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Review Article

Epitranscriptomic Revolution: Unlocking RNA Modifications as Dynamic Biomarkers for Elite Equine Endurance

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Abstract
Beyond DNA sequence alone, the burgeoning field of epitranscriptomics, which focuses on RNA fluctuations, has changed our knowledge of gene regulation. Because they demonstrate physiological alteration, metabolic efficiency, and stress resilience, these dynamic RNA differences are important biomarkers for comprehending equine endurance athletes. Significant RNA vicissitudes like pseudouridylation, N6-methyladenosine (m6A), and adenosine-to-inosine editing are highlighted in this review manuscript, highlighting their importance in the cellular response to stress and endurance training. This review article focuses on the potential applications of recent developments in biomarker discovery, RNA functionality dynamics, and epitranscriptomic profiling to enhance performance evaluation and training plans for elite equestrian athletes. Understanding the connection between RNA changes and endurance-related traits opens the door to new methods in veterinary medicine, equine sports science, and tailored performance enhancement.
Keywords: Epitranscriptomic, RNA Modifications, Biomarkers, Equine Endurance.

Introduction

Equine endurance racing is a physically challenging sport that requires horses to thrive on prolonged exercise over distances ranging from 40 kilometers to 160 kilometers [1, 2]. Physiological parameters such as metabolic efficiency, cardiovascular fitness, strength of muscles, and recuperation capacity all have an impact on equine endurance race performances [3, 4]. Oxidative stress can cause degenerative changes linked to aging, stress, muscular damage and neurological illnesses and drastically reduce equine performance [5]. Horse endurance and strenuous exercise, as well as eventing competition, have been linked to increased oxidative stress and altered antioxidant status [6]. Oxidative stress refers to a disparity in the body's oxidant-antioxidant equilibrium [7]. Antioxidants are vitamins, minerals, enzymes, and proteins that must be generated in the body or received from diet [8]. Traditional biomarkers such as lactate levels, heart rate variability, and muscle enzyme activity have been used to assess equine fitness and performance [9, 10]. In healthy people, miRNAs appear to mediate physiological adaptations to aendurance exercise [11]. Numerous muscle-related miRNAs have been described in adult human tissue, and these miRNAs exhibit dynamic expression patterns during aerobic exercise [12]. Recent research has demonstrated the impact of frequent sport exercise on miRNA regulation [13]. Furthermore, miRNAs appear to play essential roles in acute and chronic resistance training (RT), endurance training (ET), in athletes, and in animal models [14]. The regulation of miRNAs in human skeletal muscle is controlled by physical activity and is dependent on the variety, intensity, and duration of the training [13]. Nevertheless, new advancements in molecular biology imply that RNA alterations collectively termed as "epitranscriptomic" may serve as dynamic indicators for equine endurance performance [15].

RNA changes influence post-transcriptional gene expression, impacting protein synthesis, metabolic adaption, and stress responses [16]. These variations in equine endurance racing may provide real-time insights into physiological adaptations, fatigue resistance, and recuperation mechanisms [17, 18, 19]. This review paper explores the clinical potential of RNA modifications as biomarkers for equine endurance performance, focusing on their role in metabolic regulation, muscle adaptation, and stress response.

RNA Modifications: An Overview

Modifying RNA are chemical changes made to RNA molecules that affect their reliability, translation effectiveness, and liaison to proteins [20]. The m6A gene was discovered to increase pre-mRNA processing and mRNA transport in mammalian cells and is required for mammals [52]. The m6A influences the translation and persistence of the modified transcripts, providing a mechanism for coordinating the regulation of groups of transcripts during cell state maintenance and transition [53]. Similarly, some modifications in transfer RNAs are required for RNA structure and function [52]. More than 170 dissimilar RNA variations have been acknowledged, with N6-methyladenosine (m6A), pseudouridine (Ψ), and 5-methylcytosine (m5C) that exist amongst the predominantly studied [21, 22, 23, 24]. These adjustments transpire on messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), and non-coding RNAs, upsetting cellular function and adaptation to stress [25, 26].

