Review Article

A narrative review of the role of m6A in oxidative stress and inflammation

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Objective: To provide a comprehensive overview of the role and possible mechanism of N6-methyladenosine (m6A) in oxidative stress and inflammation.

Background: Oxidative stress and inflammation are involved in many pathophysiological processes. How oxidative stress and inflammation participate in the occurrence and development of diseases, and what factors regulate them have not yet been clarified. In recent years, more and more attention has been paid to the research of m6A. Due to its extensive role in RNA internal modification and maintaining stability, more and more scientists began to study the relationship between m6A modification and diseases. However, the research about m6A on oxidative stress and inflammation is rare.

Methods: We performed a systematic literature search of the MEDLINE literature database through PubMed on m6A, oxidative stress and inflammation. Subsequently, the main findings in the literature were summarized.

Conclusions: Oxidative stress and inflammation are involved in many pathophysiological processes, including tumor, aging, diabetes, cardiovascular disease and so on. Post-transcriptional epigenetic modification of RNA mainly, m6A, is an emerging concept in the scientific community. m6A mediates its effect through the various reader, writer, and eraser proteins, regulating gene expression and involving many biological processes, including oxidative stress and inflammation. This article mainly reviews the role and molecular mechanism of m6A in the occurrence and development of many diseases by regulating oxidative stress and inflammation. There are many problems in the process of oxidative stress and inflammation, which are worthy of further study. m6A plays a key role in the occurrence and development of many diseases by regulating oxidative stress and inflammation.

Keywords: N6-methyladenosine (m6A); oxidative stress; inflammation

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Introduction

N6-methyladenosine (m6A) is the most common modification in higher organisms. Studies have shown that m6A modification widely exists in mammals, plants, fungi and other organisms (1). The modification of m6A mainly occurs on the adenine of DRACH sequence (2,3). After high-throughput sequencing, m6A was found mainly distributed in stop codons, mRNA exons, 3'UTRs and protein coding regions (4). The biological function of RNA is based on a variety of modifications, among which methylation accounts for a large proportion (5,6). m6A modification plays a fundamental role in the regulation of gene expression (7). At the same time, m6A modification is also involved in RNA translation, degradation, splicing, enucleation and folding (5,8,9). The regulation of m6A mainly depends on the enzyme system of m6A, including "Writer", "Eraser", "Reader". "Writer" is a kind of methyltransferase, and mainly includes METTL3, METTL14 and WTAP. These methyltransferases transfer the methyl group from the methyl donor S-adenosylmethionine (SAM) to the sixth N atom of RNA adenine. "Eraser" is a kind of demethylase, and mainly includes fat mass and obesity-associated protein (FTO) and ALKBH5. FTO is a demethylase first identified in m6A modification (9,10). It has been found that FTO is knocked out by siRNA, the content of M6A in mRNA increases, and the overexpression of FTO can decrease the intracellular m6A level (11). However, some scholars believe that FTO has no obvious effect on m6A, especially for small nuclear RNA. In contrast to the view that FTO acts as a demethylation enzyme, some scholars believe that the regulatory sites of FTO and ALKBH5 tend to maintain the stability of the non-methylated state in order to reverse methylation (12). In the case of FTO inhibition or removal, abnormal m6Am interferes with the output mechanism and may lead to abnormal pre-splicing of mRNA (13). Combined with the above views, the role of FTO and other proteins in the m6A enzyme system needs to be more balanced and fully studied. In order to realize its biological functions, methylated modification needs to be combined with corresponding recognition proteins, which are "Reader", including the YT521-B homology domain family (YTHDF) proteins (14). Current studies focus more on YTHDF1/2/3. Although these three are considered to have different roles, due to the similarity of their sequences and convergence of binding targets, they are likely to have superimposed or synergistic effects (15). According to the present results, Readers include proteins such as YTHDF and IGF2BP3, whose functions are closer to influencing the stability of mRNA or interacting with associated binding sites (16,17). The specific role of these proteins in the m6A system needs to be further studied. We present the following article in accordance with the Narrative Review reporting checklist (available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-1/rc).

