muscle dysfunction plays an important role in the underlying mechanism of muscle weakness associated with RA. In this review, we highlight the present understanding of RA-associated muscle weakness with special focus on how enhanced Ca²⁺ release from the ryanodine receptor and free radicals (reactive oxygen/nitrogen species) contributes to muscle weakness, and recent developments of novel therapeutic interventions.

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1. Introduction

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases (Alamanos et al., 2006; van Vliet et al., 2015). In addition to the primary symptoms arising from inflammatory processes in
the joints, muscle weakness is commonly reported by patients with RA (Sokka et al., 2008). Muscle weakness not only reduces the quality of life for the affected patients, but since patients’ ability to work decreases it will also dramatically increase the burden on society (e.g. increased costs for long-term sick leave). Thus, RA severely affects both the individual and the society (Sokka et al., 2008; van Vliet et al., 2015).

In patients with RA, a 25–70% reduction in muscular strength (including both grip strength and isometric and isokinetic knee muscle strength) has been observed when compared with age-matched healthy controls (Ekdahl and Broman, 1992; Fraser et al., 1999; Helliwell and Jackson, 1994; Stenström and Minor, 2003). Reduced muscle strength is usually considered to be a result of decreased muscle mass due to disuse atrophy. Rheumatoid cachexia, a term used in RA, is defined as a loss of skeletal muscle mass and with no, or little weight loss in fat mass (Londhe and Guttridge, 2015; Walsmith and Roubenoff, 2002). However, Helliwell and Jackson stated already in 1994 that the reduction in grip strength of patients with RA is larger than what could be explained by the reduction in muscle size (Helliwell and Jackson, 1994), and this phenomenon has been reported later by others (Fraser et al., 1999; Lemmy et al., 2016). Structural analysis using electron microscopy of muscle biopsies (from e.g. vastus medialis, glutus maximus, extensor digitorum communis) from patients with RA display dilated sarcotubular system, pleomorphic mitochondria and myofibril ﬂaking, all signs of altered intramuscular function (de Palma et al., 2000). Thus, intracellular (intracellular) contractile dysfunction appears to play an important role in the underlying mechanism of muscle weakness associated with RA. Indeed, force production normalized to the cross-sectional area of the muscle (i.e. the speciﬁc force, which assesses the muscle ﬁbre’s intrinsic capacity to generate force) has been shown to be markedly reduced (~30%) in both fast-twitch and slow-twitch skeletal muscle from two widely used rodent models of RA; collagen-induced arthritis (CIA) in mice and adjuvant-induced arthritis (AIA) in rats (Yamada et al., 2015a,b, 2009). In the first part of this review we will discuss intrinsic muscle weakness and how altered Ca2+ and free radical signaling (reactive oxygen/reactive nitrogen species, ROS/RNS) contribute to RA-induced muscle weakness. In the latter part, we discuss therapeutic interventions to counteract RA-induced muscle weakness.

2. Intrinsic Muscle Dysfunction

The events leading to contraction of skeletal muscle ﬁbers (excitation-contraction coupling, EC coupling) start with action potentials travelling down the transverse tubular (t-tubular) system and activating the voltage-sensitive dihydropyridine receptors (DHPR or Cav1.1). Activated DHPR mechanically trigger the ryanodine receptor type 1 (RyR1), which is the major intracellular Ca2+ release channel that releases Ca2+ from the sarcoplasmic reticulum (SR). Ca2+ then binds to the troponin complex, which moves the position of the tropomyosin filaments. This uncovers the active sites of actin for myosin binding, hence enabling and turning on myosin ATPase (Serca) (5) and [Ca2+]i returns to resting levels and the contraction ceases. At rest, when the intracellular Ca2+ concentration is low (~50 nM), the tropomyosin ﬁlaments hide the myosin binding sites on actin (6), hence no force can be produced.