Key RNA Modifications Relevant to Equine Endurance Performance

N6-Methyladenosine (m6A): Regulates mRNA stability and translation, influencing muscle adaptation and metabolic efficiency [19]. Interestingly, m6A changes exhibit broad, intimate interactions with oxidative stress; alterations to m6A affect the expression of oxidative stress-related genes, which have various effects on oxidative stress, hence altering the formation and development of diseases [54]. The m6A exerts its influence via the numerous reader, writer, and eraser proteins, which regulate gene expression and participate in a variety of biological processes, including the occurrence and development of many diseases by regulating oxidative stress and inflammation [55]. The transcriptional and post-transcriptional pathways regulated by m6A and associated regulators may aid in developing new strategies to maintain muscle homeostasis, making them potential targets for muscle-specific trait breeding and treating metabolic disorders [56].

Pseudouridine (Ψ): Enhances RNA stability and translation fidelity, could potentially improve endurance-related protein synthesis [20]. Pseudouridine synthases have been linked to a variety of human diseases, including cancer, neurodevelopmental disorders, degenerative disorders, autoimmune disorders, viral infections, metabolic disorders and others [57, 58].

5-Methylcytosine (m5C): Curbs RNA conveyance and transformation, impacting mitochondrial function and oxidative metabolism [21]. The m5C deposition does not change the base pairing edges, but it drastically changes the physicochemical properties of the original nucleobase, changing its interaction with proteins [38]. Additionally, there is a positive reciprocal interaction between m5C and m6A [38]. The m5C increases mRNA stability and promotes mRNA export from the nucleus to the cytoplasm; moreover, m5C influences protein translation, both favorably and negatively [38].

The m5C detection techniques have since been used to RNAs from a wide range of animals and cell types, including mouse embryonic stem cells and several mouse tissues such as the small intestine, heart, muscle, brain, kidney, and liver [59]. Mutations in the genes encoding these enzymes have been associated to a variety of human disorders, and alterations in m5C methyltransferase expression levels have been detected in a variety of malignancies, confirming their importance in RNA metabolism [59]. The m5C has been found in patients with a mitochondrial deficiency illness that is characterized by developmental impairment, microcephaly, failure to thrive, recurring elevated lactate levels in plasma, and muscle weakness [59].

Inosine (I): Alters codon recognition, simplifying adaptive protein synthesis under stress conditions [22]. Inosine plays an interesting role in viral hepatitis and other disorders [60]. In this regard, inosine (I), a deamination product of adenosine monophosphate (AMP), is particularly relevant. Inosine has mostly been investigated in healthy individuals, where enhanced inosine production was consistently observed after exercise [61]. The increased inosine production during exercise is thought to represent an imbalance between adenosine triphosphate (ATP) use and resynthesis [61]. Muscle inosine levels are undetectable or very low in healthy individuals at rest [61].

Similarly, inosine was implicated in skeletal muscle adaptation to disease states [62]. Inosine generation is important in maintaining cellular energy status by preventing ADP levels from rising above the threshold required to initiate energy generation pathways [63]. However, inosine production resulted in an inadequate recovery of [ATP], which was linked to lower muscle oxidative capacity after contractions [63]. These findings are likely to have ramifications for the ability of producing appropriate energy throughout repeated bouts of muscle effort [63]. These modifications could dynamically respond to physiological stressors, making them promising biomarkers for equine endurance performance assessment.

RNA Modifications and Metabolic Adaptation in Endurance Horses

Equine endurance racing imposes significant metabolic demands, requiring efficient energy utilization and resistance to fatigue [23, 24]. Genome-wide studies have discovered genetic variants that influence exercise performance, namely KCNQ1OT1, SLC39A12, and SORCS3, which have been linked to endurance racing and cardiac rhythm control [64, 67]. Furthermore, SLC16A1, a gene involved in lactate metabolism, was recently correlated with adaptability to prolonged physical activity, while selection signatures in CBLB, GAD1, ADCY1, and COX4I1 imply their roles in ATP synthesis, blood vessel activity, and oxidative metabolism [65, 66, 67]. Analysis of transcriptomic has identified important genes associated with metabolic adaptability, muscle transformation, and fatigue response; genes that regulate fatty acid degradation (CPT2, CPT1B, ACSL1, ACADM, ACADS, and ACAA2) exhibit substantial expression in Arabian horses undergoing training of endurance, emphasizing their role in energy metabolism [74, 67].