Methods

We performed a literature search using the online database (Medline) of articles through PubMed. We included the following search terms/phrases "m6A", "inflammation" and "oxidative stress" between January, 2001 to July, 2021, that only English language articles were reviewed.

m6A and inflammation related diseases

Inflammation, a defensive response of living tissue with vascular system to foreign body stimulation or injury factors, is mediated by various inflammatory mediators, and participates in and accompanies most diseases, which are characterized by redness, swelling, heat, pain and dysfunction (18). Usually, inflammation is beneficial and an automatic defense response of the human body, but sometimes inflammation is harmful. For example, inflammation attacks the body's own tissues or inflammation occurs in transparent tissues. Although inflammation is a common reaction in the human body, it generally does not lead to serious diseases. However, some inflammations can develop into life-threatening and fatal diseases. Long term inflammation is one of the important causes of many major diseases, including atherosclerosis, cancer, stroke and diabetes (19-23).

In recent years, with the development of medical theory, progress in molecular biology, immunology and various technologies, we have a better understanding of the nature of inflammation. On the whole, inflammation can be roughly divided into infectious inflammation and aseptic inflammation. When the human body is infected by pathogenic microorganisms, bacteria, viruses and protozoa, it causes exudation, necrosis and proliferation of the human body, which is collectively referred to as infectious inflammation. If inflammation is caused by physical and chemical factors, it is called aseptic inflammation. As an intracellular signal platform, inflammation can not only respond to pathogenic components, but also to various endogenous signals, inorganic environmental

components or vaccine adjuvants that may occur under sterile conditions (24-27). The tissue system in the body has many commonalities in participating in various inflammatory responses. That is, in different inflammation, there is the same organ, tissue system involved. The local or overall manifestations of inflammation can be summarized as: arterial congestion, edema, decreased membrane permeability, tissue cell proliferation, abnormal expression of cytokines, etc. Although there are few studies on the relationship between various types of inflammation and m6A, we can analyze the possible role of m6A from the perspective of basic changes and mechanisms of inflammation. We can reasonably speculate that m6A may be widely involved in the process of inflammation at the cellular level. This conjecture has been confirmed in many research experiments in recent years.

m6A and cancer

Inflammation is a recognized feature of cancer. Inflammation is closely related to the development and progression of cancer. Recent studies also show that cancer is closely related to chronic inflammation (28-32). In the enzyme system of m6A, the writer and eraser have been studied more and more. A large number of studies have shown that METTL3 and FTO has a synergistic effect on the occurrence and development of cancer (33-36). A large number of studies have shown that METTL3 and FTO are involved in the abnormal regulation of cells. Han et al found that METTL3 may interact with DGCR8 and positively modulate the pri-miR221/222 process in bladder cancer (37). METTL3 mediated m6A modified AFF4/NF-κB/MYC signaling network involved in the progress of bladder cancer (38). Chen *et al.* found that METTL3 is often up-regulated in human hepatocellular carcinoma (HCC) and participates in the progression of HCC. METTL3 inhibits SOCS2 expression in HCC via a m6A-YTHDF2 dependent mechanism (39). METTL3 knockout significantly inhibited the abundance of SOCS2 mRNA m6A. FTO showed higher expression in in human melanoma, and knockdown of FTO increased m6A methylation in PD-1 mRNA, CXCR4 mRNA, and SOX10 mRNA, leading to increased RNA decay through YTHDF2 in melanoma. Thus, the sensitivity of melanoma to anti-PD-1 therapy is increased (40). ALKBH5 showed higher expression in ovarian cancer tissue and promotes ovarian carcinogenesis in through activating NF-κB pathway (41). In the study of various types of cancer, we found that m6A has a wide range of regulatory effects on AHR/SOCS2, TLR4/NF-κB, TNF-α-NF-κB inflammatory signaling pathways (37,39). This further suggests that m6A may be involved in tumorigenesis and development by regulating inflammatory signaling pathway.

