Exercise, skeletal muscle and inflammation: ARE-binding proteins as key regulators in inflammatory and adaptive networks

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ABSTRACT

The role of inflammation in skeletal muscle adaptation to exercise is complex and has hardly been elucidated so far. While the acute inflammatory response to exercise seems to promote skeletal muscle training adaptation and regeneration, persistent, low-grade inflammation, as seen in a multitude of chronic diseases, is obviously detrimental. The regulation of cytokine production in skeletal muscle cells has been relatively well studied, yet little is known about the compensatory and anti-inflammatory mechanisms that resolve inflammation and restore tissue homeostasis. One important strategy to ensure sequential, timely and controlled resolution of inflammation relies on the regulated stability of mRNAs encoding pro-inflammatory mediators. Many key transcripts in early immune responses are characterized by the presence of AU-rich elements (AREs) in the 3'-untranslated regions of their mRNAs, allowing efficient fine-tuning of gene expression patterns at the post-transcriptional level. AREs exert their function by recruiting particular RNA-binding proteins, resulting, in most cases, in de-stabilization of the target transcripts. The best-characterized ARE-binding proteins are HuR, CUGBP1, KSRP, AUF1, and the three ZFP36 proteins, especially TTP/ZFP36. Here, we give a general introduction into the role of inflammation in the adaptation of skeletal muscle to exercise. Subsequently, we focus on potential roles of ARE-binding proteins in skeletal muscle tissue in general and specifically exercise-induced skeletal muscle remodeling. Finally, we present novel data suggesting a specific function of TTP/ZFP36 in exercise-induced skeletal muscle plasticity.

Keywords: skeletal muscle, exercise, regeneration, inflammation, resolution of inflammation, cachexia, mRNA stability, AU-rich element binding protein (ABP), ZFP36/TTP, HuR

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1. INFLAMMATION AND SKELETAL MUSCLE PLASTICITY

Skeletal muscle shows an enormous plasticity to regulate its functional, structural and metabolic properties in order to adapt to varying physiological demands. Specifically, skeletal muscle maintenance, remodeling, growth, and repair depend on sequential gene expression programs that orchestrate complex protein synthesis and degradation pathways to determine fiber type composition and metabolic profiles, as well as satellite cell activation status and myogenic differentiation (22, 67). Prolonged disturbance of metabolic and immune homeostasis inevitably results in loss of skeletal muscle mass, power and/or functional capacity, as evidenced during aging (sarcopenia), inactivity (atrophy), or disease (cachexia). In particular, chronic diseases with features of persistent inflammation and immune dysregulation profoundly impair skeletal muscle strength, endurance capacity, and regeneration potential. Examples of clinical conditions associated with excessive loss of muscle mass and strength include atherosclerosis and cardiovascular conditions, rheumatoid arthritis, chronic obstructive pulmonary disease, obesity, and type-2 diabetes, as well as several malignant diseases (3, 92, 106, 109).

Physical activity is well recognized as an important strategy not only to prevent, but also to improve and—in some cases—even cure chronic inflammatory disease states which threaten to become the worldwide scourge of the new millennium (142). In recent years, an intricate crosstalk between skeletal muscle tissue and multiple levels of host immunity has become apparent. Specifically, myocytes are capable of producing a variety of immune-relevant receptors, mediators, attractants, and immunomodulatory cytokines. In this way, insulted, mechanically stretched, as well as contracting muscle fibers have a remarkable capacity to specifically alter the local inflammatory milieu, and thus, to attract distinct subsets of leukocytes that exert essential supportive functions in skeletal muscle adaptation, remodeling, and repair processes (56, 60, 91, 118). This inflammatory response is both an inevitable consequence of myofiber damage by eccentric overload, but also an indispensable prerequisite for subsequent structural remodeling and functional adaptation of skeletal muscle tissue (for review, see 95, 108). How this response is fine-tuned to meet the specific demands of different exercise regimens is only poorly understood.

Quite evidently, a short-lived inflammatory response, initiated or promoted by the exercising muscle itself, is necessary to initiate its adaptation to exercise. By contrast, chronic systemic inflammation, as well as a disturbed metabolism, have a profound negative impact on skeletal muscle homeostasis, resulting in unbalanced proteolytic activity and impaired regenerative capacity (for review see 8, 9, 23, 70, 81, 87). Conversely, the exercising muscle seems well-equipped with signaling devices to actively resolve inflammatory responses, and thus, to prevent and even counteract chronic inflammation.

Surprisingly, while the mediators and signaling pathways that initiate and promote the inflammatory response are relatively well known, little is known on the question how acute inflammation resolves to prevent chronic inflammation. We have to consider the fact that inflammation generally does not passively subside, not even when the initial trigger has ceased. By contrast, resolution of inflammation is an active process that involves activation of multiple well-timed counter-regulatory mechanisms that promote a sequential, timely and controlled decline of the inflammatory response (for review, see 28, 93, 97, 123). With regard to skeletal muscle, there are still large knowledge gaps concerning the molecular pathways that are involved in disrupting the physiological inflammatory phase during repair and remodeling, thereby allowing proper return to homeostasis.

It has long been thought that the magnitude and duration of an inflammatory response is mainly controlled by the transcriptional up-regulation of anti-inflammatory as well as by the repression of pro-inflammatory gene activity. However, in recent years, a plethora of post-transcriptional regulatory mechanisms have emerged that are involved in immediate and effective fine-tuning of gene expression programs at multiple levels. There is increasing evidence suggesting that proper regulation of inflammatory gene expression, besides transcriptional regulation, involves a variety of post-transcriptional checkpoints that function at the levels of mRNA splicing, mRNA polyadenylation, mRNA stability, and protein translation (for review, 36). Among these, particularly regulated decay of mRNAs encoding inflammatory mediators emerges as an important inflammatory control mechanism.

Many inflammatory key transcripts are equipped with adjustable "sell by date" labels, located within their 3'-untranslated regions (3'-UTRs). Specific RNA-binding proteins recognize these labels and decide whether to postpone or extinguish the 'expiration date', thereby allowing immediate control of inflammatory transcript levels. Remarkably, similar control mechanisms can orchestrate gene expression in the stepwise differentiation of tissue-specific stem cells, such as satellite cells, in skeletal muscle tissue. In the following review, we focus on the most important mRNA de-stabilizing motif, the adenylate/uridylate (AU)-rich element (ARE), which is present in a broad variety of mRNAs encoding inflammatory mediators and cell cycle regulators. We will summarize accumulating knowledge on ARE-mediated gene expression control during myogenic differentiation, and discuss its potential relevance in orchestrating the inflammatory response of skeletal muscle tissue to physical exercise. Specifically, we discuss the effects of different ARE-binding proteins in skeletal muscle regeneration, remodeling and repair processes.