Longstanding exercise also stimulates inflammatory and immunological responses, as demonstrated by the overexpression of ITGA4, IL6R, IL6ST, and IL7R [67]. Vicissitudes in SH3RF2, which governs tissue regeneration and apoptosis, also help with muscle remodeling processes [67, 68]. A number of genes, comprising PRKCG, ME3, FOXO3, PPARA, ACTN3, TPM3, TNNI3, TNNC1, TGFBR2, TGFBR1, and FABP3, have been recognized as possibly impacting racing performance in Arabian horses [67]. Furthermore, miRNA expression studies have demonstrated their significance in controlling physiological adaptability to exercise [67]. The miR-505-5p, miR-21-5p, and miR-181b-5p have been substantially linked to endurance adaptability, whereas transcription factors such as NRF1, IRF3, SPI1, FOXO3, and ZFP42 influence oxidative stress and metabolic pathways via miRNA interactions [67]. Further research has identified miR-92a-3p, miR-16-5p, let-7b-5p, and miR-192-5p as important controllers of metabolic adaptability in response to exercise in endurance horses [69]. RNA modifications regulate metabolic adaptability pathways by influencing gene expression and protein synthesis [25].

Mitochondrial Function and Energy Metabolism: Mitochondria are central to endurance performance, generating ATP through oxidative phosphorylation [26]. Muscle contraction requires ATP, and oxidative phosphorylation is the primary method for generating energy during aerobic activity and recovering from anaerobic exercise [70]. A hallmark feature of human patients with oxidative phosphorylation abnormalities is a significantly lower VO_2max[2] with an associated deficiency in peripheral oxygen extraction [23]. The use of heart rate in horses suffering from exercise intolerance is a powerful diagnostic technique for functional evaluation of mitochondrial diseases [70]. RNA modifications such as m6A and m5C regulate mitochondrial gene expression, enhancing energy production efficiency [19, 21]. Studies in human athletes have shown that m6A-modified mRNAs encode proteins involved in mitochondrial biogenesis and fatty acid oxidation [27], suggesting similar roles in endurance horses.

Glucose and Fatty Acid Utilization: Endurance horses rely on both glucose and fatty acids for energy [28]. There was no training impact on blood hormone responses to exercise distance, however serum glycerol, glucagon, and cortisol concentrations increased as run distance increased, whereas insulin concentrations declined [28]. Cortisol and glucagon concentrations were found to be linked [28]. Serum TG reduced with activity but at a slower rate after training, while serum FFA levels increased during exercise after training compared to the partially trained state [28]. Ultimately, endurance training improved peripheral fat mobilization and use by working muscle, whereas resting muscle glycogen reserves increased. RNA modifications influence the expression of enzymes involved in glycolysis and lipid metabolism. For example, m6A modification enhances the translation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key regulator of mitochondrial function and endurance adaptation [25, 29].

Lactate Clearance and Recovery: Accumulation of lactate leads to muscle fatigue [30]. There was significant heterogeneity among horses, as well as group random effects for horse and field standardized exercise tests. Furthermore, blood lactate levels are influenced by both meteorological conditions and horse specific characteristics [71]. RNA modifications regulate lactate metabolism by modulating the expression of lactate transporters and enzymes such as lactate dehydrogenase (LDH) [31]. Horses with efficient RNA-mediated lactate clearance mechanisms may exhibit superior endurance performance and faster recovery.

RNA Modifications and Muscle Adaptation

Muscle of endurance horses depends on fiber composition, oxidative capacity, and resistance to damage [32]. In horse skeletal muscles, a fast-to-slow muscle fiber transition occurred, accompanied by an increase in oxidative enzyme activity and a decrease in glycolytic enzyme activity. Traditional Mongolian endurance exercise causes muscle fiber changeover, as well as metabolic and transcriptional alterations [72]. Muscle-

specific non-coding RNAs may contribute to these transcriptome alterations during training [72]. RNA modifications play a crucial role in muscle adaptation by influencing protein synthesis and repair mechanisms [33].