preceeded by a substantial and significant increase in Ca2+ release over the whole range of stimulation frequencies in muscle from mice with arthritis as compared with control muscle (Fig. 2) (Yamada et al., 2015b, 2009). In fact, the free intracellular Ca2+ concentration ([Ca2+]i) was almost twice as high in muscle ﬁbers from CIA mice than in control ﬁbers at the higher stimulation frequencies (50–120 Hz) (Yamada et al., 2015b). Caffeine is a potent RyR1 agonist, which is widely used in muscle research as an agent which increases Ca2+ release from SR and thereby increases myoplasmic free Ca2+ concentrations (Allen and Westerblad, 1995; Shirokova and Rios, 1996). In the presence of caffeine (5 mM), there was no longer a difference in the Ca2+ release between muscle ﬁbers from control mice or mice with arthritis (Yamada et al., 2015b). This indicates that the increased Ca2+ release was caused by facilitated RyR1 Ca2+ release and was not the result of more Ca2+ stored in SR in muscles from mice with RA.

Altered RyR1 Ca2+ release has been linked to muscle weakness in several clinical aspects, e.g. bone cancer (Waning et al., 2015), muscle dystrophies (Bellinger et al., 2009; Hernández-Ochoa et al., 2015; Lanner et al., 2012), heart failure (Rullman et al., 2013) and even in normal ageing (Andersson et al., 2011). Altered RyR1 Ca2+ release often manifests as low-grade basal Ca2+ release (Ca2+ leak), i.e. Ca2+ leaking out from the RyR1 channel under basal (non-stimulated) conditions when the channel supposedly should be in its closed conformation. RyR1 Ca2+ leak is associated with reduced Ca2+ release upon stimulation, decreased SR Ca2+ load and impaired contractility in both cardiac and skeletal muscle (Andronache et al., 2009; Aydin et al., 2008; Lanner et al., 2012; Santulli et al., 2017; Tong et al., 1999). However in Yamada et al. (2015b), a signiﬁcant reduction in force production was preceded by enhanced/increased tetanic Ca2+ release and unaltered SR Ca2+ store content in muscles from mice with arthritis (Yamada et al., 2015b).

Altered gating properties of RyR1, hence altered Ca2+ release, is thought to be the result of post-translational modiﬁcations of the channel (Aydin et al., 2008; Durham et al., 2008; Lanner et al., 2012; Waning et al., 2015). For instance, phosphorylation of RyR1 Ser2841 induced by resistance exercise or β-adrenergic stimulation have been shown to activate the channel (Andersson et al., 2012; Gehlert et al., 2012; Reiken et al., 2003). On the other hand, phosphorylation of cardiac RyR2
(S2030 and S2808) has been associated with enhanced SR Ca\(^{2+}\) leak and reduced SR Ca\(^{2+}\) load, which may contribute to arrhythmias and contractile dysfunction in heart failure (Lanner et al., 2010; Marx et al., 2000). Moreover, RyR1 is known to be sensitive to ROS/RNS-induced modifications. For example, protein carbonylation (oxidations yielding reactive carbonyl groups, DNP (Fedorova et al., 2014)) and nitrosylation (nitric oxide (NO) covalently bound to cysteines (S-nitrosylation, CysNO)) are known to alter the gating properties of RyR1 (Lanner et al., 2010). For instance, S-nitrosylation of Cys3635 on RyR1 has been shown to activate the channel (Sun et al., 2001). High-levels of DNP and CysNO on RyR1 have been found in age- and disease-induced muscle dysfunction (Andersson et al., 2011; Bellinger et al., 2009; Durham et al., 2008; Lanner et al., 2012; Rullman et al., 2013; Waning et al., 2015).

