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REVIEW OPEN ACCESS

VEGFA Induction in Skeletal Muscle Under Hypoxia and Exercise: A Review of the Epigenetic Role of H3K27me3

Hannah Birley, BSc Student [1]*

[1] Faculty of Science, University of Western Ontario, London, Ontario, Canada N6A 3K7

Corresponding Author: hbirley@uwo.ca or birley.hannah@gmail.com

Abstract

Skeletal muscle adapts through various structural and molecular changes that support vascular remodelling. Among these, angiogenesis enhances capillary density and improves oxygen and nutrient delivery to active muscle fibres. Vascular endothelial growth factor A (VEGFA) is a key regulator of this process and is robustly induced in skeletal muscle during exercise, largely via activation of Hypoxia-inducible Factor 1-alpha (HIF-1α). However, HIF-1α activity diminishes with prolonged training, suggesting the need for additional mechanisms to sustain VEGFA expression. This review synthesizes findings from vascular biology, epigenetics, and exercise physiology to explore the potential role of histone modification H3K27me3 in regulating VEGFA expression during hypoxic and exercise-induced stress in skeletal muscle. Evidence from endothelial cells indicates that H3K27me3, a repressive histone mark, can be removed by the demethylase JMJD3 to enable VEGFA transcription in response to hypoxia. Although this mechanism is well characterized in vascular tissue, recent studies suggest similar epigenetic changes occur in skeletal muscle, particularly at promoters of exercise-responsive genes like PGC-1α. These findings support the hypothesis that epigenetic regulation through H3K27me3 demethylation may contribute to sustained VEGFA expression as HIF-1α activity declines with training. However, direct evidence in human skeletal muscle remains limited. Histone demethylation may represent a key mechanism supporting angiogenesis in skeletal muscle under exercise and hypoxic conditions. These epigenetic mechanisms may also be relevant for skeletal muscle adaptation to exercise.

Keywords: VEGFA; skeletal muscle; exercise; hypoxia; H3K27me3; angiogenesis; histone modifications; JMJD3; blood flow restriction; epigenetic regulation

Introduction

Cardiovascular disease is the leading cause of death globally, accounting for approximately 19.42 million deaths in 2021 [1]. Sedentary behaviour, metabolic dysfunction, and impaired vascular health are major contributors. Exercise is one of the most effective non-pharmacological strategies to reduce disease burden and improve cardiovascular outcomes [2]. It promotes vascular function, capillary growth, and metabolic adaptations across many tissues. These effects are especially evident in skeletal muscle, a metabolically active tissue that comprises roughly 40 percent of body mass and supports movement, glucose regulation, and endocrine signalling [3, 4].

Skeletal muscle adapts to physical activity through changes in fibre type, mitochondrial function, and capillary density [5]. Angiogenesis, the formation of new capillaries, enhances oxygen and nutrient delivery and supports endurance [6]. Vascular endothelial growth factor A (VEGFA) is the primary regulator of angiogenesis and is strongly upregulated during exercise, largely in response to hypoxia-inducible factor 1-alpha (HIF-1α) activation under low oxygen conditions [7–9]. While acute exercise consistently increases VEGFA expression, long-term regulation is more complex and influenced by intensity, oxygen availability, and training status [10–12].

As HIF-1α signalling decreases with endurance training, other mechanisms may sustain VEGFA expression. Epigenetic processes such as histone modifications, including tri-methylation of lysine 27 on histone 3 (H3K27me3), influence chromatin accessibility and gene transcription [13]. The enzymes EZH2 (Enhancer of Zeste Homolog 2) and JMJD3 (Jumonji Domain-Containing Protein 3) regulate this mark and are responsive to exercise [14]. In endothelial cells, JMJD3-mediated removal of H3K27me3 at the VEGFA promoter has been shown to enhance VEGFA transcription during hypoxia through chromatin immunoprecipitation assays [15]. Although this work was performed in a non-muscle cell type, skeletal muscle displays similar angiogenic responses to exercise and hypoxia, with VEGFA consistently upregulated following both acute and chronic training interventions (8, 16–18).

Although epigenetic regulation of skeletal muscle adaptation is increasingly recognised, it is not yet clear whether H3K27me3 directly regulates VEGFA in response to exercise. This review evaluates current evidence to explore whether H3K27me3 demethylation contributes to

VEGFA expression during exercise-induced hypoxia in human skeletal muscle.