Muscle Fiber Type Regulation: Endurance horses predominantly utilize slow-twitch (Type I) muscle fibers, which are rich in mitochondria and resistant to fatigue [34]. Studies on equine muscle genomics have uncovered genes linked to top performance, as well as alterations in structural and metabolic genes after exercise and training [73]. Genes related to muscle growth, contraction, and metabolic pathways are important for assessing early performance in elite horses [73]. Fibre-type makeup fluctuates greatly between and within horse muscles, depending primarily on function [73]. In average, forelimb muscles contain more type 1 and type 2A fibers and less type 2X fibers than hindlimb muscles [74]. This discrepancy reflects the physiological specificity of the horse's thoracic and pelvic limbs [75] and supports the general notion that muscle architecture and fibre-type makeup are significantly associated in mammals [76]. Equine locomotor muscles often have large percentages of types 1 and 2A fibers in deep regions and a predominance of 2X fibers in superficial regions [81]. RNA variations regulate the expression of genes involved in muscle fiber disparity. The m6A-modified mRNAs encoding myogenic regulatory features (MRFs) augment slow-twitch fiber enlargement, improving endurance ability [7, 35].

Protein Synthesis and Muscle Repair: Endurance workout prompts muscle microdamage, necessitating effectual restoration mechanisms [36]. The stimulating of the mechanistic focus on rapamycin (mTOR)-controlled anabolic signaling pathways in rodent and human skeletal muscle is adaptable to dietary protein supply, with peak performance stimulation and rates of protein synthesis accomplished at 0.2 to 0.4 g protein/kg body weight (BW) [77]. Over time, oxidative stress levels decreased, and the amount of muscle protein mRNA transcripts increased for CD36, CPT1, PDK4, MYF5, and MYOG [78]. Transcript abundance for metabolic and myogenic genes was increased in post-exercise muscle samples, with no benefit from supplementing antioxidants with branched-chain amino acids over antioxidants alone [78]. According to [79], endurance-exercise training causes a reversible transformation in MHC composition in equine muscle in the order IIX→IIA→I, accompanied by alterations in the muscle's metabolic characteristics. Furthermore, there was a dose-response association between total training duration and magnitude of muscle changes [79]. Pseudouridine and m6A alterations augment the firmness and transformation of mRNAs encoding muscle restoration proteins such as myosin heavy chain and actin [37, 38]. Horses with heightened RNA modification profiles may unveil faster muscle recovery and reduced injury risk [39, 40].

Oxidative Stress Resistance: Exercise considerably enhanced the redox ratios of uric acid, ascorbic acid, and glutathione, while glutathione-reduced and vitamin A fell dramatically [80]. Training led to increases in uric acid, superoxide dismutase, glutathione peroxidase, and selenium, but lowered glutathione, α-tocopherol, and zinc levels [80]. Exercise intensity significantly raised uric acid and ascorbic acid, but glutathione levels declined dramatically [80]. A strong association between superoxide dismutase and VO_2max^2 was found. Taken together, the study conducted by [80] showed that training and exercise intensity have a considerable impact on blood antioxidant levels in healthy Standardbred horses. Prolonged effort engenders reactive oxygen species (ROS), leading to oxidative stress [41]. RNA changes regulate antioxidant enzyme expression, enhancing cellular defense mechanisms. For instance, m6A-modified mRNAs encoding glutathione peroxidase (GPx) and superoxide dismutase (SOD) to improve oxidative stress resistance in supporting equine endurance performance [42].

RNA Modifications and Stress Response in Endurance Horses

Endurance racing subjects horses to physiological and psychological stress, which affects performance and recuperation [43]. Endurance exercise in horses necessitates adaptation processes comprising physiological, biochemical, and cognitive-behavioral responses in order to regain homeostasis [69]. The study of the interactions between the blood metabolome, transcriptome, and miRNome during endurance exercise in horses could provide important insights into the molecular response to exercise [69]. Evaluating the transcriptional landscape before and after physical stress in equine athletes' revealed differential expression of multiple genes associated with inflammation and immune system activation, as well as a significant shift in expression from coding to non-coding transcripts [81]. The latter discovery implies that the stress response involves the regulation and activation of novel, uncharacterized transcriptionally active areas [81]. These differentially expressed genes are involved in activities and pathways associated to stress response (inflammatory system activation, interleukin production), as well as metabolism [46]. The most important genes involved in these processes, such as ACOD1, CCL5, CD40LG, FOS, IL1R2, IL20RA, and IL22RA2, are thus good candidates for monitoring and evaluating horse performance in order to avoid excessive demands

when endurance performance is required, as well as for assessing a horse's suitability for endurance races, such as GATA2, GYG1, HIF1A, MOGAT1, PFKFB3, PLIN5, SIK1, and STBD1 [46]. RNA changes affect stress response pathways include cortisol regulation, inflammation management, and immunological function [44].