Elevated levels of several ROS/RNS-induced modifications including, CysNO, DNP, malonaldehyde (MDA, highly reactive aldehydes formed by lipid peroxidation), and 3-nitrotyrosine (3-NT, a marker of peroxynitrite (ONOO\(^{-}\))) have been observed in serum, synovial fluid and synovial tissue from patients with RA (Grönwall et al., 2017; Hilliquin et al., 1997; Kaur and Halliwell, 1994). To our knowledge, the level of DNP, CysNO, MDA on RyR1 have not yet been studied in skeletal muscle from mice with arthritis (Yamada et al., 2015b). Thus, the observed force decrease (both submaximal and maximal Ca\(^{2+}\)-activated force) was markedly lower (\(-33\%\)) in myofibrils from mice with arthritis than in myofibrils from control mice. The [Ca\(^{2+}\)], required to produce 50% of the maximum force (Ca\(_{50}\)) was increased in muscles from arthritis mice, suggesting a reduced myofibrillar Ca\(^{2+}\) sensitivity (Yamada et al., 2015b). Moreover, myofibrils from arthritis mice showed a decreased rate of force redevelopment after shortening the fully activated myofibrils, which is consistent with slower cross-bridge attachment, reduced Ca\(^{2+}\) sensitivity and overall lower force generating capacity (Gordon et al., 2000; Yamada et al., 2015b). Thus, the observed force depression appears as a result of reduced myofibrillar force generating capacity and decreased myofibrillar Ca\(^{2+}\) sensitivity. In line with this, skeletal muscle actomyosin ATPase activity was shown to be reduced in rodents with RA (Yamada et al., 2015a). Moreover, myofibrillar irregularities, e.g. wider separation of myofibrils, dilated t-tubular system, pleomorphic mitochondria and myofibril flaking, have also been observed in muscle biopsies from patients with RA, and were correlated with muscle weakness (de Palma et al., 2000; Russell and Hanna, 1988). Thus, muscles from rodent models of RA and biopsies from patients with RA suggests that impaired myofibrillar function is a prominent factor in RA-induced muscle weakness and muscle dysfunction.

5. ROS/RNS Interfere with the Contractile Machinery in RA Muscles

Free radicals (ROS/RNS) are believed to be involved in the pathogenesis of chronic arthritis and RA, but how and to which extent is not fully understood (Datta et al., 2014; Khojah et al., 2016; Kurien et al., 2006; Mateen et al., 2016; Ozkan et al., 2007; Pacher et al., 2007). Intriguingly, extensive amount of data supports both positive (e.g. involved in gene expression, cell growth and remodeling) and negative effects (DNA damage and protein dysfunction) of ROS/RNS on cell function (Cheng et al., 2016; Kurien et al., 2006; Lambeth, 2004; Ristow, 2014; Supinski and Callahan, 2007). However, whether ROS/RNS have a protective and modulatory role or lead to damaging effects most probably depends on several factors, e.g. the type and amount of ROS/RNS as well as its localization. In skeletal muscle, several ROS/RNS species (superoxide (O\(_2^{-}\)), hydrogen peroxide (H\(_2\)O\(_2\)), hydroxyl radicals (\(^{\bullet}\)OH), nitric oxide (NO), peroxynitrite (ONOO\(^{-}\))) have been shown to directly contractile protein function, and data suggests that ROS/RNS also have important effects on SR function, mitochondrial function and on
6. Possible Sources of ROS/RNS in RA Muscles

Increased levels of ONOO\(^-\)-induced 3-NT footprints have been consistently shown in skeletal muscles from different animal models of RA (Yamada et al., 2015a,b, 2009). ONOO\(^-\) is a potent oxidizing and nitrating agent able to react with a wide range of cellular targets within \(-5-20\) μM (Carballal et al., 2014; Radi, 2004; Szabó et al., 2007). ONOO\(^-\) is formed by the reaction between NO and superoxide (O\(_2\)-\(^-\)), with a fast formation rate constant of \(-4 - 16 \times 10^9\) M\(^{-1}\) s\(^{-1}\) (Botti et al., 2010). The rate constant for ONOO\(^-\) is six times faster than the rate constant for superoxide dismutase (SOD) to convert O\(_2\)-\(^-\) to H\(_2\)O\(_2\) (\(-1-2 \times 10^9\) M\(^{-1}\) s\(^{-1}\)). Thus, when NO is produced at a high rate, it will rapidly react with O\(_2\)-\(^-\) to produce significant amounts of ONOO\(^-\) even in the presence of the high physiological concentrations of superoxide dismutase (SOD, \(-10\) to \(20\) μM) (Hsu et al., 1996). However, which intracellular sources of ROS/RNS are responsible for the increased redox stress that has been observed in skeletal muscle associated with RA-induced muscle weakness?

