

Review

Regulatory Mechanisms of Fumonisin Biosynthesis and Applications in Food Safety and Biotechnology

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Abstract

Fumonisin, a major class of mycotoxins, pose significant health risks to humans and animals due to their widespread contamination and potent toxicity. Recent advances in molecular biology, biochemistry, and enzymology have greatly enhanced the understanding of fumonisin biosynthesis and its genetic regulation. The key biosynthetic genes are typically organized in clusters and regulated by specific transcription factors; increasing evidence also highlights the involvement of complex transcriptional and epigenetic mechanisms. Environmental factors such as nitrogen, carbon, and pH also modulate these regulatory networks. Despite substantial progress, critical gaps remain in fully elucidating the regulatory pathways that control fumonisin production. This review synthesizes current knowledge regarding fumonisin biosynthesis, gene clusters, and multi-level regulatory mechanisms, while emphasizing recent trends, existing challenges, and potential applications in food safety and biotechnology to enhance food security and promote sustainable development.

Keywords: mycotoxin; fumonisin; biosynthesis; gene regulation; applications

1. Introduction

Fumonisin is a polyketide-derived mycotoxin, primarily produced by several *Fusarium* species, including *F. verticillioides*, *F. proliferatum*, *F. fujikuroi*, and *F. oxysporum* [1]. Certain *Aspergillus* species have also been reported to produce fumonisins in crops [2]. These toxigenic fungi generate more than 28 fumonisin homologs, which can be divided into four groups (A, B, C, and P) based on their chemical structures. All of these homologs can yield additional derivatives when metabolized by animals after ingestion. Among them, B-series fumonisins are the most important: fumonisin B₁ (FB₁) is the most prevalent and most toxic type, causing the majority of contamination occurrences; this is followed by fumonisin B₂ (FB₂) and fumonisin B₃ (FB₃) [3].

Fumonisin contamination is globally widespread, primarily affecting maize and maize-based products. According to the World Health Organization (WHO), approximately 50% of these products are contaminated with FB₁ [4]. This issue is particularly severe in Latin America, South America, Africa, and South/Southeast Asia. In Brazil, fumonisin was the predominant mycotoxin in maize and maize-derived products, with 85.9% of samples testing positive. The median concentration reached 1695 µg/kg, and the maximum level was 31,420 µg/kg [5]. In Southern Africa, fumonisins were detected in 90% of maize samples, reaching up to 40,000 µg/kg; notably, 53.9% exceeded the European Union regulatory limit for fumonisins (1000 µg/kg) [6]. In China, new-season corn showed an 87.16% positive rate,



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with an average level of 3549.65 µg/kg and a maximum of 41,600 µg/kg [7]. Beyond maize, fumonisins have also been detected in crops such as sorghum, soybean, and rice, as well as in postharvest fruits and processed products (e.g., dried figs), contributing to additional food safety concerns [8]. Fumonisins exert their toxic effects on humans and animals by inhibiting ceramide synthase and disrupting sphingolipid metabolism. FB₁ is associated with several diseases, including leukoencephalomalacia in horses, pulmonary edema in pigs, growth impairment in children, liver and kidney toxicity, neural tube defects, and esophageal cancer [9]. Based on these effects, FB₁ is classified as a Group 2B possible human carcinogen by the International Agency for Research on Cancer [10].

Given the substantial economic and health impacts, the European Food Safety Authority has classified fumonisins as critical mycotoxins, underscoring the urgency for stringent global management [11]. In recent decades, diverse strategies to mitigate fumonisin contamination have been proposed or implemented, including adoption of good agricultural practices, regulation of environmental factors, application of biocontrol agents or natural compounds, enhancement of host crop resistance, and deployment of effective detoxification technologies [8,12]. Despite these efforts, it remains highly challenging to control fumonisin contamination across agricultural production and its subsequent food chain, with persistent difficulties in fully interrupting contamination pathways.

Consequently, fumonisin production has become one of the most extensively studied fungal secondary metabolite processes. As in other fungi, fumonisins are synthesized through a complex biosynthetic pathway involving multiple enzymatic reactions [3]. The genes encoding these enzymes are organized into a cluster, and their coordinated expression is regulated by gene cluster-specific regulators such as Fum21, Fum19, and ZBD1 [13]. However, as a secondary metabolite, fumonisin biosynthesis also depends on multifaceted regulatory mechanisms elicited by environmental cues such as pH fluctuations, light exposure, nutrient availability, and oxidative stress. These external stimuli activate various intracellular signaling pathways that ultimately influence the transcriptional regulation of toxin biosynthetic genes [14]. Additionally, post-translational modifications, RNA polymerase-associated factors, proteins related to organelles (e.g., vacuoles, mitochondria, and peroxisomes), and cytoskeletal components further contribute to the regulation of fumonisin biosynthesis. Although a wide range of regulatory factors have been identified, their precise mechanisms of action and interrelationships remain poorly understood. Elucidating these regulatory networks will not only provide a comprehensive framework for understanding fumonisin biosynthesis and associated metabolic pathways in eukaryotic organisms but also facilitate the design of novel strategies to reduce fumonisin production by targeting upstream regulatory components—advances that could ultimately support innovative biotechnological applications [8,15].

This review updates recent advances in fumonisin synthesis, emphasizing the biosynthetic pathways (Figures 1 and 2) and the multiple levels of molecular regulation (Figure 3). A comprehensive list of relevant genes is provided in Supplementary Table S1, categorized as biosynthetic genes, fumonisin cluster regulators, environmental response factors, cell signaling components, RNA polymerase II complex subunits, and factors involved in post-translational modifications. Finally, potential applications of these genes are briefly discussed.