Methods

This review was informed by a targeted literature search conducted between February and April 2025 using PubMed and Google Scholar. The search was limited to English-language articles published between 1980 and 2025. Search terms included "VEGFA," "skeletal muscle," "exercise," "hypoxia," "angiogenesis," and "H3K27me3," as well as combinations such as "VEGFA and exercise," "skeletal muscle and angiogenesis," and "H3K27me3 and VEGFA." Articles were included if they examined VEGFA regulation in skeletal muscle in response to exercise or hypoxia, or if they investigated histone modifications, particularly H3K27me3, as regulators of gene expression in muscle or endothelial cells. Review articles were included to provide background and context. Studies were excluded if they were non-peer-reviewed, not available in English, or focused exclusively on non-muscle tissues without mechanistic relevance. To minimize confirmation bias, both supporting and contradictory findings were incorporated, and reference lists of key articles were screened to identify additional relevant work. In total, approximately 50 peer-reviewed articles were synthesised to support the arguments and conclusions of this review.

Results

Skeletal Muscle Tissue, an Organ Crucial for Whole-Body Health

Skeletal muscle comprises approximately 40 percent of total body mass and is one of the most plastic tissues in the human body. It is essential not only for locomotion but also for systemic metabolic health [3]. This tissue contains a variety of fibre types with distinct metabolic and contractile properties [19]. Fast-twitch (Type II) fibres generate rapid, powerful contractions using glycolytic metabolism, while slow-twitch (Type I) fibres are rich in mitochondria and capillaries and rely on oxidative metabolism for sustained activity [3, 19]. Beyond movement, skeletal muscle regulates glucose homeostasis through GLUT4-mediated uptake and functions as an endocrine organ by secreting myokines that influence inflammation, metabolism, and tissue signalling [4, 20].

Skeletal Muscle Adaptation to Exercise: Capillaries, a Key Valve Supplying Oxygen and Nutrient-Rich Blood

Skeletal muscle adapts to a wide range of physiological and environmental stimuli, with exercise being a primary driver of this remodelling. Exercise triggers metabolic and structural adaptations that improve both performance and fatigue resistance [21].These changes involve mitochondrial function, substrate metabolism, angiogenesis, and fibre-type shifts [5]. Resistance training promotes hypertrophy through increased muscle protein synthesis and satellite cell activation, while endurance training enhances mitochondrial content and expands the capillary network [5, 21].

Capillaries support skeletal muscle health by delivering oxygen and nutrients, removing by-products, dissipating heat, and circulating signalling molecules such as myokines [22, 23]. Their density is closely linked to the muscle's oxidative capacity [22]. A key adaptation to exercise is angiogenesis, which improves the efficiency of oxygen and substrate exchange and enhances fatigue resistance. This process is regulated primarily by vascular endothelial growth factor A (VEGFA), a potent mediator that promotes endothelial cell proliferation and migration [7]. Skeletal muscle-specific VEGFA knockout mice ($Skm^{-/-}$ VEGFA) show reduced capillarization and a blunted angiogenic response to endurance exercise, resulting in decreased time to exhaustion and lower maximal running speed compared to wild-type mice [24, 25].

Hypoxia, defined as reduced oxygen availability, is a well-established stimulus for VEGFA expression. This occurs through stabilisation of hypoxia-inducible factor 1-alpha (HIF-1α), which binds to a hypoxia-responsive element within the VEGFA promoter to initiate transcription [26]. Exercise is a physiological trigger of hypoxia in skeletal muscle. During a single bout of dynamic knee-extensor activity, the intracellular partial pressure of oxygen can fall from resting values of around 27 millimetres of mercury to 3 to 5 millimetres of mercury at peak intensity [9, 27, 28]. Consistent with these findings, acute exercise increases VEGFA mRNA and protein expression and promotes the nuclear accumulation and activation of HIF-1α [10, 11, 29].

Histone Modifications, Key Epigenetic Players in Dictating Skeletal Muscle Response to Exercise and Exercise Training

Within the nucleus, DNA is organised as chromatin, with nucleosomes composed of DNA wrapped around histone proteins [30]. Post-translational modifications of histones, such as acetylation and methylation, influence chromatin structure and gene accessibility [13, 31, 32].

