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Review Article

The Epitranscriptomic Edge: Revolutionizing Equine Laminitis through RNA Modifications

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Abstract

Equine laminitis, an agonizing hoof disease with unknown origins, has long tormented horses' hooves. A recent work in epitranscriptomics, which investigates RNA alterations that affect gene expression after transcription, sheds fresh light on the molecular mechanisms underlying this disease. This in-depth study looks into the relationship between RNA changes, metabolic problems, and inflammatory pathways in laminitis. Examining key epitranscriptomic regulators such as N6-methyladenosine (m6A), pseudouridine, and inosine indicates their potential role in disease genesis and treatment strategies. The incorporation of contemporary sequencing technology and individualized epitranscriptomic therapy has the potential to improve the accuracy of laminitis diagnosis and treatment, ushering in a new era in horse health care.

Keywords: RNA Epigenetics; Laminar Inflammation; N6-Methyladenosine; Pseudouridine; Inosine

Introduction

According to Bamford [1], laminitis is a painful and incapacitating condition that affects horse hooves and is marked by inflammation and lamellar destruction. Laminitis occurs when the distal phalanx fails to connect to the lamellae on the inside of the hoof [2]. Chronic laminitis is defined by persistent lameness and morphological breakdown of the hoof, including changes to the coronary band, the formation of a depressed sole, and aberrant hoof development [3]. Laminitis, which affects 15-25% of the equine population, poses a significant danger to equine health and well-being. Significant morbidity and death are usually associated with the illness, leading in substantial financial losses for the equestrian sector [4].

According to current knowledge, laminitis is a multifaceted illness caused by a complicated interaction of genetic, environmental, and hormonal elements [5,6]. Carbohydrate overloading [7], endotoxemia or mechanical overload [8], and hormonal imbalances [9,34] are also known risk factors for laminitis. The specific mechanisms causing the onset of laminitis are undisclosed. Basic treatments for laminitis include alleviating pain, mechanical support, and metabolic management. However, recent advances in molecular biology have yielded an indispensable tool known as epitranscriptomics [10]. This review study investigates the significance of RNA alterations, their possible applications in equine medicine, and how they may improve laminitis care.

This developing discipline, which investigates chemical changes in RNA molecules, offers new insights into cellular functions and disease causes, ultimately leading to novel treatment choices for laminitis.

Epitranscriptomics: A paradigm shift

Epitranscriptomics refers to reversible alterations in RNA molecules that influence gene expression without affecting DNA sequences [11-13].

- **N6-methyladenosine (m6A):** has an effect on RNA integrity and translation, both of which are essential for inflammation-related activities [14,15]. N6-methyladenosine (m6A) alterations are essential for modulating gene expression at the RNA level, and their impact on equine laminitis may be important [16]. Although there is limited information on the role of m6A in laminitis, RNA remodeling may contribute to the disease through inflammatory pathways and immunological modulation. Alterations to the m6A gene can impact the stability and translation of pro-inflammatory cytokines such TNF-α, IL-6, and IL-1β, leading to laminitis. Dysfunctional m6A patterns can cause inflammatory responses, resulting in enhanced immune activation and tissue damage in the hoof laminae.
- **Circulatory Disruption and Endothelial Integrity:** Laminitis impairs the vascular system, reducing blood flow to the hoof laminae [17]. Changes in m6A vascular endothelial growth factor (VEGF) transcripts may affect angiogenesis and endothelial function, contributing to ischemic injury in laminitic hooves.
- **Metabolic instability and insulin resistance:** Equine metabolic syndrome (EMS) is a significant risk factor for laminitis. Changes to m6A in insulin signaling genes may affect glucose metabolism, aggravating metabolic dysfunction and increasing the incidence of laminitis.
- **Epitranscriptomic Biomarkers for Diagnosis:** Identifying m6A signatures in laminitic horses may lead to the development of biomarkers that enable early detection and individualized treatment. Advanced sequencing approaches may uncover m6A-modified transcripts that contribute to laminitis development. While research into m6A in horse laminitis is still in its early stages, its potential role in inflammation, vascular dysfunction, and metabolic control provides a promising area for future investigation.
- **Pseudouridylation:** Integra improves RNA efficiency and protein synthesis, which affects tissue repair [13, 18]. Pseudouridylation, which converts uridine to pseudouridine (Ψ) in RNA, is crucial for RNA stability, translation efficiency, and stress response. Advanced sequencing technology and targeted epitranscriptomic treatments have the potential to completely transform laminitis diagnosis and treatment, ushering in a new era of horse health care. Pseudouridylation may contribute to equine laminitis via inflammatory pathways and immune regulation, although its precise role is uncertain. Pseudouridylation may enhance mRNA retention of inflammatory cytokines including as TNF-α, IL-6, and IL-1β, potentially sustaining inflammation in laminitic hooves. Modified RNA transcripts may interfere with immunological signaling, aggravate laminar inflammation, and induce tissue damage.
- **Vascular Disruption and Endothelial Integrity:** Laminitis weakens the vascular system, reducing blood flow to the hooves. Pseudouridylation may change endothelial cell function, affecting angiogenesis and vascular permeability, both of which are important for hoof health. Equine metabolic syndrome (EMS) is a major risk factor for laminitis due to impaired metabolism and insulin resistance [19]. Pseudouridylation in insulin signaling genes may disrupt glucose metabolism, causing metabolic dysfunction and increasing the risk of laminitis.
- **Stress Response and Cellular Mitigation:** Pseudouridylation improves RNA stability during stress, perhaps influencing cellular responses to oxidative stress and mechanical pressure in the hooves. This change may impair the survival of laminar epithelial cells, influencing disease progression.

