Epigenetic Regulation by Resveratrol in Animals and Its Mechanism of Action: A Postprint

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Abstract

Resveratrol is a non-flavonoid polyphenolic compound and a natural phytoalexin that is widely distributed in various plants. Resveratrol exhibits diverse biological activities and pharmacological effects, including antioxidant, anti-tumor, neuroprotective, cardiovascular protective, and anti-aging properties. Recent studies have revealed that these effects of resveratrol are intimately associated with the regulation of intrinsic gene expression through epigenetic modifications. This review summarizes the primary mechanisms of epigenetic modifications and the research progress regarding resveratrol' s involvement in DNA methylation, histone acetylation, microRNA, and other aspects of animal and human genes, and provides an overview of the pathways through which resveratrol exerts its effects in animals and humans at the epigenetic modification level.

Full Text

Resveratrol' s Epigenetic Regulation in Animals and Its Mechanism of Action

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Abstract: Resveratrol is a non-flavonoid polyphenolic compound and a natural phytoalexin widely found in various plants. It exhibits diverse biological activities and pharmacological effects, including antioxidant, anti-tumor, neuroprotective and cardioprotective properties, as well as anti-aging functions. Recent studies have demonstrated that these effects are closely associated with epigenetic modifications that regulate intrinsic gene expression. This review summarizes the primary mechanisms of epigenetic modification and the research

progress on resveratrol' s involvement in DNA methylation, histone acetylation, and microRNA (miRNA) regulation in animals and humans, providing an overview of the pathways through which resveratrol exerts its effects at the epigenetic modification level.

Key words: resveratrol; epigenetics; regulation; DNA methylation; histone acetylation; microRNA

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Resveratrol is a polyphenolic compound with the chemical name 3,4,5' -trihydroxy-trans-stilbene. First discovered in grapevines by Langcake and Pryce in 1976, natural resveratrol exists in various plants including grapes (particularly in grape skins and seeds), peanuts, and the traditional Chinese medicinal herb *Polygonum cuspidatum*. As a phytoalexin, it is produced in response to adverse conditions such as ultraviolet radiation or fungal and microbial infections [1]. Like most phenolic compounds, natural resveratrol is synthesized from phenylalanine via the shikimic acid pathway, which involves three rate-limiting enzymes: phenylalanine ammonia-lyase, coenzyme A ligase, and stilbene synthase. The biosynthesis of these enzymes can be induced by stress [2].

For many years, resveratrol has been recognized for its cardioprotective effects and its potential role in explaining the "French Paradox" —the observation that French populations exhibit lower incidence of cardiovascular disease compared to other developed countries despite similar dietary patterns [2-3]. Subsequent extensive research has revealed that resveratrol possesses multiple biological activities and pharmacological properties, including antioxidant [2], neuroprotective and cardioprotective [2], anti-tumor [1-2], anti-diabetic [2], and anti-aging effects [4-6]. Recent studies have demonstrated that these functions are largely mediated through epigenetic modifications that regulate intrinsic gene expression.

Since the early 20th century, genetics has advanced remarkably rapidly. Although only 150 years have passed since Mendel introduced his laws of inheritance based on pea plants, researchers have observed phenomena that defy Mendelian inheritance patterns despite identical DNA sequences, as well as the differentiation of a single fertilized egg into diverse cell types. In the 1940s, biologist Waddington coined the term "epigenetics" [7]. Epigenetics is an emerging discipline that investigates gene expression and inheritance without alterations to the DNA sequence itself, encompassing DNA methylation, histone modifications, and non-coding RNAs. In recent years, significant progress has been made in understanding how environmental factors and genes interact to modify gene expression and transgenerational epigenetic characteristics [8-9]. This review summarizes the primary mechanisms of epigenetic modification and the

research progress on resveratrol' s involvement in DNA methylation, histone acetylation, and microRNA (miRNA) regulation in animals and humans, providing an overview of the pathways through which resveratrol exerts its effects at the epigenetic modification level.