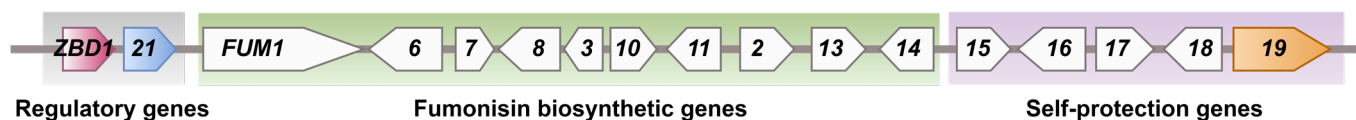


Figure 1. The fumonisin gene cluster in *F. verticillioides*. Genes (*FUM1*–*FUM14*) encoding fumonisin biosynthetic enzymes are highlighted in green box. The regulatory genes embedded within the cluster—*FUM21*, *FUM19*, and *ZBD1*—are indicated in blue, orange, and red, respectively. The self-protection genes (*FUM15*, *FUM16*, *FUM17*, *FUM18*, and *FUM19*) are marked with purple boxes.

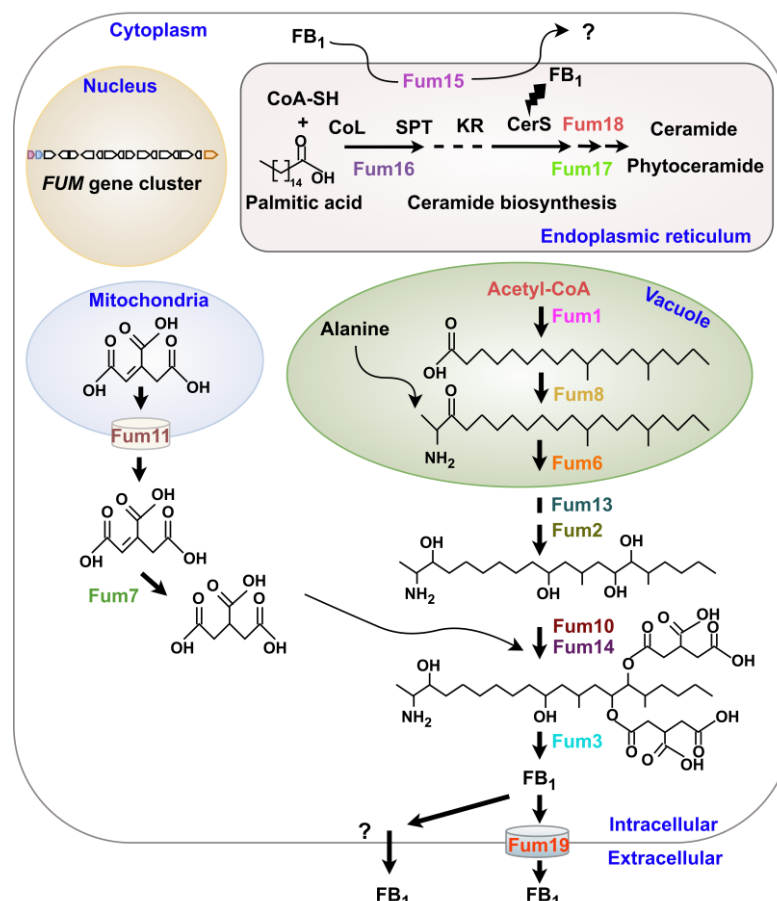


Figure 2. Fumonisin B₁ (FB₁) biosynthesis and self-protection strategies in *F. verticillioides*. Fum1–Fum14 are involved in the compartmentalized biosynthetic pathway of FB₁. Fum15, Fum16, Fum17, and Fum18 contribute to fungal self-protection against FB₁ by participating in or modulating ceramide biosynthesis, whereas the ABC transporter Fum19 mediates FB₁ export. FB₁ may also be transported to the extracellular space via other, as-yet-unidentified factors, which is indicated by a question mark. Fum15 may chemically modify FB₁ and thereby detoxify it; however, the modification product remains unknown and is therefore also indicated by a question mark. The dashed arrows represent multiple intermediate steps that are not shown.

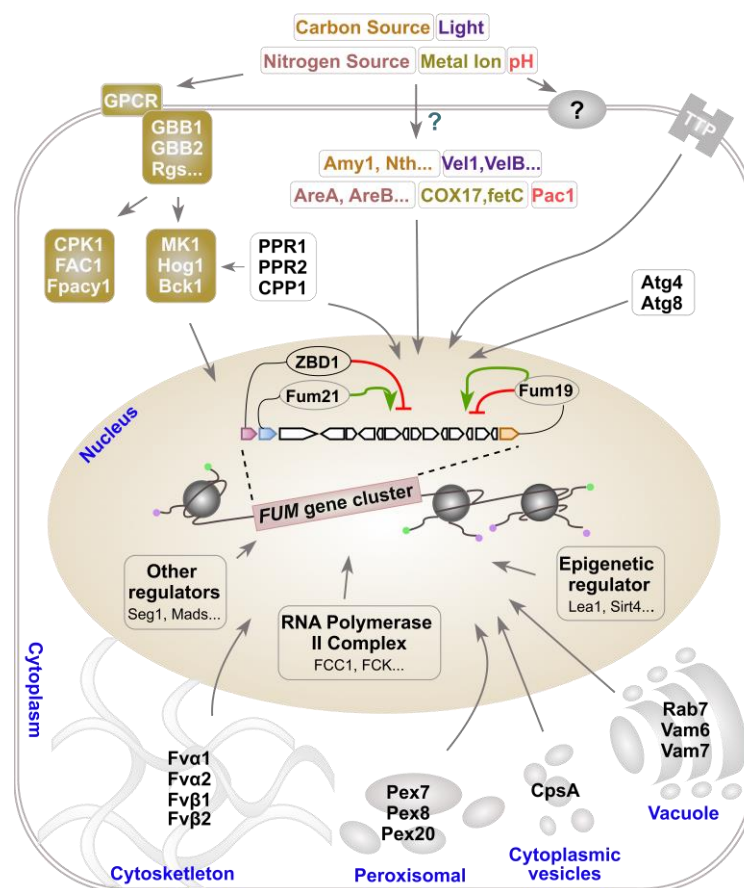


Figure 3. Regulatory model of the expression of the fumonisin biosynthetic gene cluster. This model integrates fumonisin cluster-specific regulators, environmental response factors, cell signaling components, RNA polymerase II complex subunits, factors involved in post-translational modifications, and organelle-associated regulatory factors. In this model, green arrows indicate activation, red arrows represent repression, and gray arrows depict regulatory relationships without specifying activation or repression, or whether the interaction is direct or indirect. Ellipses denote additional, unlisted regulatory factors. The question mark denotes unknown factor(s). G protein signaling factors: GBB1, GBB2, and Rgs; MAPK signaling factors: MK1, Hog1, and Bck1; cAMP signaling factors: CPK1, FAC1, and Fpacy1; Phosphatases: PPR1, PPR2, and CPP1; Glycosyltransferase: CpsA; Autophagy-related proteins: Atg4 and Atg8.