One important repressive modification is tri-methylation of lysine 27 on histone 3 (H3K27me3), which is catalysed by EZH2, a component of the polycomb repressive complex 2 [33]. Demethylation of H3K27me3 by JMJD3 promotes chromatin relaxation and increased transcriptional accessibility at the VEGFA promoter during exercise [34] (Fig 1). H3K27me3 is developmentally regulated during muscle differentiation and dynamically responsive to acute exercise, underscoring its dual role in both developmental and activity-induced muscle remodelling [35–37]. In response to endurance training, expression of EZH2 decreases while JMJD3 increases in rat skeletal muscle, suggesting epigenetic regulation during adaptation [14]. Reduced H3K27me3 enrichment at the promoter of PGC-1α, a regulator of mitochondrial metabolism, is associated with increased transcription and enhanced oxidative capacity [14, 38].

Although H3K27me3 has been linked to metabolism, fibre-type transitions, and satellite cell differentiation, its role in VEGFA regulation during exercise remains unclear [14, 35–37]. In endothelial cells, JMJD3 removes H3K27me3 near the VEGFA gene, promoting transcription and angiogenic function. Loss of JMJD3 reduces VEGFA expression and impairs endothelial proliferation [15]. These findings raise the possibility that H3K27me3 demethylation may also influence VEGFA expression in skeletal muscle during exercise. Some studies suggest that stress-induced H3K27me3 demethylation enhances VEGFA transcription in endothelial cells but whether this mechanism occurs in skeletal muscle remains unknown [15]. The parallels between endothelial and skeletal muscle cells provide a rationale for this comparison. Both cell types rely on VEGFA signaling for angiogenesis, and skeletal muscle itself secretes VEGFA to drive capillary growth [8, 39]. In addition, epigenetic and transcriptional regulators such as Notch, EZH2, and JMJD3 are expressed in skeletal muscle [40] supporting the idea that mechanisms observed in endothelial models may also apply to myofibres. These shared pathways strengthen the rationale for exploring whether hypoxia-driven H3K27me3 demethylation contributes to VEGFA regulation in skeletal muscle. Further research should examine how exercise and hypoxia regulate H3K27me3 at the VEGFA promoter, as this may reveal new insights into the epigenetic control of skeletal muscle vascular adaptation.