1.1 DNA Methylation

DNA methylation is the most extensively studied epigenetic mechanism, which cells utilize to establish and maintain a controlled pattern of gene expression [10]. As the only covalent modification of DNA itself, DNA methylation is crucial for embryonic development [11-12] and stem cell differentiation [13] in mammals. In mammalian systems, DNA methylation predominantly occurs at CpG dinucleotides. However, Zemach et al. [14] have identified methylation at other cytosine positions in plants, fungi, and some invertebrates. Khatib [7] reported that DNA replication does not erase methylation marks at CpG sites, demonstrating that DNA methylation is heritable. This modification serves as the foundation for various epigenetic phenomena, including genomic imprinting, X-chromosome inactivation, and chromatin compaction [15-17]. Generally, DNA methylation at promoter regions correlates negatively with gene expression [18]. In cancer cells, CpG islands within promoters are frequently hypermethylated, leading to gene silencing [19].

The regulation of DNA methylation in normal tissues depends on the activities of DNA methyltransferases (DNMTs) and demethylases, whose expression can be controlled at both transcriptional and post-transcriptional levels. DNMTs constitute a family of proteins that maintain DNA methylation levels within cells. Four DNA methyltransferases have been identified in humans and mice, with DNMT3 responsible for de novo methylation, DNMT1 for maintaining methylation patterns, and DNMT2 exhibiting minimal methyltransferase activity in vitro [7]. Current understanding of DNMTs in livestock remains limited. While several DNMTs have been cloned in chickens, pigs, cattle, and sheep, different isoforms—Dnmt1, Dnmt3a, and Dnmt3b—have been identified in cattle [7], though their specific roles in DNA methylation processes remain unknown. In contrast to the relatively well-studied DNMTs, research on DNA demethylases is still in its infancy, with the demethylation mechanism remaining unclear even in humans and mice [7].

1.2 Histone Modifications

Histones can undergo various covalent modifications, including methylation, acetylation, phosphorylation, ubiquitination, and SUMOylation [20]. Recent research has focused primarily on acetylation. Most histone modifications are dynamic processes regulated by two sets of enzymes that maintain the balance of histone acetylation: histone acetyltransferases (HATs) and histone deacetylases (HDACs) [21]. HATs acetylate the N-terminal tails of histones, loosening nucleosome structure and activating gene transcription, whereas HDACs remove these

acetyl groups, suppressing transcription and potentially inducing apoptosis and cell death [22].

In animals, HATs comprise three families, while HDACs are grouped into four classes. The three HAT families include the Gcn5-related N-acetyltransferase (GNAT) superfamily, the p300/CBP family, and the MYST family [MOZ (monocytic leukemia zinc finger protein), Ybf2/Sas3 and Sas2 (something about silencing) in yeast, and Tip60 (Tat-interactive protein, 60 kDa) in mammals], all of which are associated with gene activation [23]. HDACs, identified based on homology with yeast genes, function as transcriptional repressors. In humans, four classes of HDACs have been discovered: Class I (HDAC1, 2, 3, 8), Class II (HDAC4, 5, 6, 7, 9, 10), Class III (SIRT1-7), and Class IV (HDAC11) [24]. However, not all HDACs share identical catalytic and inhibitor-binding domains. Classes I, II, and IV require zinc ions for catalysis [23], while Class III (sirtuins) requires nicotinamide adenine dinucleotide (NAD+) as a cofactor [25].

1.3 microRNA

microRNAs (miRNAs) are a newly identified class of approximately 22-nucleotide-long single-stranded RNA molecules that do not encode proteins but regulate gene expression post-transcriptionally. In the nucleus, miRNA genes are transcribed by RNA polymerase II or III into long primary miRNA precursors [26]. After maturation, short single-stranded miRNAs are incorporated into the RNA-induced silencing complex (RISC), where they recognize target mRNAs through base pairing, typically triggering mRNA deadenylation, translational repression, or occasionally mRNA degradation at the 3' untranslated region, thereby reducing corresponding protein levels [27].

The first characterized miRNA family member, lin-4, was discovered in *Caenorhabditis elegans* and plays a critical role in post-embryonic development by negatively regulating LIN-14 protein expression. Since the discovery of the lin-4 and lin-14 interaction, miRNA regulation has emerged as an essential control mechanism in animal development, metabolism, homeostasis, and particularly immune system function [7].