2. Fumonisin Biosynthetic Pathway

2.1. The Fumonisin Gene Cluster

Fumonisin is primarily produced by *F. verticillioides*. In this fungus, the genome is organized into 11 chromosomes, with the genes responsible for fumonisin biosynthesis located within a 42-kb region on chromosome 1 [3,16]. This biosynthetic gene cluster consists of 17 genes, including biosynthetic, regulatory, and self-protection genes (Figure 1; Supplementary Table S1) [17]. Other species within the *F. fujikuroi* complex and *F. oxysporum* can also produce fumonisins but often lack complete biosynthetic gene clusters (BGCs) [18,19]. In contrast, more distantly related fungi such as *Aspergillus niger* exhibit substantial differences in fumonisin production. *A. niger* can produce FB₂, FB₄, and FB₆, but not the most toxic form, FB₁, because its truncated BGCs lack the hydroxylation gene *FUM2* [2,14]. Phylogenetic evidence suggests that these clusters originated via horizontal gene transfer, followed by gene loss and rearrangement, explaining the evolutionary divergence in toxin profiles [20].

2.2. Enzymatic Cascade Leading to Fumonisin Synthesis

Fumonisin biosynthesis involves a series of enzymatic reactions that convert simple precursors into the complex final structure [3]. These reactions occur in various compartments within fungal cells, with compartmentalization proposed as a self-protection mechanism against the toxic effects of these mycotoxins (Figure 2) [13]. The major steps are outlined below:

Polyketide Backbone Formation: The process begins with Fum1, a polyketide synthase (PKS) that catalyzes the condensation of nine acetate units and two methyl groups to form an 18-carbon linear polyketide. This intermediate—structurally similar to 10,14-dimethyl octadecanoic acid—remains covalently bound to the PKS cofactor during early steps [21]. *FUM1* is essential for initiating FB₁ biosynthesis, and its disruption completely abolishes toxin production [22–24].

Alanine Condensation: Fum8, an α -oxoamine synthase homolog, condenses the polyketide with alanine to generate a 20-carbon backbone with an amine group at C-2. This step differentiates B-series fumonisins from C-series fumonisins, as species-specific *FUM8* orthologs determine whether glycine or alanine is incorporated [18].

Early Hydroxylations and Carbonyl Reduction: Fum6, a cytochrome P450 monooxygenase and reductase, hydroxylates C-14 and C-15 to generate a 3-keto intermediate [25,26]. Fum13, a short-chain dehydrogenase/reductase, subsequently reduces the C-3 ketone to a hydroxyl group [27,28]. Mutants lacking *FUM6* or *FUM13* accumulate precursors with unmodified carbonyl groups [25,27]. Localization studies of Fum8 in ER-derived vesicles have indicated that early fumonisin biosynthesis occurs within these compartments [17]. However, a recent study reported that Fum1, Fum8, and Fum6—key enzymes in the early steps of FB₁ biosynthesis—co-localize in the vacuole. Additionally, two vacuole-associated proteins, FvRab7 and FvAm7, are essential for FB₁ production [29], suggesting that Fum protein localization may vary among species.

C-10 Hydroxylation: Fum2, another cytochrome P450 enzyme, hydroxylates C-10 of fumonisins. Loss-of-function mutants produce fumonisins lacking this modification [30].

Tricarballic Acid Esterification: The formation of the tricarballic (C3) side chains is catalyzed by Fum7 (a dehydrogenase) and Fum10 (an acyl-CoA synthetase), followed by esterification to C-14 and C-15 via Fum14, a nonribosomal peptide synthetase (NRPS) domain-containing enzyme [31,32]. Fum11, a mitochondrial membrane-associated protein, functions as a tricarboxylic acid transporter, exporting intermediates for esterification. Mutations in these genes result in hydrolyzed or partially esterified analogs [31]. Although C-3 ketone reduction, C-10 hydroxylation, and C-14/C-15 esterification are considered the fourth, fifth, and sixth steps in fumonisin biosynthesis, production profiles from *F. verticillioides* mutants indicate that these reactions can occur independently, suggesting that the order is not strictly conserved [3].

Final C-5 Hydroxylation: Fum3, a dioxygenase localized in the cytoplasm, performs the terminal C-5 hydroxylation [33]. This reaction requires prior C-3 reduction and side-chain esterification.

Together, the enzymes encoded by the fumonisin biosynthetic genes described above perform all major enzymatic functions required for fumonisin production. In addition to *FUM21*, a key regulatory gene [34,35], five adjacent non-biosynthetic genes (*FUM15*–*FUM19*) contribute to self-protection. Among these, *FUM19* encodes an ATP-binding cassette (ABC) transporter that regulates intracellular and secreted levels of FB₁ [17,36]. In *F. verticillioides*, *FUM15*–*FUM18* encode a P450 monooxygenase, a CoA ligase, and two of the five ceramide synthase (CerS) homologs, respectively. These enzymes are co-localized with ceramide synthases in the endoplasmic reticulum, where they contribute to ceramide biosynthesis and help mitigate FB₁-induced toxicity [17,37].