2. REGULATION OF mRNA STABILITY BY AREs

AU-rich elements (AREs), located within the 3'-UTRs of 8-10% of all human transcripts, are the most common recruiting motifs (*cis*-acting factors) for RNA-binding proteins (*trans*-acting factors) (14). They all contain one or more core pentamers (AUUUA), often arranged in tandem repeats, and integrated in a U-rich region (158). Generally, AREs are characteristic for mRNAs encoding short-lived proteins, such as proto-oncogenes, cell cycle regulators, and—most importantly—pro-inflammatory cytokines (73). Upon binding to their target sequences, ARE-binding proteins (ABPs) exert specific effects on the respective transcripts. These effects include regulation of their translation, intracellular localization/transport, interaction with miRNAs, as well as their stabilization/destabilization. In general, destabilizing ABPs stimulate poly(A) shortening and decapping of their target transcripts, and subsequent 5'-3' or 3'-5' exonuclease degradation (Fig.1, for review, see 98).

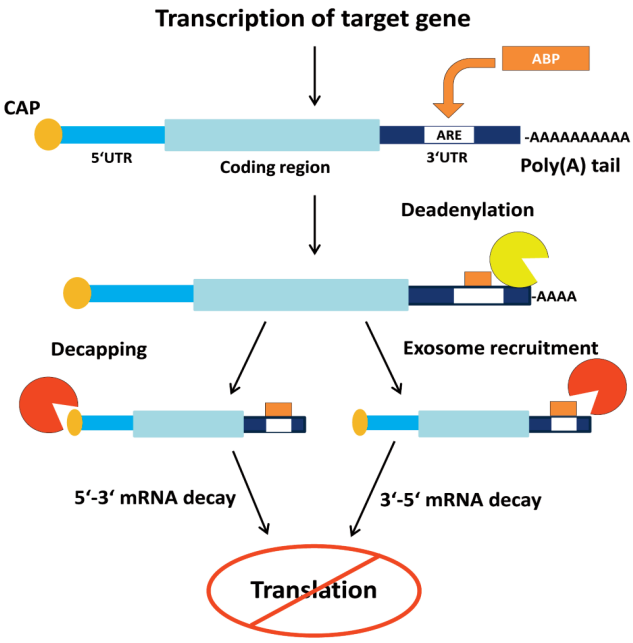

Fig.1. General mechanism of ARE-mediated mRNA decay. Upon binding to the AU-rich element (ARE) in the 3' untranslated region (3'UTR) of the target transcript, ABPs (ARE-binding proteins) activate degradation of the poly(A) tail (deadenylation) and removal of the 5' cap structure (decapping), resulting in subsequent recruitment of the exosome, and eventual 3'-5'- or 5'-3' exonucleolytic decay.

Within the last few years, specific algorithms, like AREScore (126), as well as databases, such as ARED (14) or AREsite (58), have been established to gather and connect information on AREs and ABPs. Using these devices, it is now possible to identify (potential) AREs, to investigate selected AREs in more detail, and to gain information on experimentally validated targets for specific AREs. .

Relatively well-characterized ABPs include the human antigen R (HuR), the CUG-binding protein 1 (CUGBP1), the KH-type splicing regulatory protein (KSRP), the AU-rich element

RNA-binding protein 1 (AUF1), and members of the tristetraprolin (TTP) family of tandem CCCH zinc finger proteins (ZFPs). Whereas HuR binding generally (but not exclusively) stabilizes the respective target transcripts, binding of CUGBP1, KSRP, AUF1, or TTP proteins commonly promotes destabilization of mRNAs and initiates their rapid decay. This can lead to temporal and spatial competition of antagonistic ABPs for the same mRNA binding sites. In turn, this allows translational control of the respective targets in a refined manner (for review, see 1). For a summary of these five ABPs and their characteristics, see Table 1.

Tab.1. Overview of all ABPs discussed in this review.

	HuR (human antigen R)	**CUGBP1** (CUG-binding protein 1)	**KSRP** (KH-type splicing regulatory protein)	**AUF1** (AU-rich element RNA-binding protein-1)	**ZFP36** (zinc finger protein 36)	**ZFP36L1** (zinc finger protein 36 like 1)
Alternative names	ELAV-like protein 1	-	KHSRP	hnRNP D	Tristetraprolin (TTP), TIS11, Nup34	TIS11B, ERF1, BRF1, berg36
Main effect on ARE-containing transcript	Stabilization	Destabilization	Destabilization	Destabilization	Destabilization	Destabilization
Other effects	Regulation of translation	Regulation of mRNA splicing and translation	mRNA splicing, miRNA processing	mRNA stabilization, regulation of translation	Regulation of transcription, translation, mRNA transport, interaction with miRNA pathways	
Induction in muscle during exercise	Chronic electrical stimulation (rat) (78)	Treadmill exercise (mouse) (88)		Chronic electrical stimulation (rat) (78) Treadmill exercise (mouse) (88)	Eccentric exercise (human) (68) Treadmill exercise (mouse) (this study) Cycling exercise (human) (this study)	

3. ABPs IN SKELETAL MUSCLE DEVELOPMENT, GROWTH AND REGENERATION

Thanks to a small population of dormant myogenic stem cells, termed satellite cells, adult skeletal muscle tissue has a remarkable capacity to regenerate and restore its structure and function after acute injury (for review, see 146). Upon activation, satellite cells partly recapitulate some myogenic pathways of embryonic muscle development by use of analogous, but not necessarily identical, mechanisms. Similar to their embryonic counterparts, the so-called myoblasts, satellite cells are capable of self-renewal and new fiber formation. When activated, they undergo a staged and controlled process of proliferation, fusion and differentiation. Each step is dependent on a timely sequence of activation and resolution of stage-specific differential gene expression patterns (150).

It appears that ABPs are essential gatekeepers and caretakers to ensure controlled progression through the myogenic differentiation program (for review, see 7). In particular, ABPs are involved in regulating the transition from myoblasts to myotubes. The latter is a complex process, requiring the well-coordinated crosstalk of a multitude of external and internal stimuli. These stimuli include growth factors and proteins of the extracellular matrix, signal transduction pathways, transcription factors, and cell cycle regulatory proteins. Of particular importance are the myogenic transcription factors of the MRF (myogenic regulatory factor) and MEF2 (myocyte enhancer factor-2) families, as well as diverse cell cycle stimulators (e.g., cyclin D1) and inhibitors (e.g., p21) (reviewed in 89).

In the following section, the specific roles of the five ARE-binding proteins mentioned above (i.e., HuR, CUGBP1, KSRP, AUF1, and ZFP36/TTP) in skeletal muscle cells will be discussed in more detail.

HuR (human antigen R)

HuR is a member of the ELAV-1 (embryonic lethal abnormal vision in *Drosophila*) protein family. The *HuR* gene is believed to be ubiquitously expressed in all tissues and cell types. HuR is involved in the regulation of a multitude of processes, such as proliferation, cell death, and inflammation. In contrast to most other ABPs that promote mRNA degradation, HuR generally stabilizes its target mRNAs and promotes enhanced translation (for review, see (143)). Thus, it appears that differential occupation of 3'UTR-binding sites by HuR versus other ABPs can antagonistically dictate the posttranscriptional fate of target transcripts.