- **Epitranscriptomic Biomarkers for Diagnosis:** Detecting pseudouridylation signals in laminitic horses could lead to the development of biomarkers that enable earlier diagnoses and more targeted treatment. Sophisticated sequencing techniques may discover Ψ-modified transcripts linked to laminitis development. While research into pseudouridylation in horse laminitis is still in its early stages, its potential role in inflammation, vascular dysfunction, and metabolic control presents a promising area for future inquiry.
- **RNA editing (A-to-I and C-to-U conversions):** Changes mRNA coding capability, which influences cellular stress responses [20]. Emerging evidence suggests that these alterations are also involved in inflammatory and metabolic pathways associated with laminitis. RNA editing, notably A-to-I (adenosine-to-inosine) and C-to-U (cytosine-to-uracil) conversions, are essential for post-transcriptional gene control. Although their exact significance in equine laminitis is unknown, these changes may contribute to the disease.
- **Inflammatory pathways and immune response:** ADAR (adenosine deaminase acting on RNA) enzymes can modify mRNA sequences encoding inflammatory mediators, which could affect the expression of cytokines and immune regulators involved in laminitis development. C-to-U editing, mediated by APOBEC family enzymes, may change transcripts associated with oxidative stress and immunological signaling, aggravating inflammation in laminitic hooves.
- **Vascular Dysfunction and Endothelial Regulation:** RNA editing in endothelial cells may affect vascular authenticity, which is a key element in laminitis. A-to-I conversions in transcripts encoding vascular endothelial growth factor (VEGF) or nitric oxide synthase may affect blood flow regulation, contributing to ischemic injury in the hoof.
- **Metabolic Dysregulation and Insulin Resistance:** Laminitis is usually associated with equine metabolic syndrome (EMS), and RNA editing may disrupt insulin signaling pathways, changing glucose metabolism and hastening illness progression. C-to-U editing in metabolic genes may have an impact on lipid metabolism, leading to systemic inflammation and laminar disintegration.
- **Epitranscriptomic Biomarkers for Diagnosis:** Noticing RNA editing characteristics in laminitic horses could lead to the discovery of biomarkers that allow for early detection and targeted therapy. Cutting-edge sequencing technologies may reveal editing hotspots in important regulatory genes associated with laminitis. While research into RNA editing in equine laminitis is still in its early stages,

Epitranscriptomic mechanisms in laminitis

Recent research on systemic inflammation and cellular metabolism reveals considerable epitranscriptomic alterations [21]. The most striking discoveries include

- **m6A overexpression in inflammatory cytokines:** Increased levels of modified mRNA in laminitic tissues suggest that m6A has a role in exacerbating inflammation [22].
- **MicroRNA interactions:** MicroRNAs' epitranscriptomic flexibility influences gene networks involved in tissue degradation [23].
- **RNA-binding proteins:** Improper regulation of proteins such YTH N6-methyladenosine RNA binding protein 1 (YTHDF1) might reduce RNA stability and impair the prognosis of laminitis [24]. YTHDF1, an m6A reader, detects and stimulates translation of m6A-methylated mRNAs [24]. As a result of increased expression, cardiomyocytes (CMs) re-enter the cell cycle, at least by increasing the accumulation of YAP1 (Yes-associated protein 1), a transcriptional cofactor that governs cardiac regeneration by promoting embryonic and regenerative gene programs in CMs [25,26]. Consequently, YTHDF1 stimulates heart regeneration through accelerated translation of its target mRNAs, but its translation and functionality are also post-transcriptionally controlled by ALKBH5-mediated demethylation.