3. Regulatory Mechanisms of Fumonisin Biosynthesis

Extensive research has identified multiple factors influencing fumonisin production, revealing a complex regulatory network. Although several key regulatory mechanisms have been elucidated, they are part of a broader hierarchical system that integrates cluster-specific regulators, environmental signals, cell signaling pathways, epigenetic modifications, and organelle/cytoskeleton-associated factors (Figure 3; Supplementary Table S1).

3.1. Fumonisin Cluster Regulators

The *FUM* gene cluster contains multiple regulatory components essential for controlling fumonisin biosynthesis (Figure 1). Among them, the Zn(II)₂Cys₆ transcription factor Fum21, encoded by a gene adjacent to the polyketide synthase gene *FUM1*, regulates the expression of cluster genes. In Δ *fum21* mutants, transcript levels of *FUM1* and *FUM8* are significantly reduced, resulting in undetectable fumonisin production [35,38]. This regulatory role is conserved in *A. niger*, where deletion of *FUM21* abolishes fumonisin synthesis and downregulates 10 of the 12 *FUM* cluster genes [34].

Fum19, an ABC transporter, functions as a repressor of the *FUM* gene cluster in *F. verticillioides*; its activity is dependent on ATP hydrolysis. Deletion of *FUM19* increases *FUM17*, *FUM18*, and *FUM8* expression, elevating FB₁ production. Conversely, overexpression of *FUM19* reduces both intracellular and secreted FB₁ levels [17]. In *F. proliferatum*, however, *FUM19* appears to play a positive role in FB₁ biosynthesis, as its deletion causes a modest 14.7% reduction in FB₁ levels relative to the wild type [38].

Additionally, the zinc-binding dehydrogenase gene *ZBD1*, a non-canonical component of the fumonisin biosynthetic cluster located near the *FUM* gene cluster, also represses fumonisin production. Δ *fzbd1* mutants exhibit dramatically increased FB₁, FB₂, and FB₃ levels. Pyrrocidine likely targets *ZBD1* to inhibit fumonisin biosynthesis [39]. Further research is warranted to clarify the regulatory role of *ZBD1* in *FUM* gene expression and to elucidate potential interactions among Fum21, Fum19, and *ZBD1* in controlling fumonisin biosynthesis.

3.2. General Regulatory Responses to Environmental Factors

3.2.1. Carbon Sources

Carbon source availability strongly influences fumonisin biosynthesis in *Fusarium* species, though the underlying mechanisms remain incompletely understood. Recent studies have demonstrated that sucrose acts as a positive regulator of toxin production in most species but suppresses fumonisin synthesis in *F. proliferatum* via transcriptional downregulation of *FUM1*, *FUM8*, and *ZFR1* [40,41]. The replacement of sucrose with cellulose, hemicellulose, or banana peel polysaccharides decreases fumonisin levels in a similar manner [41]. The structure of starch also strongly impacts fumonisin biosynthesis. Amylopectin, but not amylose, induces FB₁ production. Disruption of the α -amylase gene *AMY1* abolishes FB₁ biosynthesis on starchy kernels [42]. In addition to polysaccharide metabolism, sugar catabolism regulates toxin production by modulating acetyl-CoA supply, a key precursor in fumonisin biosynthesis. Reduced sugar availability lowers acyl-CoA levels in *F. verticillioides*, thereby suppressing FB₁ production. Deletion of *HXK1*, a key glycolytic enzyme, decreases acetyl-CoA generation and reduces toxin synthesis [43]. Trehalose metabolism provides glucose to sustain this pathway; knockdown of *FvNTH*, which governs trehalase activity, limits glucose availability and consequently diminishes FB₁ biosynthesis [44]. Although the C2H2-type transcription factor CreA/Cre1 is a well-known global repressor of carbon catabolite metabolism in fungi, its specific role in fumonisin regulation remains to be elucidated. In contrast, other transcription factors have been more directly linked to fumonisin biosynthesis. In *F. verticillioides*, the zinc binuclear cluster

transcription factor ZFR1 regulates FB₁ biosynthesis, likely through modulation of carbohydrate sensing or uptake. Deletion of *ZFR1* significantly reduces FB₁ levels, alters the expression of sugar transporter genes—including *FST1*, which is essential for FB₁ production during maize kernel colonization—and increases α -amylase activity [45–47]. Similarly, ART1 is required for starch degradation and FB₁ production. $\Delta art1$ mutants exhibit defects in starch hydrolysis, lower expression of key biosynthetic genes *FUM1* and *FUM12*, and significantly reduced FB₁ levels [48]. Conversely, SDA1 functions as a negative regulator of FB₁ biosynthesis and is involved in polyol metabolism. $\Delta sda1$ mutants produce higher FB₁ levels but reduced amounts of arabinol and mannitol [49]. These observations highlight the complexity of interconnected regulatory networks, in which carbon response mechanisms, carbon metabolism-related genes, and transcription factors collectively orchestrate fumonisin biosynthesis, providing new insights into the management of mycotoxin contamination in crops.

3.2.2. Nitrogen Sources

Nitrogen metabolite repression in filamentous fungi is regulated by the GATA transcription factors AreA and AreB, which play critical roles in modulating fumonisin biosynthesis [13]. In *F. fujikuroi*, both $\Delta areA$ and $\Delta areB$ mutants exhibit complete inhibition of *FUM* gene expression (e.g., *FUM1*, *FUM6*, *FUM8*) and FB₁/FB₂ production, indicating that AreA and AreB act as positive regulators of fumonisin biosynthesis [50]. Moreover, the global regulator FfSGE1, which controls multiple secondary metabolite pathways including fumonisins, shows strongly reduced expression in the $\Delta areA$ mutant. Although overexpression of *FfSGE1* partially restores gibberellin biosynthesis in this background, fumonisin production remains absent, underscoring the dominant role of *AreA* in the regulatory network governing fumonisin biosynthesis [51]. In *F. proliferatum*, the $\Delta AreA$ mutant shows reduced nitrate utilization while retaining ammonium/glutamine utilization. Although $\Delta AreA$ considerably impairs fumonisin biosynthesis, supplementation with 120 mM NH₄Cl restores FB₁ production and *FUM* gene expression [52]. Similarly, in *F. verticillioides*, deletion of *areA* leads to poor growth on mature maize kernels, though growth is rescued by ammonium phosphate supplementation. However, FB₁ production remains completely abolished under all tested conditions [53]. In addition, a fungal-specific gene designated *FUG1* in *F. verticillioides* encodes an uncharacterized protein required for maize kernel colonization and fumonisin biosynthesis. Transcriptomic analysis revealed downregulation of *areA* in the *FUG1* deletion strain, suggesting that *FUG1* influences fumonisin biosynthesis via the nitrogen regulator AreA [54]. However, there is little evidence to indicate that *FUG1* affects fumonisin biosynthesis by direct or indirect regulation of *AreA*.