Cortisol Regulation and Stress Adaptation: Cortisol is a significant stress hormone that influences equine endurance performance [45]. Exercise stress regulates hypophysiotropic TRHergic neurons, which act as metabolic integrators [82]. Several hormonal systems (insulin, leptin, ghrelin, glucose, and cortisol) are stimulated to regulate substrate utilization and mobilization [82]. Vasoactive hormone regulation is critical for fluid and electrolyte balance, including cardiovascular homeostasis during exercise [82]. Horses with adaptive RNA modification patterns may have reduced cortisol-induced muscle catabolism and better stress tolerance [46].

Inflammation Control: Equine endurance exercise induces transient inflammation, needing effectual doggedness mechanisms [47]. Following a 100-kilometer ride, endurance horses' IL-13 levels increased, as did IL-1ra levels following a 120-kilometer ride [83]. In race horses, the untrained group had a greater basal serum concentration of IL-13, which decreased following activity [83]. After exercise, trained racehorses showed an increase in IL-1ra and IL-13. IL-1ra and IL-13 react differently to different forms of exercise. Thus, they may be useful in monitoring horse fitness [83]. Endurance racing causes an acute phase response in horses, which is characterized by a decrease in calprotectin and haptoglobin values and an upsurge in ceruloplasmin and albumin concentrations, with greater intensity observed at races with higher average speeds, implying the need for extensive horse monitoring during exhausting races [84]. RNA alterations curb the expression of anti-inflammatory cytokines such as interleukin-10 (IL-10) and altering growth factor-beta (TGF-β), decreasing extreme inflammation and stimulating recovery [48].

Immune Function and Recovery: Endurance horses are susceptible to immune suppression due to prolonged effort [34, 49]. The hemogram analysis comprised numerous hematological indices such as lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), red blood cell distribution width-to-platelet ratio (RDW/PLT), platelet-to- monocyte-to-lymphocyte ratio (MLR), hemoglobin-to-red blood cell distribution width ratio (Hb/RDW), hemoglobin-to-platelet ratio (Hb/PLT), systemic inflammatory response index (SIRI), systemic inflammation index (SII), adaptation intensity index of L. Harkavy (AI) and leukocyte shift index (LSI) [43]. The results showed that various indices, including RDW/PLT, NLR, PLR, SIRI, SII, MLR, and LSI were sensitive to acute physiological changes caused by the endurance race [43]. These indices exhibited substantial changes soon following the race, suggesting an inflammatory and stress response [43]. RNA adjustments augment the stability and translation of immune-related mRNAs, supporting post-race recovery and reducing infection risk [50].

Clinical Applications of RNA Modifications as Biomarkers

Because of their dynamic character, RNA changes are good biomarkers for evaluating equine endurance performance in real time [51]. Potential clinical applications include:

- **Pre-Race Capability Assessment:** RNA alteration profiles can be utilized to evaluate a horse's metabolic fitness, muscle versatility, and stress tolerance prior to a race.
- **Race Checking:** RNA variations in blood samples can indicate tiredness levels, metabolic effectiveness, and oxidative damage during endurance races.
- **Post-Race Restorative Improvement:** RNA alteration profiling can aid in the development of individualized recovery strategies such as nutritional therapy and training changes.
- **Genetic Selection and Breeding:** Breeding initiatives can use RNA variation profiling to classify horses with higher endurance qualities, hence improving genetic enhancement tactics.

Conclusion

RNA vicissitudes are an auspicious frontline in equine endurance performance assessment. The incessantly changing metabolic versatility, muscle functionality, and stress response make them useful indicators for fitness monitoring, training effectiveness, and recovery strategy optimization.

Future research ought to concentrate on creating consistent RNA modification assays for equine athletes, which will pave the road for precision medicine methods in equine endurance racing. Introducing RNA

modification assessment into equine sports medicine allows veterinarians and trainers to acquire a better understanding of physiological changes, ultimately enhancing performance outcomes and horse welfare in equine endurance racing.

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