During myogenic differentiation, the nuclear import of HuR is blocked by a caspase-dependent mechanism, resulting in cytoplasmic accumulation of the protein (16). Cytoplasmic HuR has been shown to stabilize several transcripts that are

essential for myogenesis. These include, for example, the myogenic transcription factors MyoD and myogenin, as well as the p21 transcript whose translation product enhances myoblast exit from the cell cycle (51, 125). In the early phase of myogenesis, HuR appears to stabilize the mRNA encoding the cell cycle regulator cyclin D1, thereby allowing myoblast proliferation and subsequent expansion of the pool of myogenic cells. At later stages, HuR dissociates from the cyclin D1 mRNA, which, as a consequence, becomes less stable, thus paving the way for the cells to exit the cell cycle and enter the differentiation program (for review, see 6). Moreover, at the early stages of myogenesis, HuR seems to 'collaborate' with its counterpart KSRP (see below), a known destabilizer of the p21 and myogenin transcripts, by promoting the rapid decay of the mRNA encoding the cell cycle promoter nucleophosmin (31).

HuR also appears to play a role in the development of the neuromuscular junction. Increased levels of mRNA encoding acetylcholinesterase in differentiated myotubes versus undifferentiated myoblasts have in part been attributed to the stabilizing effect of ARE-mediated HuR binding (45, 46). HuR has further been shown to promote the translation of the endogenous danger signaling molecule HMGB1 (high-mobility-group box 1), which promotes inflammatory as well as tissue repair processes upon its release during infection, injury, or strenuous exercise (17, 32). In skeletal muscle, HMGB1 expression is up-regulated during regeneration, and the HMGB1 protein has been shown to promote the commitment of myoblasts to myogenesis (112). Obviously, this process has to be tightly controlled. Here, HuR exerts a key regulatory function by antagonizing miRNA-mediated translational repression of HMGB1 (49).

Finally, HuR is a good example for the frequent observation that the same ABP may exert divergent and even opposing functions on the same target transcript. These functions depend on the respective external trigger, the ABP's intracellular localization, its binding partner, or its phosphorylation status. For instance, in cachectic muscle, HuR does not seem to be involved in the induction, but rather in the repression of myogenic differentiation. Here, HuR, being predominantly confined to the nucleus, appears to be a driving force towards inflammation-associated degradation of the MyoD transcript. In particular, HuR stabilizes and promotes nuclear export of the *iNOS* gene transcript, encoding the inducible nitric oxide synthase, thereby enhancing production of NO as well as subsequent formation of peroxynitrite, which has been shown to decrease mRNA levels of MyoD (47).

CUGBP1 (CUG-binding protein 1)

CUGBP1 belongs to a protein family termed CELF (CUGBP- and ETR-3-like factors). The protein not only binds to AREs, but, as its name indicates, also to GC- and GU-rich elements, and, as a consequence, regulates not only mRNA stability, but also other features, such as translation or mRNA splicing (for review, see 143).

Particularly interesting is the binding of CUGBP1 to the tumor necrosis factor (TNF)-α transcript, since the role of this cytokine in myogenesis is complex and not completely understood. On the one hand, prolonged exposure to elevated levels of TNF-α inhibits myogenesis, and promotes muscle wasting and cachexia (for review, see (96)). On the other hand, a certain amount of this cytokine appears to be necessary to allow progression of early myogenesis, characterized by expansion of the pool of myogenic cells and early differentiation steps (for review, see 138). Thus, CUGBP1 might be an important player here, regulating TNF-α mRNA stability in a well-coordinated manner and, as a consequence, restricting TNF-α autocrine effects on the muscle cells themselves (155).

Finally, CUGBP1 is involved in the pathogenesis of myotonic dystrophies, multisystemic disorders associated with myotonia, muscle atrophy, and muscle weakness. Here, expanded (C)CTG repeats within the non-coding regions of specific mRNAs appear to be targeted for enforced degradation by CUGBP1 and MBNL1 (muscleblind-like 1), another RNA-binding protein (for review, see 139).

KSRP (KH-type splicing regulatory protein)

KSRP is a member of the FUSE (far upstream element binding) protein family. The protein appears to be involved in the regulation of RNA splicing and miRNA processing, however, its role as an ARE-dependent mRNA decay factor has been most extensively studied. The binding of KSRP and HuR to a specific ARE is mutually exclusive. Thus, these two factors are considered as competitors with regard to binding to a particular transcript, especially since they exert opposite effects (destabilization versus stabilization) on their targets (for review, see 24).

Interestingly, the MyoD, myogenin, and p21 transcripts, which, as mentioned, are important HuR targets, can also be bound by KSRP. Early in myogenesis, when cells still proliferate, the predominant binding partner for these transcripts is KSRP, which induces their destabilization and rapid decay. Upon the initiation of differentiation, activation of p38 mitogen-activated protein kinase (MAPK) leads to phosphorylation of KSRP, which reduces its affinity for the AREs in the 3'-UTR of the three mRNAs (7, 24, 25, 75). By contrast, these mRNAs are stabilized by increasing cytosolic HuR levels, as mentioned above.

The physiological relevance of KSRP in skeletal muscle is further underscored by the phenotype of *KSRP*-deficient mice, which show defects with respect to skeletal muscle regeneration, suggesting a crucial role for KSRP in this process (26).

AUF1 (AU-rich Element RNA-binding)

The AUF1 protein family consists of four members (p37, p40, p42, and p45), which are generated by alternative splicing of the same transcript. AUF1 proteins predominantly promote mRNA decay; nevertheless, they have also been described to engage in other activities, such as RNA stabilization and translation. Their target transcripts mainly encode mediators of the inflammatory response, such as cytokines, but also proto-oncogenes, such as c-myc and c-fos, and cell cycle regulators (for review, see 148). Because these factors are central players in myogenesis (48), it is likely that AUF1 proteins regulate this process in a similar manner to HuR, CUGBP1, and KSRP, even though this has not been studied in detail.

Furthermore, it is interesting that AUF1 can also influence the impact of transcripts encoding regulators of myogenesis through mechanisms other than transcript (de)stabilization. Specifically, binding of AUF1 to the 3'-UTR of the MEF2C transcript promotes translation of the latter, without affecting mRNA stability (99). The respective mechanism awaits further investigation.

ZFP36 (Tristetraprolin, TTP)

The ZFP36 family of zinc finger proteins was discovered in 1989, when cultured fibroblasts were stimulated with tetradecanoylphorbol 13-acetate (TPA), in search of rapidly induced target genes (141). The acronym "TIS" in the alternative name "TIS11" thus stands for "TPA-induced sequence".

Tristetraprolin (ZFP36/TTP, TIS11, Nup34) is the founding member of the ZFP36 family of ABPs. In humans, this family comprises two other proteins, namely ZFP36L1 (TIS11B, ERF1, BRF1, berg36) and ZFP36L2 (TIS11D, BRF2), while in rodent placenta, a fourth ZFP36 protein family member (ZFP36L3) has been identified (20).