3.2.3. pH Conditions

pH is another critical extracellular factor modulating fungal secondary metabolite production. The Pal-pH pathway and its transcription factor PacC play central roles in this process [55]. Under alkaline conditions, PacC undergoes pH-dependent PalB-mediated proteolytic cleavage—with assistance from PalA and PalC—to generate nuclear-localized PacC²⁷, which binds the 5'-GCCARG-3' DNA motif to activate alkaline-expressed genes and suppress acid-responsive genes [56]. In *A. nidulans*, *pacC*^c mutations bypass the requirement for pH signal transduction [57].

Pac1, a PACC-like gene, may function as a repressor of fumonisin biosynthesis. In *F. verticillioides*, deletion of *PAC1* increases FB₁ production and elevates *FUM1* expression under both acidic (pH 4.5) and alkaline (pH 8.4) conditions relative to the wild type [58]. Fumonisin biosynthesis is generally repressed under alkaline pH; however, this inhibitory effect can vary with culture conditions. *F. proliferatum* exhibits distinct pH-dependent

patterns: under nitrogen-limited conditions, it grows normally but produces minimal FB₁ at pH levels above 5.0, whereas at pH levels below 5.0, growth is reduced but FB₁ production substantially increases [59]. Notably, Li et al. reported that cultivation in Czapek's broth medium (CB) at pH 5 specifically inhibits fumonisin production compared with pH 10 in this species. Proteomic analysis further revealed that pH 10 upregulates enzymes such as polyketide synthase, cytochrome P450, and methyltransferases associated with fumonisin biosynthesis, whereas pH 5 elevates inhibitors such as citrate lyase, isocitrate dehydrogenase and L-amino-acid oxidase, potentially suppressing the condensation of the fumonisin backbone [60].

The pH response is modulated by nitrogen availability because the nitrogen source can influence medium pH and regulate nitrogen-responsive transcription factors. When ammonium sulfate is used as the nitrogen source, ammonia assimilation is accompanied by the release of H⁺ ions, leading to medium acidification. In *Colletotrichum gloeosporioides*, PacC represses acid-expressed genes through *AreB* [61]. However, it remains unclear whether PacC suppresses acid-expressed genes via *AreB* to regulate fumonisin production or directly binds to fumonisin biosynthetic gene promoters.

3.2.4. Light

Light response mechanisms in filamentous fungi are closely associated with the Velvet complex, which regulates secondary metabolism and developmental processes in a light-dependent manner [62]. This system has been extensively studied in *A. nidulans*, where VeA—a light-responsive global regulator—mediates transitions between sexual and asexual reproduction. In darkness, VeA translocates to the nucleus via KapA-mediated import, promoting LaeA–VelA–VelB trimer formation to activate secondary metabolism while suppressing asexual development. Conversely, light exposure retains VeA in the cytoplasm, reducing VelB/VosA levels to favor asexual reproduction and repress secondary metabolism [63]. Although this mechanism is well-characterized in *Aspergillus*, its direct application to fumonisin regulation in *Fusarium* species remains unclear.

Unlike the light-mediated repression of secondary metabolism observed in *Aspergillus*, light conditions positively influence fumonisin production compared with dark incubation in *Fusarium* species. For instance, *F. proliferatum* strains show the greatest FB₁ increases under blue light; white, red, green, and yellow light also stimulate FB₁ biosynthesis relative to dark conditions [64,65]. Similarly, *F. verticillioides* exhibits enhanced FB₁ production under yellow and green light—and other light conditions also activate FB₁ biosynthesis [65,66].

Despite these differences, Velvet-domain proteins remain central to fumonisin regulation across *Fusarium* species. In *F. verticillioides*, *FvVE1* (a VeA ortholog) is essential for fumonisin biosynthesis, given that its deletion abolishes FB₁ production by repressing the expression of *FUM21* and the structural genes within the *FUM* cluster [67,68]. Consistent with this role, *FvVelB* also contributes to fumonisin regulation, whereas *FvVelC* appears to be dispensable [69]. Similarly, in *F. fujikuroi*, the FfVel1–FfLae1 complex is required for fumonisin production. $\Delta Ffvel1$ mutants produce reduced FB₂ (2%) and undetectable FB₁. Notably, *Ffvel1* expression is strongly repressed under high-nitrogen conditions (e.g., 60 mM glutamine). Transcript levels of *Ffvel1* are comparable between the wild type and the $\Delta areA$ mutant, suggesting that *FfVel1* may partially alleviate nitrogen repression of fumonisin genes and modulate their AreA-dependent activation [70]. Although Velvet-domain proteins are conserved, the specific light-sensing mechanisms that connect Velvet complex activity to fumonisin biosynthesis remain unclear among *Fusarium* species.