m6A and atherosclerosis

There are few studies on the cell structure and properties of m6A. However, in the inflammatory response, the change of vascular properties is more significant. Some studies have found that the expression of METTL14 increases in calcified arteries and human aortic smooth muscle cells (HASMCs) induced by indole sulfate, which increases the level of m6A in RNA and reduces the vascular repair function (42). In the characteristics of the disease, atherosclerosis includes the proliferation of cells and tissues, fatty necrotic lesions, and vascular sclerosis. These are typical inflammatory responses. The level of m6A modification and METTL14 methyltransferase were over expressed in atherosclerotic vascular endothelial cells. The results show that METTL14 improves the level of m6A modification of pri-miR-19a, promotes the processing of mature miR-19a, and promotes the proliferation and invasion of atherosclerotic vascular endothelial cells (43). miR-19a/19b has a certain protective effect on cardiac function, which has been confirmed in the mouse model of myocardial infarction (44). These data showed that there is a high correlation between m6A and cardiovascular disease.

m6A and diabetes

m6A plays an important role in the process of metabolic diseases such as obesity, type 2 diabetes (45). Deficiency of m6A modification can lead to a variety of diseases, including type 2 diabetes mellitus (T2DM) (46). T2DM is becoming more common worldwide. T2DM is characterized by lack of insulin, insulin resistance and high-glucose. Inflammation associated with diabetes incidence rate and mortality rate increase. Although the relationship between T2DM and inflammation is still unclear, it is undeniable that inflammation is the key to the occurrence and process of diabetes. Shen et al showed that the m6A contents were significantly low, and the FTO mRNA level was significantly high in T2DM patients, which might further increase the risk of complications of T2DM (47). Yang *et al.* found that m6A contents were decreased, while METTL3, METTL14, and WTAP were increased. This phenomenon

seems to be contradictory to the low level of m6A. The author speculates that the lower m6A content might be responsible for the upregulation of methyltransferases (48). In T2DM patients, highly expressed METTL3 inhibits hepatic insulin sensitivity via m6A modification of Fasn mRNA in liver tissues (49). Li *et al.* found that METTL3 was down-regulated during inflammation and oxidative stress, and islet β-cell-specific deletion of METTL3 induces β-cell failure and hyperglycemia, which is likely due to decreased insulin secretion-related genes (50). These results suggest that m6A plays an important role in the development of diabetes, and provide a new strategy for the targeted treatment of diabetes.

Oxidative stress and inflammation

Oxidative stress is the imbalance between oxidation and antioxidation in organism, which tends to lead to neutrophil infiltration, increase of protease secretion and production of a large number of oxidation intermediates. This process can lead to cell, tissue and organ damage (51,52). The occurrence of oxidative stress is affected by many factors, including hypoxia environment, toxic smoke, ultraviolet radiation, pesticide, etc. Oxidative stress is a major contributor to the pathogenesis of various human diseases, including denervation-induced muscle atrophy (53-57). It was confirmed that the activity of superoxide dismutase (SOD) in the liver of sea bass increased and oxidative stress increased under high temperature and hypoxia (58). Oxidative stress has a great influence on protein synthesis and metabolism (59). In the study of methamphetamine induced dopaminergic neurotoxicity, it was found that methamphetamine induced mitochondrial damage enhanced the susceptibility to oxidative stress, proapoptosis and neuroinflammation in a positive feedback loop. At the same time, the intervention of oxidative stress can inhibit the apoptosis of cells (60). For example, astragalus polysaccharide can reduce the level of oxidative stress in diabetic heart cells, and resveratrol can reduce oxidative stress, alleviate the damage of intestinal epithelial cells caused by oxidative stress (61,62).