6.1. Nitric Oxide Synthase

NO is synthesized by NO synthase (NOS) from L-arginine, NADPH and O\(_2\). In addition to NO, NOS has been found to produce O\(_2\)-\(^-\), hence NOS by itself can generate ONOO\(^-\). This NOS phenomena is termed uncoupling, as O\(_2\)-\(^-\) production primarily occurs when NOS is not associated with cofactor or substrate (e.g. reduced L-arginine or tetrahydrobiopterin (BH\(_4\)) levels) (Lu et al., 2014; Stuehr et al., 2001). Three types of NOS and several different splice isoforms have been identified in skeletal muscle; constitutively expressed NOS1 (neuronal NOS), NOS2 (inducible NOS) and NOS3 (endothelial NOS) (Knowles and Moncada, 1994). Increased levels of NOS1 have been detected in skeletal muscle both from rodents with RA (three-fold increase) and in patients with RA (two-fold increase) (Yamada et al., 2015a,b). Altered levels of NOS2 and NOS3 have not been reported in skeletal muscle from subjects with RA (Yamada et al., 2015a,b). Under normal conditions, a majority of NOS1 is compartmentalized to sub-membrane scaffolds, which are part of the dystrophin glycoprotein complex (Molza et al., 2015). In addition, a small fraction of NOS1 was detectable in association with the SR and with mitochondria (Buchwald et al., 2005). Moreover, NOS1 has been shown to co-localize with the RyR1 in skeletal and cardiac muscle from mouse and human subjects (Lee et al., 2014; Salanova et al., 2008; Yamada et al., 2015b). Interestingly, the amount NOS1 co-localized with RyR1 was increased five-fold in muscles from mice with arthritis (Yamada et al., 2015b) (Fig. 3).

The free cytosolic Ca\(^{2+}\) concentration ([Ca\(^{2+}\)\(_i\)]) evoked by electrical stimulation (tetanic [Ca\(^{2+}\)\(_i\)]) but not resting [Ca\(^{2+}\)\(_i\)], has been shown to be almost two-fold higher in muscle fibers from mice with RA than healthy controls (Yamada et al., 2015b, 2009). NOS1 is a Ca\(^{2+}\)-calmodulin (CaM)-dependent enzyme and its activity increases with [Ca\(^{2+}\)\(_i\)] via calmodulin (CaM) (Fürsternann et al., 1994). K<sub>0.5</sub>[Ca\(^{2+}\)\(_i\)] for the activation of NOS1 is ~200 nM in the presence of 500 nM CaM (Bredt et al., 1990). However, the free accessible CaM concentration is ~50 nM under physiological conditions in muscle (Wu and Bers, 2007), hence the K<sub>0.5</sub> [Ca\(^{2+}\)\(_i\)], for the activation of NOS1 is most probably higher than ~200 nM in muscle. Nevertheless, a [Ca\(^{2+}\)\(_i\)] > 1 μM (see Fig. 1 for example) is readily reached when skeletal muscles contract, hence NOS1 becomes activated during contractile activities. Thus, not only is there more NOS1 in the muscle cells, the increased tetanic [Ca\(^{2+}\)\(_i\)] could allow for even higher NOS1 activity and contribute to increased ROS/RNS load in RA muscles (Fig. 3).