3.2.5. Oxidative Stress

H₂O₂-induced oxidative stress considerably alters fumonisin production in *F. verticillioides* in a strain-dependent manner. After H₂O₂ exposure, two *F. verticillioides* isolates exhibited a substantial increase in fumonisin production (>300%), whereas three others showed a pronounced decrease (<20%) relative to control cultures. Transcriptional analysis revealed elevated expression of seven fumonisin biosynthetic genes in the high-producing strains; little to no change was observed in the low-producing strains. Additionally, the *FCC1* gene—encoding a C-type cyclin involved in signal transduction that regulates fumonisin biosynthesis and fungal development—displays differential expression patterns that are both strain-dependent and H₂O₂-responsive [71,72]. These findings suggest that *F. verticillioides* exhibits complex, strain-specific responses to oxidative stress, underscoring the importance of evaluating this variability under natural conditions.

3.2.6. Metal Ions

Metal ions, particularly iron and copper, play pivotal roles in regulating fumonisin biosynthesis in *Fusarium* species. In *F. proliferatum*, deletion of the multicopper ferroxidase gene *PpfetC*, which catalyzes the oxidation of ferrous to ferric iron, results in elevated FB₁ production and the upregulation of key *FUM* genes, including *FUM1*, *FUM2*, *FUM8*, and *FUM21*. These increases are observed across various iron concentrations, indicating that *PpfetC* negatively regulates fumonisin biosynthesis independently of environmental iron levels [73]. Similarly, in *F. fujikuroi*, deletion of the copper chaperone gene *FfCOX17* leads to substantially increased expression of *FUM2* and enhanced fumonisin production [74]. Thus far, the precise molecular mechanisms by which these proteins exert negative regulatory effects on fumonisin biosynthesis remain to be elucidated.

3.3. Cell Signaling

3.3.1. G Protein Signaling Pathway

The heterotrimeric G protein signaling pathway—comprising G α , G β , and G γ subunits—is a key component in mediating diverse eukaryotic cellular responses to environmental stimuli [75]. Upon activation by G protein-coupled receptors (GPCRs), G α dissociates from G $\beta\gamma$; these components then modulate downstream effectors such as adenylyl cyclase and mitogen-activated protein kinase (MAPK). In fungi, regulators of G protein signaling (RGS) act as GTPase-activating proteins to terminate GPCR-mediated signaling by promoting GTP hydrolysis on G α subunits [75,76].

Several key G protein subunits and RGS proteins have been shown to modulate FB₁ production. In *F. verticillioides*, the canonical G α subunit FvGpa2 modulates FB₁ levels; its deletion leads to reduced FB₁ accumulation [77]. The G β subunit-encoding genes *GBB1* and *GBB2* are also critical positive regulators of FB₁ biosynthesis. Deletion of *GBB1* drastically decreases FB₁ production and abolishes the expression of *FUM1* and *FUM8*, two key FB₁ biosynthetic cluster genes [78]. Similarly, $\Delta Fvgbb2$ mutants exhibit severe defects in FB₁ biosynthesis and downregulation of *FUM1* and other *PKS* genes, although FvGbb2 appears to act independently of canonical G protein subunits (FvGpa1, FvGpa2, FvGpa3, FvGbb1, and FvGpb1). Moreover, FvGbb2 regulates fumonisin production and the cell wall stress response independently of MAP kinase pathways, as no direct physical interactions were observed between FvGbb2 and the three MAPK cascade proteins involved in cell wall integrity (FvSlt2, FvMkk1/2, and FvBck1) [77].

The RGS proteins FlbA1, FlbA2, RgsB, and RgsC1 play distinct roles in regulating FB₁ biosynthesis. Deletion of *FvflbA2* or simultaneous deletion of *FvflbA2* and *FvflbA1* ($\Delta FvflbA2$ and $\Delta FvflbA2/A1$) results in increased FB₁ production; the $\Delta rgsB$ mutant also exhibits significantly elevated FB₁ levels relative to the wild type. In contrast, deletion of

FvflbA1 or *RgsC1* alone has no observable impact on FB₁ synthesis, suggesting that *FlbA2* and *RgsB* act as negative regulators of fumonisin biosynthesis. Furthermore, split-luciferase assays demonstrated that FvFlbA paralogs physically interact with key heterotrimeric G protein components, thereby modulating G protein—mediated signaling pathways that govern FB₁ production [79,80]. In *A. niger*, *FlbA* may also regulate fumonisin production, as the expression of *FUM21*, is significantly downregulated in the $\Delta flbA$ strain [34].

Additionally, the monomeric G-protein GBP1 inhibits FB₁ biosynthesis in *F. verticillioides*— $\Delta gbp1$ mutants accumulate higher levels of FB₁ [81]. Conversely, the Rab GTPase FvSec4 is essential for FB₁ synthesis; $\Delta Fvsec4$ mutants display reduced *FUM1* and *FUM8* expression and lower FB₁ levels, potentially due to impaired trafficking of LCP1, a secreted protein linked to FB₁ biosynthesis [82,83].

The intricate interactions among G protein subunits, RGS proteins, and effector molecules in the precise regulation of FB₁ biosynthesis remain unclear. Detailed functional characterization of these components is essential for elucidating species-specific regulatory mechanisms that underlie FB₁ production.

3.3.2. cAMP Signaling Pathway

The cAMP signaling pathway plays a critical role in fungal development, pathogenesis, and toxin biosynthesis. This pathway operates via the second messenger cAMP, which is synthesized by adenylate cyclase (AC) and degraded by phosphodiesterases. cAMP activates protein kinase A by promoting the dissociation of its regulatory subunits from the catalytic subunit (CPK1), thereby enabling phosphorylation of downstream targets [84]. However, genetic analyses in *F. verticillioides* revealed that deletion of *CPK1* or *FAC1* (encoding the catalytic subunit of protein kinase A and AC, respectively) impairs radial growth and microconidiation but does not affect FB₁ biosynthesis [85]. Similarly, in *F. proliferatum*, disruption of *Fpacy1* (an AC homolog) results in developmental defects, including reduced vegetative growth, altered conidiation, and impaired female fertility during sexual reproduction; FB₁ synthesis remains unaffected [86]. Collectively, these findings demonstrate that although cAMP signaling regulates morphological and reproductive processes in *Fusarium*, it is functionally uncoupled from FB₁ biosynthesis, highlighting distinct regulatory mechanisms that govern fungal development and secondary metabolite production.