Inflammation can cause oxidative stress, and oxidative stress can also cause inflammation (63,64). The proliferation of inflammatory cells can be seen in infectious inflammation. Take neutrophils as an example, when they are activated by pathogens, oxygen consumption increases and a large number of oxygen free radicals are generated, which are used to kill pathogenic microorganisms. The production of large amount of oxygen free radicals is also the manifestation of oxidative stress, producing a variety of chemotactic substances, such as C3 fragment and leukotriene, to attract and activate neutrophils. A mechanism similar to positive feedback is formed. Even in non-infectious inflammation, many factors, such as degenerative and necrotic tissue cells and their products, ischemia, hypoxia, and immune complexes, can activate inflammatory cells. Oxidative stress can also activate inflammatory cells by causing cell death. Therefore, it can be said that inflammatory response and oxidative stress may not have a fixed sequence, but it must exist at the same time.

m6A and oxidative stress

In a recent experiment, it has been found that there is a regulatory relationship between m6A and oxidative stress. Anders et al found that the number of m6A peaks increased significantly in response to oxidative stress, and described a previously unappreciated function for RNA m6A modification in oxidative-stress response (65). Zhao *et al.* found that induced oxidative stress increased the level of m6A in human keratinocytes, and suggested that this effect may be achieved by increasing the expression levels of WTAP and METTL14. The increase of m6A contents in arsenite-induced oxidative stress might be involved in apoptotic process and platelet activation (66). Highly expressed METTL3 inhibits oxidative stress and apoptosis induced by colistin (67). FB1 induced accumulation of intracellular reactive oxygen species (ROS), accompanied by an increase in METLL3, METLL14, YTHDF1, YTHDF2, YTHDF3 and YTHDC2, and a decrease in ALKBH5 and FTO in human hepatoma cells (68), which indicated that a cross-talk between m6A and redox regulators does occur. Low levels of arsenite up-regulated m6A modification, accompanied with the increase of METTL3, METTL14 and WTAP, in human HaCaT cells, and promoted HaCaT cells survival through inhibiting oxidative stress (69). Cui *et al.* found that the differential m6A modification was mainly enriched in the process associated with oxidative stress during the hepatic fibrosis (70). Mitochondrial activity was restored, and oxidative stress and ROS were induced in Von Hippel-Lindau-deficient cells in which FTO was overexpressed (71). In conclusion, oxidative stress can induce the change of m6A modification, and the change of m6A modification can also change the state of oxidative stress.

Conclusions

Oxidative stress and inflammation are involved in many pathophysiological processes, including tumor, aging, diabetes, cardiovascular disease and so on. As a kind of post transcription modification, m6A is involved in gene expression regulation and involves many biological processes, including oxidative stress and inflammation. This article mainly reviews the role and molecular mechanism of m6A in the occurrence and development of many diseases by regulating oxidative stress and inflammation. There are many problems in the process of oxidative stress and inflammation, which are worthy of further study.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-1/rc