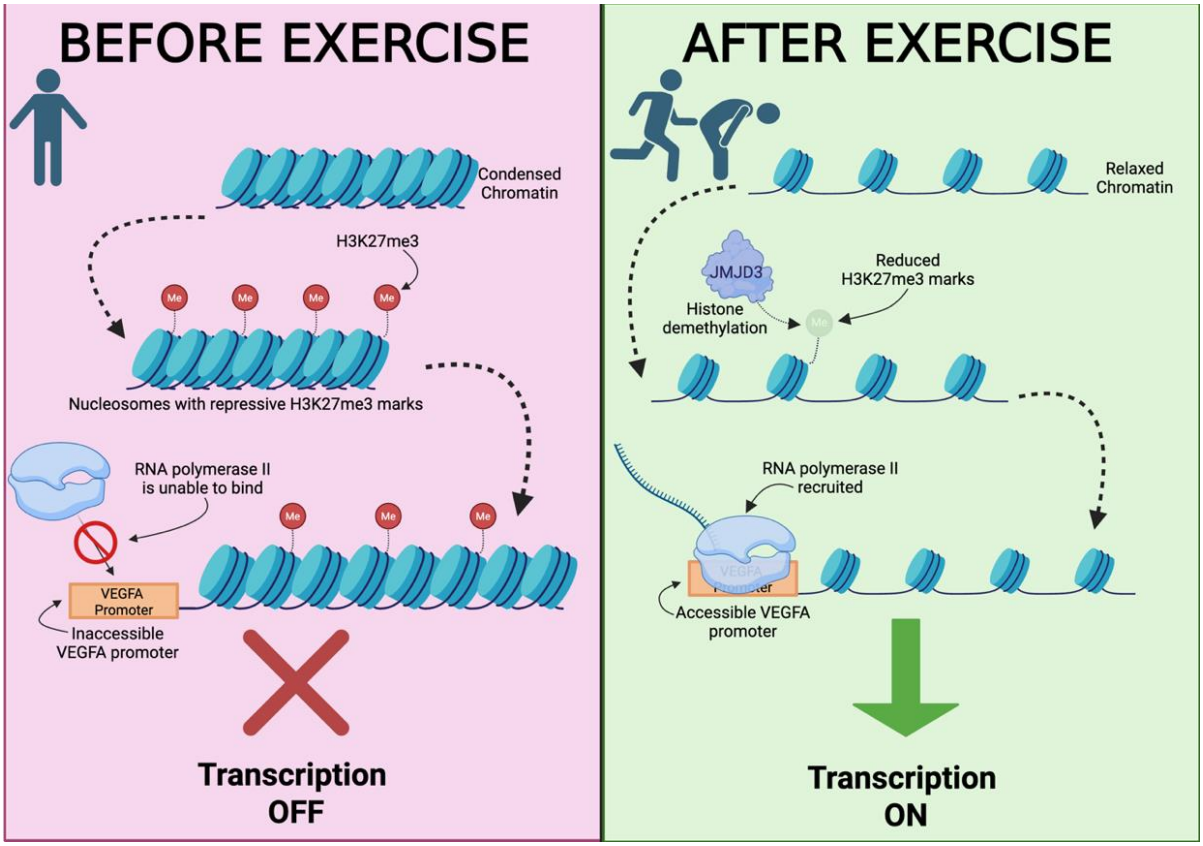

Figure 1. Epigenetic regulation of VEGFA expression in skeletal muscle before and after exercise. (**Left Panel)** Before exercise, skeletal muscle chromatin is condensed (heterochromatin) and enriched with repressive H3K27me3 marks, preventing RNA polymerase II from accessing the VEGFA promoter and resulting in transcriptional silencing. (**Right Panel**) After exercise, JMJD3 (a histone demethylase) removes H3K27me3 marks, leading to chromatin relaxation (euchromatin) and increased VEGFA promoter accessibility. RNA polymerase II is recruited to the promoter, enabling active VEGFA transcription and promoting angiogenesis in response to exercise-induced hypoxia. (Created with BioRender.com)

Discussion

This review examined whether tri-methylation of histone H3 at lysine 27 (H3K27me3), a repressive histone modification, may regulate VEGFA expression in skeletal muscle during exercise-induced hypoxia. Skeletal muscle is uniquely suited to respond to the physiological stress of exercise due to its high metabolic activity, contractile function, and capacity for plasticity. During acute bouts, contracting myofibres rapidly consume oxygen, generating a localised hypoxic environment. With repeated exposure, such as in training, these hypoxic episodes stimulate capillary remodelling and expansion through angiogenesis, improving

tissue oxygen conductance. Central to this response is vascular endothelial growth factor A (VEGFA), a potent mitogen that promotes endothelial cell proliferation, migration, and tube formation [12, 24, 25, 39].

VEGFA expression is tightly controlled and induced by hypoxia through stabilisation of HIF-1α [10]. Its responsiveness to acute exercise is well established. For example, VEGFA mRNA is significantly upregulated in human vastus lateralis following dynamic knee-extensor activity, where intramuscular partial pressure of oxygen drops to as low as 5 mmHg [10, 27]. However, during chronic hypoxia, VEGFA and VEGF receptor-2 expression may be attenuated, possibly due to physiological adaptation or metabolic remodelling [12]. Interestingly, studies have shown that VEGFA mRNA expression increases significantly only in individuals undergoing high-intensity endurance training under hypoxic conditions, while those training under normoxia or at lower intensities do not show the same response. This effect occurs despite no change in VO_2 max, highlighting the roles of both oxygen tension and mechanical load [40].

In addition to systemic hypoxia, blood flow restriction (BFR) training may represent another means of amplifying local hypoxic stress. By limiting venous return during exercise, BFR creates a localised low-oxygen environment within muscle tissue. This condition has been shown to enhance VEGFA and PGC-1α expression and activate both angiogenic and oxidative pathways, ultimately driving adaptations similar to those observed with traditional high-volume or hypoxic endurance training [16–18, 41, 42].

As endurance training progresses, HIF-1α activation declines due to reduced glycolytic reliance, suggesting that other regulators sustain VEGFA expression [43]. H3K27me3, a histone mark associated with transcriptional repression, may serve this function. In endothelial cells, hypoxia recruits JMJD3 to the VEGFA promoter, where it removes H3K27me3 and promotes transcription [15]. Notably, loss of JMJD3 reduces VEGFA expression and impairs endothelial proliferation, suggesting a causal role for this epigenetic mechanism. While this regulatory pathway has not yet been confirmed in skeletal muscle, it presents a promising model for investigation. Experimental approaches such as chromatin immunoprecipitation (ChIP) at the VEGFA promoter, conducted before and after exercise, or the use of muscle-specific JMJD3 knockdown models, could help determine whether H3K27me3 plays a similar role in the regulation of VEGFA in this context.