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6.2. Pro-inflammatory Cytokines and NADPH Oxidase

A number of pro-inflammatory cytokines, including TNFα, IL-1, IL-6 and IL-23 are recognized as important mediators in the processes that cause inflammation and comorbidities (e.g. bone erosion, cartilage destruction) associated with RA (Brennan and McInnes, 2008; Londhe and Guttridge, 2015; Noack and Miossec, 2017). For instance, pro-inflammatory cytokines are thought to induce ROS/RNS and apoptosis in the synovial joints and thereby contribute to the pathogenesis of RA (Croft and Siegel, 2017; Li et al., 2012). Recently Huffman et al., reported that patients with RA have 75% greater muscle concentration of IL-6 protein than healthy controls (Huffman et al., 2017). In addition to IL-6, increased levels of IL-1α, IL-8, TNF-α, and toll-like receptor (TLR)-4 has been observed in skeletal muscle from patients with RA (Huffman et al., 2017). In addition to IL-6, TNFα and IL-6 have been shown to promote ROS/RNS stress in skeletal muscle (Landskron et al., 2014; Reid and Moylan, 2011). In turn, ROS/RNS are suggested inducers of e.g. TNFα and IL-6 expression in various inflammatory conditions (Blaser et al., 2016; Pacher et al., 2007). Thus, a complex, and far from fully understood, crosstalk is present between cytokines and ROS/RNS in inflammation. The ROS/RNS source(s) behind cytokine-induced ROS/RNS stress are not fully established, but both NOS and NADPH oxidases type 1, 2 and 4 (NOX1, NOX2, NOX4) are suggested as downstream targets of TNFα in inflammatory processes (Blaser et al., 2016; Cangemi et al., 2014; Moe et al., 2011). Brief exposure of skeletal muscle to TNFα has been shown to increase ROS/RNS stress and reduce the force generation capacity (Alloatti et al., 2000; Reid and Moylan, 2011; Stasko et al., 2013). In these studies, the TNFα effect was blunted by addition of the NOS1 inhibitor L-NG-Nitroarginine methyl ester (L-NAME) in skeletal muscle from both guinea pig and mouse (Alloatti et al., 2000; Stasko et al., 2013), hence NOS1 was identified as the source for TNFα-induced ROS/RNS production.

Activated NOXs produce 
O$_2$$^-\cdot$ and skeletal muscle is known to express NOX2 and NOX4 (as well as the dual oxidase enzymes DUOX1, DUOX2) (Sakellariou et al., 2014). Increased levels of TNFα and NOX2 were observed in skeletal muscle from rats with arthritis, i.e. TNFα (and other non yet identified cytokines) could be a potential upstream activator of NOS1 and/or NOX2. Increased NOS1 can produce both NO and 
O$_2$$^-\cdot$ and may directly increase ONOO$^-\cdot$ formation. Alternatively, NOS1-induced NO and NOX2-induced 
O$_2$$^-\cdot$ may contribute to the ONOO$^-\cdot$ formation observed in RA muscles (Fig. 3). In support of this notion, an enhanced expression of NOX1 and NOX4 isoforms were associated with elevated levels of 3-NT in the ischemic hemisphere following cerebral ischemia-reperfusion injury in mice (Lu et al., 2011). Furthermore, the enzyme sphingomyelinase (SMase) is activated by TNFα and has been shown to be elevated in acute systemic inflammation (e.g. sepsis) (Okazaki et al., 2014; Wong et al., 2000). Skeletal muscle exposed to SMase exhibits muscle weakness, which is thought to be the result of SMase-induced NOX2 activation (Bost et al., 2015; Loehr et al., 2014). Thus, SMase appears to be a mediator in the ROS/RNS stress in skeletal muscle. Its role in RA-associated muscle weakness is unknown, but worth investigating further. Nevertheless, ROS/RNS are thought to be unspecific in their reactivity, reacting with whatever is close (Kumar et al., 2012); i.e. to gain further detailed knowledge of the involvement of the free radical sources associated with RA and other inflammatory diseases, we believe that it will be important to localize and quantify intracellular hotspots of ROS/RNS production in skeletal muscle afflicted with RA. Advanced knowledge in this area of redox-induced muscle dysfunction could identify targets and lay the groundwork for future therapeutic interventions to counteract muscle dysfunction associated with inflammatory conditions.