Conflict of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-1/coif). HS serves as an unpaid Executive Editor-in-Chief of *Biotarget*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Liu J, Jia G. Methylation modifications in eukaryotic messenger RNA. J Genet Genomics 2014;41:21-33.
2. Zepecki JP, Karambizi D, Fajardo JE, et al. miRNA-mediated loss of m6A increases nascent translation in glioblastoma. PLoS Genet 2021;17:e1009086.
3. Linder B, Grozhik AV, Olarerin-George AO, et al. Single-nucleotide-resolution mapping of m6A and m6Am throughout the transcriptome. Nat Methods 2015;12:767-72.
4. Meyer KD, Saletore Y, Zumbo P, et al. Comprehensive analysis of mRNA methylation reveals enrichment in 3' UTRs and near stop codons. Cell 2012;149:1635-46.
5. Cao G, Li HB, Yin Z, et al. Recent advances in dynamic m6A RNA modification. Open Biol 2016;6:160003.
6. Dimitrova DG, Teysset L, Carré C. RNA 2'-O-Methylation (Nm) Modification in Human Diseases. Genes (Basel) 2019;10:117.
7. Dominissini D, Moshitch-Moshkovitz S, Schwartz S, et al. Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq. Nature 2012;485:201-6.
8. Mao Y, Dong L, Liu XM, et al. m6A in mRNA coding regions promotes translation via the RNA helicase-containing YTHDC2. Nat Commun 2019;10:5332.
9. Niu Y, Zhao X, Wu YS, et al. N6-methyl-adenosine (m6A) in RNA: an old modification with a novel epigenetic function. Genomics Proteomics Bioinformatics 2013;11:8-17.
10. Zaccara S, Ries RJ, Jaffrey SR. Reading, writing and erasing mRNA methylation. Nat Rev Mol Cell Biol 2019;20:608-24.
11. Jia G, Fu Y, Zhao X, et al. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol 2011;7:885-7.
12. Mauer J, Sindelar M, Despic V, et al. FTO controls reversible m6Am RNA methylation during snRNA biogenesis. Nat Chem Biol 2019;15:340-7.
13. Koh CWQ, Goh YT, Goh WSS. Atlas of quantitative single-base-resolution N6-methyl-adenine methylomes. Nat Commun 2019;10:5636.
14. Xu C, Wang X, Liu K, et al. Structural basis for selective binding of m6A RNA by the YTHDC1 YTH domain. Nat Chem Biol 2014;10:927-9.
15. Lasman L, Krupalnik V, Viukov S, et al. Context-dependent functional compensation between Ythdf m6A reader proteins. Genes Dev 2020;34:1373-91.

16. Sun L, Fazal FM, Li P, et al. RNA structure maps across mammalian cellular compartments. Nat Struct Mol Biol 2019;26:322-30.
17. Zaccara S, Jaffrey SR. A Unified Model for the Function of YTHDF Proteins in Regulating m6A-Modified mRNA. Cell 2020;181:1582-1595.e18.
18. Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. FASEB J 2017;31:1273-88.
19. Murata M. Inflammation and cancer. Environ Health Prev Med 2018;23:50.
20. Shawki S, Ashburn J, Signs SA, et al. Colon Cancer: Inflammation-Associated Cancer. Surg Oncol Clin N Am 2018;27:269-87.
21. Shekhar S, Cunningham MW, Pabbidi MR, et al. Targeting vascular inflammation in ischemic stroke: Recent developments on novel immunomodulatory approaches. Eur J Pharmacol 2018;833:531-44.
22. Shi K, Tian DC, Li ZG, et al. Global brain inflammation in stroke. Lancet Neurol 2019;18:1058-66.
23. Turkmen K. Inflammation, oxidative stress, apoptosis, and autophagy in diabetes mellitus and diabetic kidney disease: the Four Horsemen of the Apocalypse. Int Urol Nephrol 2017;49:837-44.