All ZFP36 proteins share a tandem zinc finger motif, which mediates their binding to AREs (53). Otherwise, ZFP36L1 and ZFP36L2 are more similar to each other than each one of them to ZFP36. Known ZFP36 targets are mainly transcripts encoding pro-inflammatory cytokines, such as the TNF-α transcript, but also mRNAs coding for growth factors, such as VEGF, or cell cycle regulators (e.g., cyclin D1 or p21). For a summary of the most important ZFP36 targets, see Table 2. Expression of the *ZFP36* genes themselves is particularly and immediately induced by pro-inflammatory cytokines. Thus, it appears that these ABPs function as 'rapid reaction force' to efficiently attenuate inflammatory gene expression at the post-transcriptional level by immediately destabilizing transcripts encoding pro-inflammatory cytokines (for review, see 15, 40, 116).

Besides their function as mRNA-destabilizing agents, ZFP36 proteins act as regulators of transcription, translation, and RNA transport. In addition, a complex crosstalk with miRNA pathways has been described (71). These diverse, and occasionally opposing, functions seem to be determined by multisite post-translational modifications. Specifically for ZFP36/TTP, a complex pattern of phosphorylation, which regulates the protein's mRNA binding activity, as well as its interaction with other proteins and its nucleocytoplasmic shuttling, has been demonstrated (for review, see 15, 40, 116). Moreover, ZFP36 has been shown to bind to the ARE of its own gene transcript, suggesting the existence of an auto-regulatory feedback loop (137). In addition, interestingly, transcription of the *HuR* gene is regulated by ZFP36/TTP, indicating intimate regulatory connections between these two pathways (4).

Furthermore, in addition to regulating the stability of mRNAs encoding pro-inflammatory cytokines, ZFP36/TTP can also influence inflammation through an alternative mechanism. The protein has been shown to directly interact with the p65 subunit of NF-κB (nuclear factor kappa B), a transcription factor which plays a central role in inflammatory signaling pathways. Binding of ZFP36/TTP to p65 attenuates NF-κB nuclear translocation, and thus prevents the transcriptional activation of NF-κB target genes, including those encoding pro-inflammatory cytokines (59, 82, 120). In addition, ZFP36/TTP appears to recruit specific histone deacetylases to NF-κB target promoters, thereby repressing NF-κB-dependent transcription (82). Taken together, ZFP36/TTP appears to regulate inflammation in a highly complex manner at multiple levels (Fig.2).

Despite a significant overlap with regard to their mRNA targets, the functions of the three ZFP36 proteins are probably mostly non-redundant. *ZFP36/TTP* knockout mice are viable but exhibit a hyperinflammatory phenotype with features of cachexia, conjunctivitis, and dermatitis (136). Deletion of the *ZFP36L1* gene is lethal in embryogenesis, and *ZFP36L2*-deficient mice die during the early postnatal period, mainly as a result of defective hematopoiesis (Table 2) (19, 133, 134).

Tab.2. Characteristics of the ZFP36 protein family.

	ZFP36	ZFP36L1	ZFP36L2
Aliases	TIS11, TTP, Nup475	TIS11B, BRF1, ERF1, BERG36	TIS11D, BRF2, ERF2
Mechanism of action	mRNA destabilization	mRNA destabilization, regulation of translation (VEGF transcript) (19)	mRNA destabilization
Targets	TNF-α (34), IL-6 (130), IL-3 (129), IL-10 (131), p21 (100), cyclin D1 (86), GM-CSF(35), ZFP36 (27), c-myc (86)	IL-3 (128), VEGF (39), TNF-α (80), GM-CSF(79)	TNF-α (80), GM-CSF(79), IL-3 (79)
Mouse knockout phenotype	Hyperinflammation, treatable with anti-TNF-α antibody (136)	Lethal at embryonic stage E10-E12 (19, 134)	Die of internal bleeding shortly after birth (133)

To date, only very few data are available on potential regulatory functions of ZFP36 proteins in the skeletal muscle context. However, interestingly, findings by Geyer et al. indicate that nicotinergic stimulation of skeletal myotubes, mimicking activation of the motor endplate by neuronal signals, leads to increased ZFP36/TTP levels. This results in reduced inflammation, as reflected by decreased production of pro-inflammatory cytokines (54). Thus, it appears that ZFP36/TTP, besides functioning in inflammation and repair, might also be involved in multiple signaling cascades of skeletal muscle homeostasis.

Finally, specific ZFP36 proteins might also play an important role in skeletal muscle regeneration, which might be an important feature in the regulation of skeletal muscle adaptation to exercise. As early as in 2002, Sachidanandan and colleagues demonstrated induction of *ZFP36/TTP* expression after skeletal muscle injury, presumably in satellite cells, suggesting that ZFP36/TTP might play a role in the regulation of skeletal muscle regeneration (114). Similarly, in 2008, we demonstrated induction of *ZFP36L1/TIS11B* gene expression in skeletal myoblast differentiation. Most importantly, we also