The closely regulated growth of a class of zinc-containing enzymes known as matrix metalloproteinases (MMPs) allows lamellae epidermis cells to rearrange and constantly improve their spatial organization. Two members of the MMP family (MMP-2 and MMP-14) are found in typical lamellae hoof walls [27,28]. Ac-

tivation of MMP-2 and MMP-9, by laminitis or APMA, resulted in separation of epidermal and dermal lamellae. Increased gene transcription of MMP-2 and MMP-9 was present during laminitis [29].

Therapeutic Potential

Using epitranscriptomic discoveries provides novel therapeutic methods

Epigenetic medications that target RNA alterations may influence inflammatory gene expression [30,31]. Epigenetic medications targeting RNA modifications offer a promising avenue for treating equine laminitis, a debilitating hoof disease. These therapies aim to regulate gene expression post-transcription, influencing inflammation, vascular function, and metabolic pathways.

- **RNA Methylation Inhibitors (m6A Modulators):** N6-methyladenosine (m6A) modifications, which regulate mRNA stability and translation. Modulating m6A levels could reduce inflammatory cytokine expression (e.g., TNF-α, IL-6), mitigating laminar inflammation. Example: Small molecule inhibitors targeting m6A methyltransferases (METTL3/METTL14) may help control excessive immune activation in laminitis.
- **RNA Editing Therapies (A-to-I and C-to-U Conversions):** Target: RNA editing enzymes such as ADAR (adenosine deaminase acting on RNA) and APOBEC family enzymes. Potential Benefit: Adjusting A-to-I and C-to-U RNA editing could fine-tune vascular endothelial function, improving blood flow to the hoof and reducing ischemic damage. Example: RNA-editing drugs could modify transcripts involved in angiogenesis and metabolic regulation, preventing laminar breakdown.
- **Pseudouridylation Modulators:** Pseudouridine (Ψ) modifications that enhance RNA stability and translation efficiency. Controlling pseudouridylation might regulate stress-response genes, increasing hoof tissue robustness and decreasing oxidative damage. For example, small compounds that target pseudouridine synthases may improve laminar epithelial cell survival under mechanical pressure.
- **RNA-Based Therapeutics (siRNA and Antisense Oligonucleotides):** RNA interference (siRNA) and antisense oligonucleotides (ASOs) are used to specifically suppress disease-related genes. Inhibiting pro-inflammatory and metabolic dysregulation genes may prevent laminitis in horses prone to equine metabolic syndrome (EMS). For example, siRNA therapies that target insulin signaling pathways may help manage glucose metabolism and reduce the incidence of laminitis.
- **Epitranscriptomic Biomarkers for Early Diagnosis:** RNA alterations serve as indicators for laminitis progression. Detecting epitranscriptomic signals in blood or hoof tissue could lead to earlier intervention and improved treatment outcomes. For example, evaluation arrays that include m6A, pseudouridylation, and RNA editing markers could help to improve laminitis risk assessments. While RNA-targeted epigenetic medicines are still under research, they have the potential to reinvent laminitis therapeutics.

M6A blockers and promoters may influence important pathways involved in laminitis progression [32]. Blockers and promoters of m6A which regulate N6-methyladenosine (m6A) RNA modifications could offer novel therapeutic strategies for equine laminitis by modulating gene expression at the post-transcriptional level.

- **Blockers (Inhibitors) of m6A for Laminitis Treatment:** Suppressing excessive m6A methylation to reduce inflammation and metabolic dysregulation. Inhibiting m6A methyltransferases (METTL3/METTL14) may reduce pro-inflammatory cytokine expression (e.g., TNF-α, IL-6), mitigating laminar inflammation. Blocking m6A modifications in vascular endothelial growth factor (VEGF) transcripts could improve hoof blood flow, preventing ischemic damage. Example: Small molecule inhibitors targeting m6A writers could help regulate immune responses and metabolic pathways in laminitic horses.
- **Promoters (Enhancers) of m6A for Tissue Repair:** Enhance m6A modifications to stabilize protective transcripts and promote tissue regeneration. Boosting m6A levels in stress-response genes may improve hoof tissue resilience, reducing oxidative damage. Enhancing m6A modifications in angiogenic factors could support vascular repair, aiding recovery from laminitis. Example: m6A activators targeting m6A readers (YTHDF/YTHDC proteins) may enhance laminar epithelial cell survival under mechanical strain.