7. Therapeutic Interventions to Counteract Arthritis-associated Muscle Weakness

According to recommendations by European Leage Against Rheumatism (EULAR), RA treatment should be initiated with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs, most commonly methotrexate) and low-dose glucocorticoids (Smolen et al., 2017). If the first line of treatment fails, patients can receive conventional synthetic DMARDs in combination with targeted synthetic DMARDs or biological DMARDs (Smolen et al., 2017). TNFα inhibitors (e.g. adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars) and anti-IL6 receptor antibodies (e.g. tocilizumab) are biological DMARDs that are considered to be efficient and safe (Smolen et al., 2017). By definition DMARDs must reduce structural damage progression, whereas anti-inflammatory drugs (e.g glucocorticoids) reduce pain and stiffness and improve physical function, i.e. do not interfere with joint damage and hence are not disease modifying. RA cannot be cured, but the current available treatment options allow for good therapeutic successes and tight control of the disease activity, by retaining the disease in a low-inflammatory state. Nevertheless, Lemmy et al., recently showed that well-managed RA patients with a low disease activity still performed –25–35% poorer than age- and weight-matched healthy control subjects on all functional muscle measurements tested, including knee extensor and handgrip strength (Lemmy et al., 2016). This strongly suggests that muscle weakness and muscle dysfunction are not directly influenced by the patient’s inflammatory status and/or disease activity. Instead, separate and unique therapy strategies appear necessary to counteract muscle dysfunction and muscle weakness present in patients with RA, and probably also translates to other chronic inflammatory disorders associated with muscle complications.

7.1. Exercise as Therapy

Regular physical exercise, both aerobic and strength exercise, are recognized as an important component of the management of RA. In patients with RA, exercise-induced beneficial effects include increased force production and muscle mass, increased aerobic capacity, lower amount of fat mass, decreased inflammation and pain, and an overall sense of well-being (Häkkinen, 2004; Häkkinen et al., 2001; Lemmy et al., 2009; Sharif et al., 2011; Sokka et al., 2008; Stenström and Minor, 2003). Thus, exercise per se appears as an effective overall therapy for patients with RA. However, this requires that the patients are active several days per week, which is not the case for many patients with RA. In fact, Sokka et al., reported that out of 5235 patients from 58 sites in 21 countries, only 14% were physically active ≥3 times per week (Sokka et al., 2008). Furthermore, Lemmy et al., 2012 reported that in their 3-year follow-up study of patients with RA that had performed a 24 week high-intensity strength training program, no one in the exercise group was still exercising. Thus, a challenge with physical exercise as therapy is to achieve sustainability and to engage the patients in regular physical activity for the rest of their life.

7.2. Antioxidant Treatment to Counteract RA-associated Muscle Weakness

Several antioxidants (e.g. Vitamin E, Vitamin C, SS31, CoQ10) have been tested in clinical trials for a range of diseases (e.g. cardiovascular and diabetes), but the outcome has often been inconclusive (Ajith and Jayakumar, 2014; Lonn et al., 2005). However, the outcome probably reflects our limited knowledge of the temporal and spatial distribution of ROS/RNS, rather than antioxidants as such being ineffective as a therapeutic tool. Nevertheless, the involvement of ROS/RNS in muscle dysfunction associated with RA, indicates that antioxidant treatment could potentially be beneficial in improving muscle function in patients with RA. Thus far, to our knowledge, antioxidant treatments have not been tested in patients to counteract RA-associated muscle weakness. Mn-Salen compounds (e.g. EUK-134) have been proposed to possess...
distinct advantages, e.g. exhibit combined SOD/catalase mimetic functions, over non-specific antioxidant scavenger effect which is how e.g. N-acetyl cysteine function. The EUK-series also exhibit high translational value as it is developed for oral administration (Baker et al., 1998; Rosenthal et al., 2009). In addition to scavenging mitochondrial O$_2^-$ / H$_2$O$_2$ formation, Mn-Salen catalyzes the removal of ONOO$^-$ and ameliorates nitrosative stress (Sharpe et al., 2002). Interestingly, EUK-134 has been shown to lower amount ONOO$^-$-induced 3-NT modifications on actin and to prevent the loss of muscle force production in rats with RA (Yamada et al., 2015b). EUK-134 treatment has also been shown to prevent ROS/RNS-associated muscle wasting and weakness in other pathological conditions, including the mouse-models of Duchenne muscle dystrophy and pulmonary hypertension (Himori et al., 2017; Kim and Lawler, 2012; Lawler et al., 2014). For that reason, despite antioxidants reported history of not being successful in clinical trials, it would be interesting to test the effects of EUK-134 on muscle function in patients with RA.