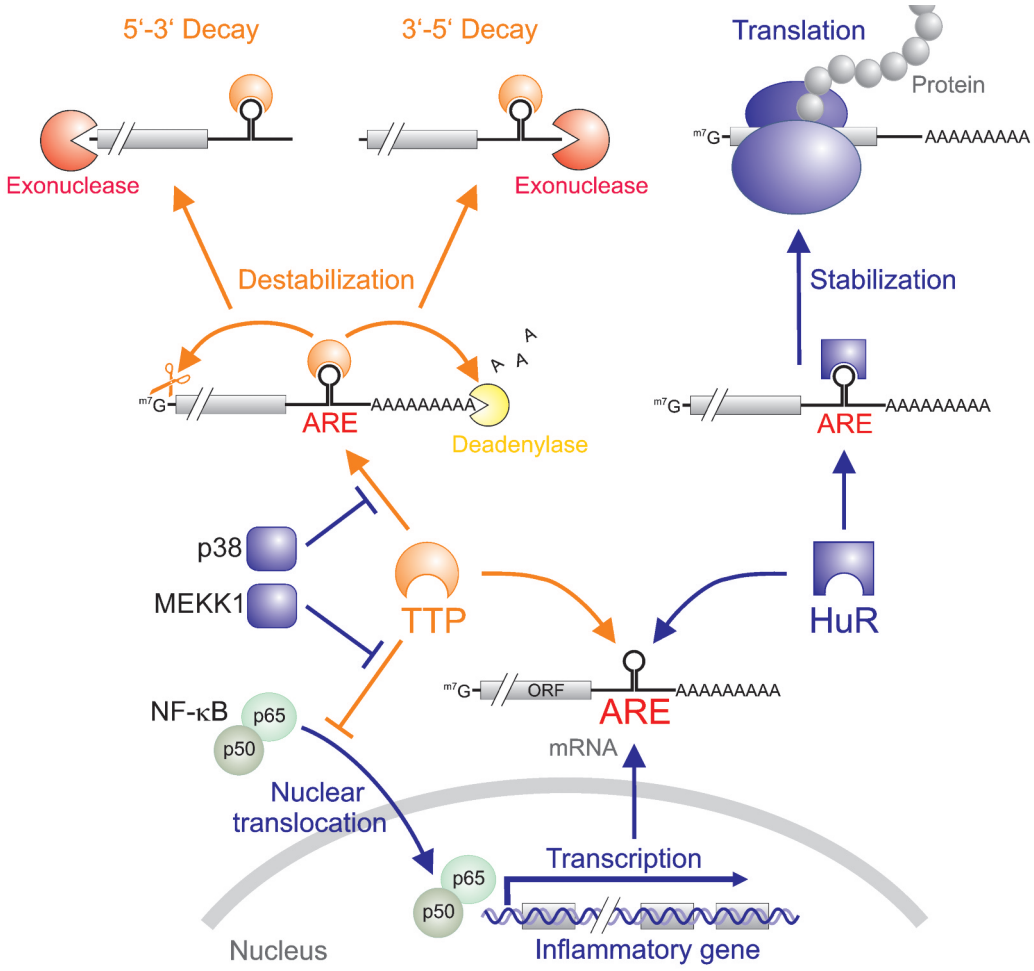

Fig.2. Reciprocal regulation of mRNA stability by ZFP36/TTP and HuR. Multiple inflammatory pathways involve activation and nuclear translocation of the transcription factor NF-κB to drive inflammatory gene expression. In the course of transcription, the nascent messenger RNA (mRNA) is spliced, 5'-capped, and 3'-polyadenylated to protect the transcript from exonucleolytic decay. The processed, mature mRNA is exported to the cytoplasm where the open reading frame (ORF) is translated into functional pro-inflammatory mediators. Many pro-inflammatory transcripts contain AU-rich elements (AREs) in their 3' untranslated regions (3'UTR) that can be recognized by specific ARE-binding proteins (ABPs). The destabilizing ABP ZFP36/TTP initiates mRNA degradation by recruiting components of the cellular mRNA decay machinery resulting in shortening of the 3' poly(A) tail, removal of the 5' 7-methylguanosine cap (^{m7}G), and subsequent degradation by 5' and 3' exonucleases. Moreover, ZFP36/TTP can interact with the p65 subunit of NF-κB to hinder its nuclear translocation, thus preventing the transcriptional activation of NF-κB target genes. In contrast, binding of the stabilizing ABP HuR to the ARE motif competes with the degradation machinery, fosters the recruitment to ribosomes, and thus ensures prolonged and enhanced translation. Likewise, specific phosphorylation of ZFP36/TTP by activation of the p38 and MEKK1-JNK pathways can promote inflammatory activity by preventing the recruitment of the RNA decay machinery to pro-inflammatory transcripts, as well as by preventing repressive interaction of ZFP36/TTP with NF-κB. Blue lines indicate pro-inflammatory pathways, anti-inflammatory pathways are marked in orange.

reported differential expression of this gene in skeletal muscle tissue from dystrophic *mdx* mice when compared to normal, healthy mice. Because *mdx* mice undergo continuous cycles of skeletal muscle degeneration and regeneration, this finding further supports a role of ZFP36 proteins in skeletal muscle regeneration (30).

4. ADAPTATION OF SKELETAL MUSCLE TO EXERCISE, INFLAMMATION, AND ABPs

Adult skeletal muscles are composed of heterogeneous fiber types that differ in the molecular organization and structure of the contractile apparatus and with respect to metabolic characteristics. Dependent upon mode (endurance/resistance), contraction type (concentric/eccentric), duration and intensity, physical exercise provokes dynamic alterations in skeletal muscle size and fiber type composition, eventually resulting in long-term adaptations with improved force production, contraction time, and/or fatigue resistance (for a comprehensive review, see 119).

As outlined in section 1, acute exercise provokes a transient pro-inflammatory state, which affects whole-body homeostasis and metabolism, and specifically targets local inflammatory circuits in the skeletal muscle microenvironment (13, 106, 145). It appears that a well-controlled inflammatory response is important for subsequent adaptive and reparative processes, including satellite cell activation and differentiation (13, 106). However, the specific contribution of the contracting muscle itself, either by passive or active release of inflammatory mediators, is still a matter of controversy. Moreover, hardly anything is known about the refined mechanisms that are