3.3.3. MAPK Signaling Pathway

In addition to cAMP signaling, MAPKs are well-known downstream targets of trimeric G proteins. MAPK cascades are conserved in eukaryotic organisms and regulate fungal secondary metabolism through phosphorylation cascades [75]. In *Fusarium* species, distinct MAPK pathways differentially influence fumonisin biosynthesis [13,87].

In *F. verticillioides*, FvMk1, a component of the FUS3/KSS1 MAPK pathway, positively regulates FB₁ production. $\Delta Fvmk1$ mutants exhibit reduced expression of *FUM1* and *FUM8*, along with decreased FB₁ levels. FvMk1 phosphorylation depends on the G β subunit Gbb1, although residual activation in $\Delta gbb1$ mutants suggests the involvement of additional upstream regulators [88].

The cell wall integrity (CWI) MAPK pathway is also closely linked to fumonisin regulation in *F. verticillioides*. FvBCK1, a MAP kinase kinase kinase (MAPKKK) homolog, is required for both cell wall integrity and FB₁ biosynthesis; $\Delta FvBck1$ mutants exhibit impaired cell wall integrity and reduced FB₁ production [89]. Studies in *Saccharomyces cerevisiae* and *A. niger* indicate that MADS-box proteins function as targets of the protein kinase C1-regulated MAPK pathway, contributing to cell wall integrity under stress. In *F. verticillioides*, the MADS-box transcription factors Mads1 and Mads2 are also important for fumonisin biosynthesis; genetic deletion studies suggest that Mads1 broadly influences

fumonisin production, Mads2 may act downstream within the polyketide biosynthetic pathway [90]. However, the precise relationship between the CWI pathway and MADS-box proteins remains unclear.

The high-osmolarity glycerol (HOG) pathway is another well-studied MAPK module in fungi. In *F. proliferatum*, the high-osmolarity glycerol (HOG)-type MAPK Fphog1 regulates nitrogen starvation-induced FB₁ biosynthesis. $\Delta Fphog1$ mutants display increased *FUM* gene expression and elevated FB₁ accumulation under nitrogen-limiting conditions [91,92]. Conversely, in *F. verticillioides*, FvHog1 functions as a positive regulator of FB₁ production. Loss of *FvHOG1* leads to a substantial decrease in FB₁ production. Under FB₁-inducing conditions, FvHog1 undergoes phosphorylation-dependent nuclear translocation, through which it orchestrates the regulation of *FUM* gene clusters and modulates Ca²⁺ homeostasis [93]. Notably, FvAtfA, a homolog of yeast Atf1 activated by a MAPK ortholog of yeast Hog1, is essential for FB₁ biosynthesis in *F. verticillioides*. Deletion of *FvAtfA* completely abolishes FB₁ production and considerably downregulates the expression of *FUM1* and *FUM8*, whereas *FUM21* expression remains unaffected. Promoter analysis has revealed the presence of putative cAMP response element motifs—potential targets of direct regulation by AtfB—in the promoters of *FUM1* and *FUM8*, but not in *FUM21*. These findings suggest that *FvAtfA* directly regulates *FUM1* and *FUM8* via cAMP response element binding. To confirm this direct interaction, further studies such as electrophoretic mobility shift assays and chromatin immunoprecipitation sequencing are warranted [94].

Thus far, the literature indicates that MAPK pathways may function as central integrators of environmental and developmental signals in *Fusarium* secondary metabolism, with distinct subfamilies (FUS3/KSS1, CWI, HOG) exerting context-dependent regulation of FB₁ biosynthesis. Consequently, a more comprehensive understanding of the specific MAPK pathways involved in FB₁ production is needed within the broader context of fungal secondary metabolism.

3.4. RNA Polymerase II Complex

RNA polymerase II (Pol II) is essential for gene expression, and its activity is regulated by the Mediator complex—a conserved multi-subunit assembly that coordinates signals between gene-specific transcriptional activators and the basal transcription machinery, serving as both a structural scaffold and a key regulator of Pol II activity [95]. Functional analyses have shown that disruption of Mediator-related components strongly affects FB₁ production. For instance, restriction enzyme-mediated integration mutagenesis indicated that the *FCC1* gene, encoding a C-type cyclin homologous to yeast Mediator protein Ssn8, is essential for FB₁ biosynthesis [72]. FCC1 and its partner FCK1, a cyclin-dependent kinase, form the FCC1/FCK1 complex, which globally regulates gene expression. Deletion of either *FCC1* or *FCK1* reduces FB₁ levels and downregulates *FUM* genes (e.g., *FUM1*) [96]. In addition, FCC1 is required for transcription of the *FUM* genes, as well as ZFR1, a positive regulator of fumonisin biosynthesis. ZFR1 may be regulated by FCC1 and potentially interacts with FCC1 and/or its cyclin-dependent kinase partner to directly control expression of fumonisin pathway genes. Further studies are needed to elucidate this regulatory mechanism [46]. During *F. verticillioides* infection of maize kernels, Mediator subunit genes (e.g., *FvMed3*, *FvMed7*, *FvMed12*) were upregulated. However, transcriptomic comparisons between moderate and high fumonisin-producing maize lines revealed no statistically significant differences in Mediator subunit expression, implying post-transcriptional or functional regulation. Deletion of 10 Mediator subunit genes (*FvMed1*, *FvMed3*, *FvMed5*, *FvMed9*, *FvMed12*, *FvMed13*, *FvMed16*, *FvMed18*, *FvMed31*, *FvFcc1*, and *FvFck1*) led to reduced FB₁ production, indicating that they constitute positive regulators [97]. Conversely, FvMed1 functions as a negative regulator, since its deletion enhances FB₁ production

and upregulates *FUM1*. *FvMed1* influences FB₁ biosynthesis by modulating amylopectin metabolism, with mutations in its motif leading to elevated amylopectin accumulation strongly associated with increased FB₁ levels. Intriguingly, *FvMed1* demonstrated relocation from the nucleus to the cytoplasm under FB₁-inducing conditions—a novel finding in filamentous fungi—implying a role in cytoplasmic signaling pathways associated with FB₁ biosynthesis [97,98]. Nevertheless, the identities of potential cytoplasmic *FvMed1*-interacting proteins have not yet been elucidated.