24. Martinon F, Pétrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237-41.
25. Wallin RP, Lundqvist A, Moré SH, et al. Heat-shock proteins as activators of the innate immune system. Trends Immunol 2002;23:130-5.
26. Dostert C, Pétrilli V, Van Bruggen R, et al. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science 2008;320:674-7.
27. Eisenbarth SC, Colegio OR, O'Connor W, et al. Crucial role for the Nalp3 inflammasome in the immunostimulatory properties of aluminium adjuvants. Nature 2008;453:1122-6.
28. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol 2013;33 Suppl 1:S79-84.
29. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.
30. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:e493-503.
31. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436-44.
32. Singh N, Baby D, Rajguru JP, et al. Inflammation and cancer. Ann Afr Med 2019;18:121-6.
33. Guo X, Li K, Jiang W, et al. RNA demethylase ALKBH5 prevents pancreatic cancer progression by posttranscriptional activation of PER1 in an m6A-YTHDF2-dependent manner. Mol Cancer 2020;19:91.
34. Ji G, Huang C, He S, et al. Comprehensive analysis of m6A regulators prognostic value in prostate cancer. Aging (Albany NY) 2020;12:14863-84.
35. Liu ZX, Li LM, Sun HL, et al. Link Between m6A Modification and Cancers. Front Bioeng Biotechnol 2018;6:89.
36. Zhang Z, Wang Q, Zhang M, et al. Comprehensive analysis of the transcriptome-wide m6A methylome in colorectal cancer by MeRIP sequencing. Epigenetics 2021;16:425-35.
37. Han J, Wang JZ, Yang X, et al. METTL3 promote tumor proliferation of bladder cancer by accelerating pri-miR221/222 maturation in m6A-dependent manner. Mol Cancer 2019;18:110.
38. Cheng M, Sheng L, Gao Q, et al. The m6A methyltransferase METTL3 promotes bladder cancer progression via AFF4/NF-κB/MYC signaling network. Oncogene 2019;38:3667-80.
39. Chen M, Wei L, Law CT, et al. RNA N6-methyladenosine methyltransferase-like 3 promotes liver cancer progression through YTHDF2-dependent posttranscriptional silencing of SOCS2. Hepatology 2018;67:2254-70.
40. Yang S, Wei J, Cui YH, et al. m6A mRNA demethylase FTO regulates melanoma tumorigenicity and response to anti-PD-1 blockade. Nat Commun 2019;10:2782.
41. Jiang Y, Wan Y, Gong M, et al. RNA demethylase ALKBH5 promotes ovarian carcinogenesis in a simulated tumour microenvironment through stimulating NF-κB pathway. J Cell Mol Med 2020;24:6137-48.
42. Chen J, Ning Y, Zhang H, et al. METTL14-dependent m6A regulates vascular calcification induced by indoxyl sulfate. Life Sci 2019;239:117034.
43. Zhang BY, Han L, Tang YF, et al. METTL14 regulates M6A methylation-modified primary miR-19a to promote cardiovascular endothelial cell proliferation and invasion. Eur Rev Med Pharmacol Sci 2020;24:7015-23.
44. Gao F, Kataoka M, Liu N, et al. Therapeutic role of miR-19a/19b in cardiac regeneration and protection from myocardial infarction. Nat Commun 2019;10:1802.
45. Zhong H, Tang HF, Kai Y. N6-methyladenine RNA Modification (m6A): An Emerging Regulator of Metabolic Diseases. Curr Drug Targets 2020;21:1056-67.
46. Wei W, Ji X, Guo X, et al. Regulatory Role of N6 -methyladenosine (m6 A) Methylation in RNA Processing