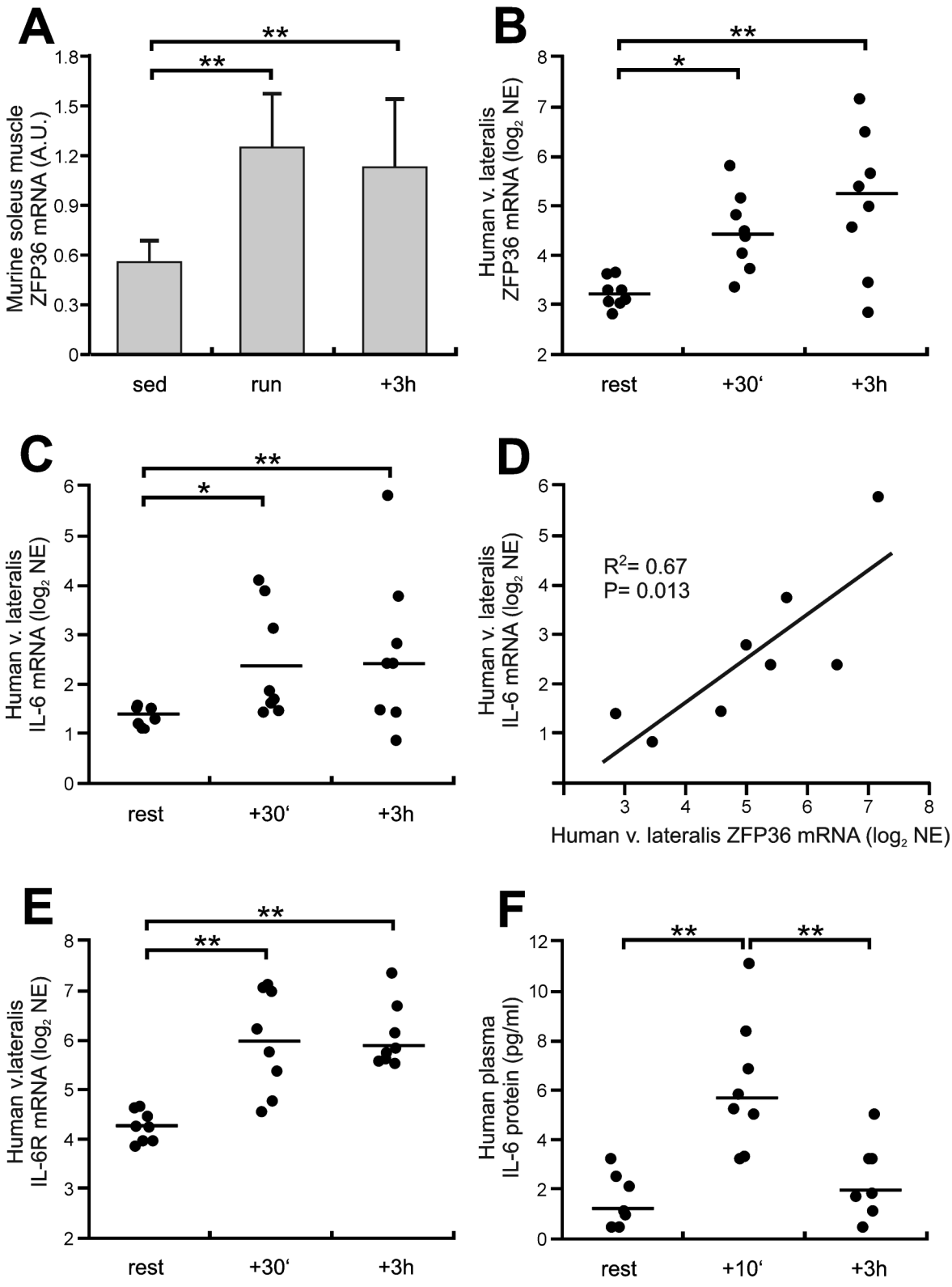

Fig.3. Induction of *ZFP36/TTP* expression in exercising skeletal muscle. (A): Expression of *ZFP36* in mouse *soleus* muscle in the sedentary state (sed), immediately after an acute bout of exercise (run), and after a recovery period of 3 hours (+3h). Male C57BL/6 mice were exercised for one hour at moderately intense conditions on an electric treadmill and were either killed immediately after the run or placed back in their cages for 3 h of recovery. mRNA was isolated from *soleus* muscles and quantified by real-time PCR. The detailed experimental procedure has been published elsewhere (64). Shown are the arithmetic means and standard deviations from n=8 mice. (B-F): Effect of one hour of cycling exercise at 80% VO_2max (262 ± 58 Watt) on gene expression levels of *ZFP36* (B), *IL-6* (C), and *IL6R* (E) in the *vastus lateralis* muscle of 8 endurance-trained male individuals (VO_2max, 67.2 ± 8.9 ml/min/kg). Values were retrieved from a microarray dataset (Affymetrix U219) of microbiopsies taken at rest, as well as 30 min (+30') and 3 hours (+3h) after the cycling protocol (unpublished data set). The bar represents the arithmetic mean of normalized log_2-transformed expression levels (*P < 0.05, **P < 0.01; paired t-test). In addition, circulating plasma levels of IL-6 were determined from blood samples taken at rest, as well as 10 min (+10') and 3 hours (+3h) after the cycling protocol (F). A significant positive association between individual gene expression levels of *ZFP36* and *IL-6* could be detected in *vastus lateralis* at 3 hours after cessation of exercise (D). Data derive from a multicenter trial performed at the facilities of Sports Medicine at the Universities of Gießen, Ulm, and Tuebingen (see supplementary methods section for details).

responsible for both induction and resolution of inflammatory circuits, and, particularly, regulation of pro- and anti-inflammatory mediators, in response to physical exercise.

Myofibrillar disruption in the course of strenuous and eccentric exercise is commonly considered a driving force in exercised-induce inflammatory responses to promote subsequent muscular adaptations in the course of damage-repair processes (101). Experimental muscle damage, as any disruption of tissue integrity, is known to provoke a transient, and locally confined inflammatory stage, initially featured by active recruitment of neutrophils, CD8 T cells, and pro-inflammatory M1-type macrophages (10, 94, 154). Within days, the leukocyte infiltrate shifts from a pro- to an anti-inflammatory phenotype, then characterized by predominantly anti-inflammatory M2 macrophage subtypes, and, most remarkably, accumulation of regulatory T cells (10, 29, 74, 110). As outlined above, tailored and short-term inflammatory activity, as well as active resolution of inflammation, are both indispensable requirements for the promotion of regeneration, repair and adaptation of skeletal muscle. These processes are intimately linked by a well-balanced pattern of pro- and anti-inflammatory mechanisms to facilitate return to tissue homeostasis (13, 74). In particular, pro-inflammatory M1 macrophages are necessarily involved in the removal of muscle debris, but have further been shown to activate satellite cell proliferation by NO-mediated mechanisms, and through the release of pro-inflammatory mediators, including interleukin (IL)-6, IL-1β, TNF-α, and granulocyte colony-stimulating factor (G-CSF) (10, 13, 110, 111). However, if initial pro-inflammatory signaling is not adequately controlled, M1 macrophages harbor destructive potential to amplify tissue damage and to block repair (13, 57, 63). Currently, there is no clear understanding as to what extent invading phagocytes may initially accelerate subtle myofiber damages caused by strenuous exercise. Moreover, there is no consensus as to whether exercise-induced mechanical damage of myofibers is an irrevocable necessity to promote skeletal muscle adaptation to specific exercise regimens, and whether contracting muscle fibers are capable of actively recruiting inflammatory cells to set the scene for subsequent remodeling processes, irrespective of a muscle-damaging insult. Indisputably, efficient regeneration and remodeling of damaged muscle fibers depends on a precise coordination of multiple staged processes, highlighted by the macrophage skewing from M1 toward M2 phenotypes at the time of resolution of inflammation (10, 74). M2 macrophages promote angiogenesis and matrix remodeling, while actively counteracting destructive immunity through the release of anti-inflammatory cytokines like IL-10. Moreover, M2 macrophages have recently been shown to contribute to the recruitment, differentiation and growth of myogenic precursor cells by production of insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β) (138, 152).

Against this background, it appears obvious that inflammation and satellite cell dynamics in response to exercise and muscle injury are intertwined, and have to be tightly controlled with respect to timing and resolution. If initial pro-inflammatory signals persist, excessive tissue damage can occur while the differentiation capacity of satellite cells is impaired. Conversely, premature initiation of the anti-inflammatory program can also disrupt efficient tissue healing. Similar to the sequel of inflammatory circuits, satellite cell activation, proliferation, differentiation, and fusion follow a tight schedule. In particular, whereas the cell cycle regulator cyclin D1 enhances satellite cell proliferation within the first few hours after activation, the gene encoding the MRF MyoD is upregulated when the cells exit the cell cycle, in parallel with the cell cycle inhibitor p21. By contrast, myogenin is a rather 'late' MRF, being upregulated during differentiation and fusion (for review, see 138, 152). At present, we are far from a clear understanding of how contracting myofibers, invading inflammatory cells and resident stem cells orchestrate their activities to promote skeletal muscle regeneration and remodeling, but also to control and restore tissue homeostasis.

This is where ABPs come into the picture, as they regulate, restrict, or fine-tune the production of inflammatory mediators. Reciprocally, expression of the genes encoding ABPs is controlled and commonly up-regulated by cytokine- and growth factor-mediated pathways (1, 2, 143). In addition, as discussed in detail in section 3, several ABPs control the expression of genes encoding regulators of satellite cell proliferation, differentiation, and fusion. These include the cell cycle regulators cyclin D1 and p21, and the MRFs MyoD and myogenin. Therefore, ABPs might control skeletal muscle adaptation to exercise at multiple levels.