2.1 Effects on DNA Methylation

Research on resveratrol' s effects on DNA methylation has primarily focused on cancer. Qin et al. [28] treated breast cancer MCF-7 cells with resveratrol at concentrations of 5, 50, and 100 mol/L for 36 hours, demonstrating demethylation of the tumor suppressor gene deleted in liver cancer-1 (DLC-1) at all doses, accompanied by dose-dependent reductions in DNMT1 and DNMT3b expression. Similar studies in non-invasive MCF-7 cells have shown that resveratrol reduces promoter methylation of the tumor suppressor gene phosphatase and tensin homolog deleted in chromosome 10 (PTEN) while increasing PTEN expression and decreasing DNMT1 expression [29]. Additionally, resveratrol inhibits acetylation of the transcription factor signal transducer and activator

of transcription-3 (STAT3), affecting DNMT1-STAT3 complex involvement in estrogen receptor α promoter methylation [30].

These in vitro findings are supported by in vivo studies. In 39 women at increased risk for breast cancer, treatment with varying doses of resveratrol resulted in dose-dependent decreases in methylation of the tumor suppressor gene Ras-association domain family 1A (RASSF-1a) [31]. Furthermore, in estrogen-treated ACI rats, a rodent model of breast cancer, high- and low-dose resveratrol administration for 21 weeks reduced DNMT3b expression in cancerous tissues compared to normal tissues. High-dose resveratrol also upregulated miRNA-21, miRNA-129, and miRNA-204 expression, while miRNA-489 expression increased two-fold. In contrast, these same miRNAs decreased by 10-50% in normal tissues [32]. However, resveratrol exhibits lower DNMT inhibitory activity compared to other bioactive compounds such as catechins [33].

2.2 Effects on Histone Acetylation

Resveratrol influences histone acetylation primarily by regulating sirtuins, silent information regulator 2 (Sir2)-related enzymes that belong to the HDAC family and play crucial roles in maintaining chromosomal silencing following histone deacetylation [25].

The mammalian sirtuin family comprises seven members, designated SIRT1 through SIRT7 [24]. Structurally, all sirtuins share a conserved catalytic domain of 275 amino acids and an NAD+-binding domain, along with unique N-terminal and/or variable-length C-terminal sequences [34], functioning as deacetylases or ADP-ribosyltransferases involved in numerous vital biological processes. Resveratrol and its derivatives directly activate the deacetylase SIRT1, promoting activation of transcription factors such as forkhead box protein O 3a (FOXO3a) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [35]. SIRT1 activation by resveratrol enhances expression of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) genes, thereby increasing lipolysis and reducing lipid droplet accumulation in pigs, potentially through PPARγ signaling pathways [36-37]. In mice, resveratrol-mediated SIRT1 activation has been shown to reduce adipogenesis, increase lipolysis, and decrease body fat deposition, with the mammalian target of rapamycin (mTOR) signaling pathway participating in this process [38].

Additionally, resveratrol induces SIRT1 expression in porcine ovarian granulosa cells, accelerating apoptosis [39]. In mouse models, resveratrol-induced SIRT1 activation stimulates PGC-1α and AMP-activated protein kinase (AMPK), reduces insulin-like growth factor-1 (IGF-1) expression, improves insulin sensitivity, enhances mitochondrial oxidative phosphorylation and aerobic metabolism, increases energy expenditure, and extends lifespan [6]. SIRT1 has been shown to negatively regulate survivin, an anti-apoptotic protein, playing an important role in aging. Resveratrol also exhibits anti-proliferative effects in several cancer types, demonstrating the ability to suppress BRCA1-related breast cancer

development by increasing tumor suppressor gene BRCA1 expression during the initiation stage through histone H3 acetylation [40]. Resveratrol reduces prostate cancer cell growth and stimulates apoptosis by activating forkhead box protein O (FOXO) transcription factors [41]. Moreover, in mice, resveratrol combined with black tea polyphenols suppresses skin cancer development and progression by inhibiting mitogen-activated protein kinase (MAPK) and tumor suppressor p53 pathways [42].

2.3 Effects on microRNAs

Since the late 1990s, extensive research on intracellular miRNA function has emerged, opening a new field of investigation. To date, over 1,500 miRNAs have been identified in human cells, demonstrating critical roles in controlling cell differentiation, homeostasis, and immune responses. Dysregulated miRNA expression has been repeatedly observed in cancer, neurodegeneration, cardiovascular disease, and autoimmune disorders. Many plant-derived secondary metabolites, primarily polyphenols, protect plants from infection and adverse environmental conditions. These polyphenols frequently exert specific biological activities that maintain cellular function and homeostasis in humans and animals. Grapes produce numerous diverse polyphenols that have been shown to mitigate or delay cardiovascular alterations, cancer, infection, and aging. Until recently, the molecular basis for resveratrol' s pleiotropic effects remained unclear despite extensive evidence of its regulation of multiple signaling pathways and transcriptional networks.