and Human Diseases. J Cell Biochem 2017;118:2534-43.
47. Shen F, Huang W, Huang JT, et al. Decreased N(6)-methyladenosine in peripheral blood RNA from diabetic patients is associated with FTO expression rather than ALKBH5. J Clin Endocrinol Metab 2015;100:E148-54.
48. Yang Y, Shen F, Huang W, et al. Glucose Is Involved in the Dynamic Regulation of m6A in Patients With Type 2 Diabetes. J Clin Endocrinol Metab 2019;104:665-73.
49. Xie W, Ma LL, Xu YQ, et al. METTL3 inhibits hepatic insulin sensitivity via N6-methyladenosine modification of Fasn mRNA and promoting fatty acid metabolism. Biochem Biophys Res Commun 2019;518:120-6.
50. Li X, Jiang Y, Sun X, et al. METTL3 is required for maintaining β-cell function. Metabolism 2021;116:154702.
51. Filomeni G, De Zio D, Cecconi F. Oxidative stress and autophagy: the clash between damage and metabolic needs. Cell Death Differ 2015;22:377-88.
52. Galati S, Boni C, Gerra MC, et al. Autophagy: A Player in response to Oxidative Stress and DNA Damage. Oxid Med Cell Longev 2019;2019:5692958.
53. Kim SH, Kim H. Inhibitory Effect of Astaxanthin on Oxidative Stress-Induced Mitochondrial Dysfunction-A Mini-Review. Nutrients 2018;10:1137.
54. Qiu J, Fang Q, Xu T, et al. Mechanistic Role of Reactive Oxygen Species and Therapeutic Potential of Antioxidants in Denervation- or Fasting-Induced Skeletal Muscle Atrophy. Front Physiol 2018;9:215.
55. Shen Y, Zhang Q, Huang Z, et al. Isoquercitrin Delays Denervated Soleus Muscle Atrophy by Inhibiting Oxidative Stress and Inflammation. Front Physiol 2020;11:988.
56. Shen Y, Zhang R, Xu L, et al. Microarray Analysis of Gene Expression Provides New Insights Into Denervation-Induced Skeletal Muscle Atrophy. Front Physiol 2019;10:1298.
57. Huang Z, Fang Q, Ma W, et al. Skeletal Muscle Atrophy Was Alleviated by Salidroside Through Suppressing Oxidative Stress and Inflammation During Denervation. Front Pharmacol 2019;10:997.
58. Sun JL, Zhao LL, Liao L, et al. Interactive effect of thermal and hypoxia on largemouth bass (Micropterus salmoides) gill and liver: Aggravation of oxidative stress, inhibition of immunity and promotion of cell apoptosis. Fish Shellfish Immunol 2020;98:923-36.
59. Hauck AK, Huang Y, Hertzel AV, et al. Adipose oxidative stress and protein carbonylation. J Biol Chem 2019;294:1083-8.
60. Shin EJ, Tran HQ, Nguyen PT, et al. Role of Mitochondria in Methamphetamine-Induced Dopaminergic Neurotoxicity: Involvement in Oxidative Stress, Neuroinflammation, and Pro-apoptosis-A Review. Neurochem Res 2018;43:66-78.
61. Chen W, Ju J, Yang Y, et al. Astragalus polysaccharides protect cardiac stem and progenitor cells by the inhibition of oxidative stress-mediated apoptosis in diabetic hearts. Drug Des Devel Ther 2018;12:943-54.
62. Zhuang Y, Wu H, Wang X, et al. Resveratrol Attenuates Oxidative Stress-Induced Intestinal Barrier Injury through PI3K/Akt-Mediated Nrf2 Signaling Pathway. Oxid Med Cell Longev 2019;2019:7591840.
63. Hussain T, Tan B, Yin Y, et al. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? Oxid Med Cell Longev 2016;2016:7432797.
64. McGarry T, Biniecka M, Veale DJ, et al. Hypoxia, oxidative stress and inflammation. Free Radic Biol Med 2018;125:15-24.
65. Anders M, Chelysheva I, Goebel I, et al. Dynamic m6A methylation facilitates mRNA triaging to stress granules. Life Sci Alliance 2018;1:e201800113.
66. Zhao T, Li X, Sun D, et al. Oxidative stress: One potential factor for arsenite-induced increase of N6-methyladenosine in human keratinocytes. Environ Toxicol Pharmacol 2019;69:95-103.
67. Wang J, Ishfaq M, Xu L, et al. METTL3/m6A/miRNA-873-5p Attenuated Oxidative Stress and Apoptosis in Colistin-Induced Kidney Injury by Modulating Keap1/Nrf2 Pathway. Front Pharmacol 2019;10:517.
68. Arumugam T, Ghazi T, Chuturgoon AA. Fumonisin B1 alters global m6A RNA methylation and epigenetically regulates Keap1-Nrf2 signaling in human hepatoma (HepG2) cells. Arch Toxicol 2021;95:1367-78.
69. Chen H, Zhao T, Sun D, et al. Changes of RNA N6-methyladenosine in the hormesis effect induced by arsenite on human keratinocyte cells. Toxicol In Vitro 2019;56:84-92.
70. Cui Z, Huang N, Liu L, et al. Dynamic analysis of m6A methylation spectroscopy during progression and reversal of hepatic fibrosis. Epigenomics 2020;12:1707-23.
71. Zhuang C, Zhuang C, Luo X, et al. N6-methyladenosine demethylase FTO suppresses clear cell renal cell carcinoma through a novel FTO-PGC-1α signalling axis. J Cell Mol Med 2019;23:2163-73.

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