Against this background, it is surprising that a potential role for ABPs in skeletal muscle adaptation to exercise has hardly been analyzed so far. However, a few studies could demonstrate differential expression of genes encoding ARE-binding proteins in response to skeletal muscle contraction and/or physical exercise. Lai et al. showed enhanced expression of both *HuR* and *AUF1* in rat muscle after electrically stimulated, chronic contractile activity (78). Matravadia et al. demonstrated long-term induction of the *CUGBP1* and *AUF1* genes in the *quadriceps* muscle of mice after treadmill training, but found no effect of acute treadmill exercise on the expression levels of *HuR, CUGBP1*, or *AUF1* (88). By comparing short bout effects of eccentric versus concentric exercise in human *vastus lateralis* muscle, Chen at al. described a more pronounced expression of *ZFP36/TTP* following eccentric contractions (38). The same group reported additive effects on post-exercise *ZFP36/TTP* expression levels after two repeated bouts of eccentric exercise, separated by four weeks (68). As illustrated in Figure 3, our own unpublished data indicate that endurance exercise is also characterized by a significant up-regulation of *ZFP36/TTP* gene expression in the murine *soleus* muscle after an acute bout of running exercise (Figure 3A), and in the human *vastus lateralis* muscle in response to one hour of intense cycling exercise (supplementary methods; Figure 3B). These novel data demonstrate immediate up-regulation of *ZFP36* gene expression in skeletal muscle in response to acute endurance exercise.

In particular, simultaneous induction of *ZFP36/TTP* gene expression along with ZFP36 target transcripts in skeletal muscle after exercise suggests the existence of concerted gene activation programs that ensure immediate modulation of inflammatory gene expression by the concomitant supply of balancing ABPs. As exemplified in Figure 3, exercise-induced levels of the IL-6 transcript are significantly correlated with the individual magnitude of *ZFP36/TTP* gene expression in *vastus lateralis* muscle after intense cycling exercise (Figure 3D). Likewise, in post-exercise samples, ZFP36/TTP mRNA levels correlate with the levels of various well-known ARE-

containing transcripts, including those encoding chemokine ligand CXCL2, urokinase plasminogen activator PLAU, thrombomodulin THBD, serum/glucocorticoid regulated kinase SGK1, and cell cycle regulators like FOS, FOSL1, and MYC (unpublished data; see supplementary methods section for details). Interestingly, as outlined by Piccirillo et al., simultaneous induction of pro- as well as counter-regulatory gene expression networks at the transcriptional level, and subsequent establishment of post-transcriptional regulatory checkpoints is emerging as a rather general mechanism in a broad variety of settings, allowing rapid changes and adaptations in the proteome in response to inflammatory or metabolic stimuli (104).

An analogous, but even more complex pattern of transcriptional and post-transcriptional feedback control is found when looking at the tight control mechanisms that determine the outcome and duration of MAPK signaling cascades. Activation of MAPK pathways is known to trigger the transcription of multiple immediately early genes, including enhanced expression of ABP-encoding genes, as well as genes encoding dual-specificity phosphatases (DUSPs) which are reciprocally destined to extinguish MAPK signaling by dephosphorylation (69). DUSP transcripts contain ARE-binding motifs and are targeted by ABPs for post-transcriptional regulation, including stabilization by HuR (77), or enhanced degradation by ZFP36/TTP (83), respectively. In addition, as outlined above, activity, localization, and binding capacity of ABPs is determined by specific phosphorylation patterns, which in turn are again controlled by the activity of MAPK signaling cascades (11).

In this way, inflammatory pathways are intrinsically coupled to multiple self-regulatory feedback mechanisms, allowing precise control whether to shut-off, resolve, perpetuate, or amplify the inflammatory response. It is thus tempting to suggest that ABPs might constitute a highly flexible toolbox in skeletal muscle to set the balance between pro- and anti-inflammatory pathways at multiple levels, allowing fine-tuning of inflammatory and functional networks in response to the demands of different exercise regimens and insults.

The importance of precise and flexible post-transcriptional coordination of inflammatory responses can be exemplified by the most extensively studied (but probably least understood) exercise-induced inflammatory mediator, namely IL-6. Circulating IL-6 functions as a ubiquitous warning signal to indicate disturbed tissue homeostasis in case of emergent events. Thus, it is commonly acknowledged that IL-6 serum levels parallel the onset, progression, and remission of the exercise-provoked acute inflammatory response (Figure 3F) (102). Apparently, the contracting muscle itself is triggered to produce and release IL-6 (127) and to up-regulate expression of the gene encoding the IL-6 receptor (IL-6R) (Figures 3C,E) (72). Exogenous IL-6 has further been shown to up-regulate its own production in skeletal muscle by stabilizing the transcribed IL-6 mRNA, thus fostering a self-promoting feedback loop of IL-6 signaling in the exercising muscle (147). Although the true contribution of skeletal muscle to exercise-provoked IL-6 serum levels is unknown, there is clear evidence that IL-6 seems to be involved in driving metabolic homeostasis and insulin sensitization (21, 66, 90). Moreover, IL-6 signaling is beneficially involved in driving muscle regeneration, satellite cell proliferation and the formation of myotubes (65, 124, 153). Conversely, persistent elevation of IL-6 has been associated with muscle wasting in chronic inflammatory conditions, including cachexia, insulin resistance, and diabetes, as well as in the progression of sarcopenia (12, 132, 149). Likewise, persistent up-regulation of *IL6R* expression, along with other genes involved in inflammatory pathways, has been observed in skeletal muscle tissue of women with metabolic syndrome and insulin resistance (107). Thus, the need for efficient strategies to control the production of this cytokine in response to exercise is obvious. Indeed, recent studies reveal complex and interweaving controlling circuits that regulate *IL-6* expression at the post-transcriptional level, governed by specific MEKK1-dependent phosphorylation patterns of the ABP ZFP36/TTP (120, 121, 156, 157).

Similar to IL-6 signaling, dichotomous functionality in inflammatory and metabolic responses is characteristic of several other inflammatory mediators that are released upon exercise, and are known to be targeted by ABPs. For instance, CXCL1 and CXCL2, two chemokines involved in neutrophil and macrophage recruitment in response to exercise and muscle injury (85, 138), have recently been shown to improve fat oxidation in skeletal muscle (103). However, they are also implicated in insulin resistance and chronic muscle inflammation in obesity (105). The transcripts of both chemokines contain ARE elements within their 3'UTRs, and are under reciprocal control of HuR and ZFP36/TTP at the post-transcriptional level (43, 50, 54, 61). Similarly, both HuR and ZFP36/TTP have been implicated in the regulation of prostaglandin production in inflamed muscle tissue by reciprocally targeting COX-2 mRNA (33), thereby shaping M1 and M2 macrophage polarization (62, 84, 151). It appears that systemic chronic inflammation with dysregulated cytokine signaling interferes with skewing from M1 towards M2 phenotypes in skeletal muscle, thereby promoting insulin resistance, fibrosis, fat deposition, exhaustion of the satellite cell pool, and muscle wasting (44, 52, 111, 113). Accumulating evidence suggests that prostaglandins can promote muscular pain, chronic inflammation and atrophy, but are also indispensable for driving myogenesis and muscle repair (76). As such, administration of COX inhibitors has the potential to block skeletal muscle inflammation, as well as to promote but also to interfere with the resolution of inflammation (122, 140). Similarly, administration of glucocorticoids in chronic inflammatory conditions may aggravate disease by triggering expression of atrophy-related genes *(FOXO1, atrogin-1, MuRF1)*, and by interfering with mammalian target of rapamycin (mTOR) signaling in skeletal muscle, thereby promoting muscle wasting (41, 115, 117). In fact, no effective drug is currently available that sufficiently attenuates chronic inflammatory symptoms without imposing an increased risk of disturbed skeletal muscle homeostasis and metabolism. Consequently, a better understanding of pro-resolving, in contrast to anti-inflammatory, mechanisms is necessary to open novel avenues for the treatment of chronic inflammatory conditions, as has recently been emphasized by Buckley et al. (28). We should also consider the fact that we already have the probably most effective 'pro-resolving drug' at hand, namely physical exercise. This further emphasizes the need for a better understanding of regulatory pathways involved in skeletal muscle adaptation to exercise.