- **RNA-Based Therapeutics Using m6A Modulation:** siRNA and Antisense Oligonucleotides: Selectively silence disease-associated genes involved in laminitis progression. Suppress excessive inflammatory and metabolic dysregulation using RNA interference (siRNA).
- **Epitranscriptomic Biomarkers:** Detecting m6A signatures in laminitic horses could enable early diagnosis and targeted interventions. While m6A-targeted therapies are still in early development, they hold immense potential for revolutionizing laminitis treatment.

CRISPR-based RNA editing could offer precise control over gene expression in afflicted tissues [33]. Earlier veterinary investigations show positive measures, but clinical trials are still in the preliminary stages. CRISPR-based RNA editing offers a groundbreaking approach to treating equine laminitis by precisely modifying RNA transcripts involved in inflammation, vascular dysfunction, and metabolic dysregulation.

- **Targeting Inflammatory Pathways:** CRISPR-Cas13, an RNA-editing variant, could selectively silence pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, reducing laminar inflammation. Modifying RNA transcripts involved in immune regulation may help control excessive inflammatory responses in laminitic hooves.
- **Enhancing Vascular Function:** CRISPR-based RNA editing has the potential to address endothelial dysfunction by changing transcripts encoding vascular endothelial growth factor (VEGF), hence increasing blood flow to the hoof. Changing RNA sequences involved in angiogenesis and nitric oxide signaling may help minimize ischemia damage in laminitis.
- **Regulating Metabolic Pathways:** Laminitis is usually associated with equine metabolic syndrome (EMS), and CRISPR-based RNA editing could fine-tune insulin signaling genes, enhancing glucose metabolism and decreasing illness risk. Editing RNA transcripts involved in lipid metabolism may potentially help to lower systemic inflammation, which is linked to laminitis progression.
- **Generating RNA-Based Therapeutics:** CRISPR-Cas13 therapy could be tailored to regulate RNA alterations such as m6A methylation, pseudouridylation, and A-to-I editing, thereby optimizing gene transcription for hoof health. Drugs that alter RNA could be given by nanoparticles or viral vectors, allowing for personalized treatment in laminitic horses.
- **Epitranscriptomic Biomarkers for Early Diagnosis:** Identifying CRISPR-modifiable RNA markers in laminitic horses could result in earlier detection and more personalized treatment approaches. Advanced sequencing techniques may uncover editing hotspots in important regulatory genes involved in laminitis. While CRISPR-based RNA editing is still in its early stages, it holds enormous potential for improving laminitis treatment.

Studying epitranscriptomics in horse laminitis presents challenges

Epitranscriptomics is a relatively young field, with limited research and data on its relevance to equine laminitis. The scarcity of comprehensive investigations makes it difficult to establish unequivocal links between RNA changes and disease development.

- **The complexity of changes in RNA:** RNA alterations such as m6A, pseudouridine, and inosine play important roles in gene regulation. Identifying the exact effects of laminitis requires cutting-edge sequencing and bioinformatics.
- **Screening Difficulties:** Clinical signs and imaging are now the predominant diagnostic modalities for laminitis; however, including epitranscriptomic markers into regular veterinary diagnostics will need significant technological improvements.
- **Clinical Improvement:** It is challenging to convert epitranscriptomic research into effective medicines. RNA-targeted therapies, such as small molecule inhibitors or RNA editing methods, are still in their early stages of development and may face problems in veterinary applications.
- **Multidisciplinary Teamwork:** Collaboration in horse medicine, molecular biology, and bioinformatics is essential for development, yet it can be difficult due to knowledge gaps and research objectives.

- **Ethical and Operational Implications:** Manipulating RNA alterations in horses raises ethical concerns, particularly when unexpected outcomes occur. Furthermore, applying epitranscriptomic-based therapy in equine healthcare may require government approval and substantial veterinary understanding. Regardless of these challenges, epitranscriptomics has the potential to transform laminitis research and treatment.

Conclusion

The use of epitranscriptomics in equine medicine marks a paradigm shift in understanding laminitis. Although more research is needed to translate molecular insights into therapeutic treatments, RNA changes have a bright future in veterinary medicine. Researchers and veterinarians can utilize this information to develop novel treatments for laminitis and enhance equine health.

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Data Availability

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Authors' Contributions

LA-conceptualization, and the manuscript writing. IAM and YKW meticulously review the manuscript. All authors have read and agreed to the published version of the manuscript.

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