Lançon et al. [43] proposed that resveratrol' s protective properties may stem from its ability to increase levels of regulated miRNAs. Kaminski et al. [44] demonstrated that resveratrol modulates miRNA expression in mouse skeletal myoblasts (C2C12 cells), identifying 25 upregulated and 20 downregulated miRNAs with potential influence on C2C12 cell differentiation. Further analysis of signaling pathways potentially regulated by resveratrol-sensitive miRNAs concluded that resveratrol slightly reduces C2C12 myoblast differentiation while upregulating PGC-1α-encoding genes, suggesting a potential role in slowing muscle aging through miRNA regulation. Resveratrol induces SIRT1 expression and promotes induced pluripotent stem cell generation from mouse embryonic fibroblasts via miRNA-34a and p35 pathways [45]. Additionally, resveratrol participates in miRNA-34a-dependent regulation of mouse neural stem cell differentiation [46].

Notably, in cancer and inflammation, certain miRNAs are upregulated or downregulated by two or more plant polyphenols, suggesting these beneficial compounds may control specific miRNA expression through common regulatory mechanisms. This finding supports the concept that combinations of different low-dose plant polyphenols may achieve similar effects as a single high-dose polyphenol without the risk of side effects [43]. Furthermore, modulating miRNA expression related to lipid metabolism using resveratrol may offer a novel therapeutic approach for metabolic diseases. For instance, resveratrol

treatment has been shown to enhance fatty acid utilization in human fibroblasts deficient in mitochondrial carnitine palmitoyltransferase 1 or mitochondrial very-long-chain fatty acid dehydrogenase [47].

DNA methylation and histone modification represent major aspects of epigenetics that have been extensively studied in gene transcription regulation. DNA hypermethylation silences tumor suppressor gene expression, whereas DNA hypomethylation activates oncogenes. In both humans and animals, miRNA expression and DNA methylation are strictly regulated, as minor disturbances can disrupt homeostasis and lead to abnormal physiological conditions. Although the regulatory mechanisms governing miRNA expression and DNA methylation remain incompletely understood, accumulating evidence indicates that they influence each other reciprocally, whether through miRNAs targeting components of the epigenetic machinery or through epigenetic regulation of miRNA biogenesis. The reversibility of epigenetic changes and epigenetic control of miRNAs may point to novel directions for disease diagnosis and treatment.

For thousands of years, typical natural compounds derived from plants have been used to treat human diseases [48]. Interestingly, some of these substances can regulate animal phenotypes at both cellular and chromatin levels. The complexity of the mammalian genome is controlled by heritable epigenetic mechanisms that are indispensable for differentiation, development, and homeostasis. These mechanisms must be stably maintained during cell division to preserve cellular identity while remaining responsive to internal signals or external environmental factors during development; deviations in epigenetic modifications can cause disease [49]. However, epigenetics research remains in its early and imperfect stage, with the establishment, maintenance, and transmission of epigenetic signals, as well as their relationships with growth, development, and environmental conditions, yet to be fully elucidated [50].

Resveratrol, as a non-flavonoid polyphenolic compound, has been extensively studied in humans and model animals, yielding remarkable results particularly regarding epigenetic regulation. However, research on intensively farmed animals (especially ruminants) has primarily focused on phenotypic aspects, with few mechanistic investigations. For example, studies in sheep have examined resveratrol' s effects on methane emission reduction [51], while dairy cows fed grape pomace showed altered ruminal bacterial and archaeal communities (though fungal and protozoal populations remained unchanged) along with approximately 20% reduced methane production [52].

Plant extracts have attracted considerable attention from researchers and the feed industry as novel, pollution-free, residue-free feed resources. Dietary supplementation with plant extracts can improve feed intake and digestibility in ruminants, inhibit methane production, increase rumen bypass protein, regulate ruminal fatty acid fermentation patterns, enhance product quality, and mitigate adverse effects of stress [53]. However, research on resveratrol as a plant extract in this context remains scarce, particularly regarding mechanistic studies. In summary, numerous gaps exist in our understanding of the relationships among

resveratrol, animal growth, nutrient digestion, and epigenetic regulatory mechanisms, necessitating systematic and detailed investigation.

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