Besides mRNAs encoding inflammatory mediators, other ABP targets encode proteins known to have diverse functions in skeletal muscle adaptation to exercise. Specifically, given the fact that ABPs target mRNAs encoding cell cycle regulators and MRFs, such as cyclin D1, p21, MyoD, or myogenin, which are all involved in the regulation of satellite cell dynamics, it is very likely that ABPs are major players in this process.

In addition, ABPs might be involved in the regulation of fiber type specification in response to exercise. For example, Chakkalakal et al. demonstrated that the stability of the mRNA encoding the skeletal muscle protein utrophin A, a structural protein located at the neuromuscular junction, is controlled by a conserved ARE within the utrophin transcript (37). This is particularly interesting, since the utrophin A transcript is more stable in slow versus fast muscle fibers (37, 55). The upstream regulator appears to depend on calcineurin signaling, which is activated in response to endurance exercise, and is generally considered to have important roles in maintaining the slow-twitch, oxidative myofiber program (135). The underlying mechanism might be less efficient binding of the mRNA de-stabilizing protein KSRP to this specific ARE, since it has been demonstrated that the p38-dependent stabilization of the utrophin A transcript is mediated by KSRP (5, 6). Thus, it is likely that both the phosphatase calcineurin and the kinase p38 initiate a signaling cascade eventually leading to decreased de-stabilizing activity of KSRP. Utrophin A is a good candidate for novel therapeutic approaches in DMD (Duchenne muscular dystrophy)—it might partially replace the dystrophin protein, which is missing in DMD patients. Thus, these findings might have important clinical implications. Furthermore, D'souza et al. presented data indicating that the stability of transcripts encoding regulators of oxidative metabolic pathways, such as PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator 1α), was different in red slow and white fast skeletal muscle fibers. This finding indicates that regulation of muscle fiber type composition is distinctively controlled at the level of mRNA stability (42). Consistently, the authors found that levels of several ABPs, specifically AUF1, HuR, KSRP, and CUGBP1, were different in red compared with white white muscle cells.

Finally, ABPs might also be important players in the regulation of exercise-associated angiogenesis. Because the VEGF transcript is an important target of the ZFP36 proteins in different cell types, the latter might be central in the control of the enhanced vascularization that is regularly observed in response to endurance exercise (144).

5. CONCLUDING REMARKS

Regulation of mRNA stability by ABPs might be a powerful strategy to control the response of skeletal muscle tissue to exercise. In particular, ABPs are involved in the regulation of genes encoding pro-inflammatory cytokines and chemokines, thus temporally and spatially restricting the inflammatory response to a training stimulus. This is of specific relevance, because ordered and timely resolution of inflammation is crucial for restoration of tissue homeostasis in response to exercise. Whether inflammation acts as a 'good guy', enhancing skeletal muscle training adaptation, or as a 'bad guy', inducing skeletal muscle decay in chronic disease, depends on an intricate network of cellular and molecular signaling circuits that are poorly understood at present. In addition, ABPs control the expression of a plethora of other, non inflammation-associated genes involved in the adaptation of skeletal muscle to exercise, such as the MRF genes or genes encoding cell cycle regulators, which are involved in the control of satellite cell proliferation and differentiation. Thus, in the future, it will be crucial to systematically identify and functionally characterize ABPs and ABP targets in the exercising skeletal muscle, via, for example transgenic mouse models. A better understanding of the multiple layers of post-transcriptional regulatory control mechanisms might eventually pave the way for the development of novel therapeutic approaches for disorders associated with chronic inflammation and skeletal muscle degeneration.

SUPPLEMENTARY METHODS SECTION

Microarray data from *musculus vastus lateralis* at rest and in response to exercise were kindly provided by Frank C. Mooren, Jürgen Steinacker, and Andreas M. Niess. Expression values of selected genes were extracted from an unpublished data set that derives from an ongoing multicenter trial performed at the facilities of Sports Medicine at the Universities of Gießen, Ulm, and Tübingen, Germany. All experimental procedures were approved by the Research Ethics Committees of the Justus-Liebig-University Gießen, the University Hospital of Tübingen, and the University of Ulm, Germany.

Briefly, expression data were derived from healthy male endurance-trained individuals (n=8; age, 25.4 ±4 years; VO_2max, 67.2 ±9 ml/min/kg) who completed 60 min of high intensity cycling on a bicycle ergometer at a power requiring 80% of the VO_2max (262 ± 58 Watt); including 10 min of warm-up cycling at 60% VO_2max. A more detailed description of the exercise protocol is given in Beiter et al. (18). Percutaneous muscle biopsies from the *musculus vastus lateralis* were taken at rest, as well as 30 min (+30'), and 3 hours (+3h) after the cycling protocol. All muscle biopsies were performed on the right leg of the participants using a biopsy gun and a fine biopsy needle (Plus Speed; Peter Pflugbeil, Zorneding, Germany) under local anesthesia (1% Meaverin). Muscle samples were immediately frozen in liquid nitrogen and stored at -80°C.

Muscle tissue was homogenized with a TissueRuptor homogenizer (Qiagen, Hilden, Germany), and total RNA was extracted using RNeasy Fibrous Tissue Mini kit (Qiagen) according to the manufacturer's recommendations. RNA integrity was assessed using the Agilent 2100 Bioanalyzer system and Agilent RNA 6000 Pico Kit (Agilent Technologies, Waldbronn, Germany). Microarray analysis was performed by the Microarray Facility Tübingen (MFT Services, Germany). Briefly, biotin-labeled cRNA synthesis and cRNA fragmentation were performed using the Affymetrix GeneChip Kit reagents, according to the procedure described in the Affymetrix GeneAtlas 3'IVT Express Kit technical manual (Affymetrix, Santa Clara, CA, USA). Samples were hybridized using Human Genome U219 microarray platform (Affymetrix). Gene expression data were analyzed using Affymetrix Expression Console software (Affymetrix) and

Partek Genomics Suite 6.5 software (Partek Incorporated, St Louis, MO, USA). Data were normalized and filtered for transcripts which were differentially expressed between sampling points. Significance was calculated using paired t-test without multiple testing corrections, selecting all transcripts with a minimum change in expression level of 1.5-fold together with $P < 0.05$. Pearson correlation and linear regression analysis was used to estimate the correlation between expression level of *ZFP36/TTP* and other exercise-affected transcripts from the list of differentially expressed probe sets. The expression changes of three selected genes *(LDHA, LDHB, PPARGC1A)* were validated by SYBR green quantitative real-time PCR.

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CONFLICTS OF INTEREST

None of the authors has any conflicts of interest to declare.

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