Emerging evidence from skeletal muscle studies supports this hypothesis. In rodent models, endurance training decreases the expression of EZH2, the methyltransferase responsible for H3K27me3 deposition, while increasing expression of JMJD3. These changes are associated with reduced H3K27me3 enrichment at the promoter of PGC-1α and increased transcriptional activity [14]. Given the shared roles of PGC-1α and VEGFA in metabolic remodelling and angiogenesis, it is plausible that similar epigenetic mechanisms coordinate their activation. Additionally, H3K27me3 has been implicated in regulating key aspects of skeletal muscle adaptation, including satellite cell differentiation, fibre-type transitions, and regeneration [35–37]. If it regulates VEGFA, this could explain sustained angiogenesis in trained muscle, even when HIF-1α signalling is diminished.

To test this possibility, future studies should investigate whether exercise-induced VEGFA expression in skeletal muscle is accompanied by dynamic changes in H3K27me3 enrichment at its promoter. ChIP assays before and after acute exercise or BFR training could clarify whether demethylation is associated with transcriptional activation. Studies in rodents have already demonstrated that acute resistance exercise can alter H3K27me3 levels at gene promoters, including those associated with metabolic regulation [44]. Time-course studies tracking EZH2 and JMJD3 expression alongside VEGFA could help determine whether changes in histone methylation enzymes temporarily align with angiogenic signalling.

To establish causality, animal models with skeletal muscle-specific JMJD3 overexpression or knockdown should be developed. Previous studies have shown that manipulating histone-modifying enzymes alters muscle gene expression and phenotypic adaptation [45]. Incorporating epigenetic profiling into human training studies, especially those involving hypoxia or BFR, could determine whether findings from animal models extend to humans. While exercise is known to influence other epigenetic marks such as DNA methylation and histone acetylation, the role of H3K27me3 in regulating VEGFA during training remains largely unexplored [46].

Finally, long non-coding RNAs may also influence VEGFA through chromatin regulation. These RNAs can recruit chromatin-modifying complexes and help fine-tune gene expression in skeletal muscle [47]. Exploring this layer may offer further insight into how VEGFA is controlled during exercise, revealing mechanisms that support vascular health and muscle adaptation.

Conclusion

This review highlights that VEGFA regulation in skeletal muscle is highly dynamic and context-specific, shaped by training modality, duration, and the interplay between transcription factor activation and chromatin accessibility. While HIF-1α is central to the acute induction of VEGFA, emerging evidence suggests that epigenetic mechanisms, such as hypoxia-driven H3K27me3 demethylation, may support sustained VEGFA expression during long-term adaptation. This introduces a new layer of control over skeletal muscle angiogenesis beyond traditional hypoxia signalling.

Understanding how histone modifications influence VEGFA regulation is important for advancing the fields of exercise physiology and vascular biology. The epigenetic axis described by Li et al. (2024) in the regulation of PGC-1α offers a compelling model that may extend to VEGFA

and other angiogenic genes. A key research question that arises from this synthesis is whether exercise-induced VEGFA expression is directly regulated by H3K27me3 dynamics at its promoter in skeletal muscle.

Future studies should aim to characterise histone methylation changes at the VEGFA locus following acute and chronic exercise, especially in response to localised hypoxic stimuli such as blood flow restriction training. Investigating the role of histone demethylases like JMJD3 may help uncover novel regulatory checkpoints in skeletal muscle vascularisation. These findings could ultimately guide therapeutic strategies to enhance vascular function in ageing and metabolic disease.

List of Abbreviations

BFR: blood flow restriction
ChIP: chromatin immunoprecipitation
EZH2: Enhancer of Zeste Homolog 2
H3K27me3: tri-methylation of lysine 27 on histone 3
HIF-1α: Hypoxia-Inducible Factor 1α)
JMJD3: Jumonji Domain-Containing Protein 3
mRNA: messenger ribonucleic acid
PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α
PRC2: polycomb repressive complex 2
PTM: post-translational modification
VEGFA: vascular endothelial growth factor A

Conflicts of Interest

The author declares no conflicts of interest.

Ethics Approval and/or Participant Consent

This review did not require ethics approval or participant consent as it did not involve human participants, animal subjects, or original experimental data.

Authors' Contributions

HB: made substantial contributions to the conception and design of the review, conducted the literature search and analysis, drafted and revised the manuscript, approved the final version to be published, and agrees to be accountable for all aspects of the work.

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