7.3. Novel Actions to Improve Muscle Function

Based on the scientific results discussed in this review, Fig. 3 illustrates a tentative vicious cycle that may contribute to the arthritis-induced muscle weakness. This model show that nitrosative modifications of the RyR1 protein complex results in facilitation and increased Ca$^{2+}$ release during muscle contractions, which further activates the Ca$^{2+}$-sensitive NOS1 that by itself can cause amplification of O$_2^-$, NO and ONOO$^-$. This results in ONOO$^-$ attacks of myofibrillar proteins and causes contractile dysfunction and muscle weakness. Thus, a novel action to counteract RA-associated muscle weakness could be to inhibit this vicious cycle by pharmacological intervention targeting RyR1 to stabilize SR Ca$^{2+}$ release, hence counteract the facilitated Ca$^{2+}$ release observed in arthritis (Yamada et al., 2015b, 2009). AICAR (5-aminomimidazole-4-carboxamidobenzoic acid) and SI07 are known to stabilize RyR1 activity, normalize Ca$^{2+}$ release and shown to reduce the ROS/RNS burden and improve muscle function in muscle dystrophy and cancer-related muscle weakness, respectively (Lanner et al., 2012; Waning et al., 2015). Thus, AICAR and SI07 could be potentially useful compounds to counteract RA-induced muscle weakness.

8. Conclusion

Muscle weakness is strongly linked with declined physical function, reduced quality of life, impaired work capacity, and increased mortality. Patients with RA are commonly afflicted by muscle weakness and also experience all listed associated risks and complications. RA is a chronic disease, but today there are effective pharmacological treatment strategies (e.g. methotrexate combined with low-dose glucocorticoids) that lower inflammation, joint damage and overall disease activity. Yet, the patients’ strength or physical function does not fully recover. Thus, it appears as the RA-induced muscle weakness cannot be counteracted with a treatment strategy that only attacks the disease itself. Instead, we suggest that future RA therapies should provide improvement in muscle strength as well as reducing the disease activity (i.e. inflammation and joint damage). For instance, EUK-134 or RyR1-stabilizing compounds and muscle strength exercises could be a potentially useful combination therapy together with methotrexate to improve intrinsic muscle function and reduce the disease activity, respectively. Ultimately, this combinational intervention (pharmacological and exercise) can significantly improve the quality of life for the afflicted patients and will also lower the burden on society since the ability to work will improve among these patients.

9. Outstanding Questions

- What is the underlying signaling that results in RA-induced muscle weakness?
- How can muscle function be improved for patients with RA?

Search Strategy and Selection Criteria

Data from this review were identified by searches of PubMed and references from relevant articles using the following keywords, alone or in combination: “Rheumatoid arthritis”, “Muscle weakness”, “Pro-inflammatory cytokines”, “Reactive nitrogen species”, “Calcium signaling”, “Antioxidant”. Only articles published in English were included. Abstracts and reports from meetings were excluded.

Author Contribution

TY and JTL performed the literature search and drafted the manuscript. TY, MMS, EK, JTL edited and revised the manuscript. All authors approved the final version of the manuscript.

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