3.5. Post-Translational Modification and Enzyme Activity Regulation

Post-translational modifications—essential for protein function—are tightly regulated by enzymatic processes such as methylation, acetylation, phosphorylation, and glycosylation to maintain cellular homeostasis. In fungi, histone post-translational modifications play crucial roles in modulating chromatin structure and gene expression. Genes involved in fumonisin production are epigenetically regulated through post-translational modifications [13].

3.5.1. Histone Methylation

Histone methylation plays a pivotal yet complex role in regulating fumonisin biosynthesis across *Fusarium* species; distinct mechanisms have been observed for various histone modifications and regulatory enzymes. *LaeA*, a global secondary metabolite regulator with methyltransferase activity, modulates chromatin structure to influence fumonisin production [13,99]. In *F. verticillioides*, deletion of *LEA1* (the *laeA* ortholog) reduces *FUM* gene expression but does not alter fumonisin levels, whereas the *LAE1*-complemented strain produces 50% more fumonisins than the wild type. *LaeA* might affect additional regulatory processes beyond transcription [100]. Similarly, in *F. fujikuroi*, loss of *lae1* reduces the expression of *PKS11* (fumonisin cluster-encoded polyketide synthase) under low-nitrogen conditions [101]. However, further analysis of the direct substrates of *Lae1* is required to fully elucidate the impact of histone modifications on fungal secondary metabolism.

Set-mediated histone methylation is critical for *FUM* gene activation. In *F. verticillioides*, deletion of *FvSet1* inhibits FB₁ production and consistently results in downregulation of *FUM* genes [102]. In *F. fujikuroi*, SET1 and KDM5 antagonistically regulate H3K4 trimethylation (H3K4me₃) levels. However, under low-nitrogen conditions, both $\Delta set1$ and $\Delta kdm5$ mutants exhibit downregulation of *PKS11* [103]. *FvSet2* catalyzes H3K36 trimethylation (H3K36me₃), which positively regulates fumonisin synthesis in *F. verticillioides*. Loss of the *FvSet2* gene reduces H3K36me₃ enrichment at the 3' regions of *FUM* genes, leading to diminished expression of genes such as *FvFUM1*, *FvFUM7* and *FvFUM10*, and consequently decreasing FB₁ production [104]. Set2 and Ash1 have been identified as specific methyltransferases responsible for catalyzing H3K36 methylation in *F. fujikuroi*, with each exhibiting distinct functional roles. Set2-mediated H3K36me₃ is primarily associated with transcriptional elongation, likely through its interaction with RNA polymerase II. In contrast, Ash1-deposited H3K36me₃ plays a crucial role in the repair of DNA double-strand breaks. In $\Delta set2$ and $\Delta ash1$ mutants, H3K36me₃ levels are greatly reduced. Under low-nitrogen conditions, *PKS11* expression is substantially downregulated in both mutants, highlighting the crucial role of H3K36 methylation in the regulation of fumonisin biosynthesis [105]. Additionally, Skb1 (also known as protein arginine methyltransferase 5, PRMT5), a type II arginine methyltransferase, positively regulates FB₁ production by modulating *FUM* gene expression and regulating the histone deacetylase gene *FvSirt4*. This suggests a compensatory mechanism and highlights the crucial interplay between histone methyltransferases and other epigenetic regulators in controlling secondary metabolism [106].

Conversely, FvDim5, a regulator of H3K9 trimethylation (H3K9me3), functions as a negative regulator of FB₁ biosynthesis. The $\Delta FvDim5$ strain promotes FB₁ biosynthesis and increases FvHog1 phosphorylation, suggesting that FvDim5 additionally regulates FB₁ biosynthesis via the HOG signaling pathway [91,93,107]. KMT6, the H3K27-specific histone methyltransferase, also negatively influences the expression of fumonisin biosynthetic genes. Disruption of *KMT6* in *F. fujikuroi* leads to upregulation of *PKS11* in complete medium (CM) [108]; *PKS11* genes in *F. graminearum* are enriched for H3K27me3, and the $\Delta kmt6$ strains express *PKS11* under low-nitrogen conditions [109].

Despite progress, the regulation of fumonisin biosynthetic genes by histone methylation, as well as crosstalk among various chromatin modifications, remains poorly understood. Further mechanistic studies are required to determine how these epigenetic regulators fine-tune fumonisin production in response to environmental cues.

3.5.2. Histone Acetylation

Histone acetylation, a conserved epigenetic modification mediated by histone acetyltransferases and histone deacetylases (HDACs), plays an important role in regulating fumonisin production [110]. In *F. verticillioides*, histone acetylation at the promoters of *FUM1* and *FUM21* has been reported to influence FB₁ biosynthesis [111].

Class I HDACs, such as FvHos2, HosA and FvRpd3, generally function as positive regulators of fumonisin biosynthesis. In *F. verticillioides*, the disruption of *Fvhos2* results in mutants with elevated H4K16 acetylation and significantly decreased expression of *FUM1*, *FUM8*, *FUM19*, and *FUM21*, leading to reduced FB₁ production [106]. In *A. niger*, $\Delta HosA$ mutants also exhibit diminished FB₁ and FB₂ biosynthesis [112]. Overexpression of *FvRpd3* leads to upregulation of *FUM1*, *FUM8*, and other *FUM* genes, thereby promoting increased FB₁ production [106].

Class II HDACs, including FvHda1 and HdaA, display species-dependent regulatory roles. In *F. verticillioides*, the deletion of *FvHda1* results in increased FB₁ accumulation along with *FUM1* upregulation, whereas the expression patterns of *FUM8*, *FUM19*, and *FUM21* remain unchanged. These observations suggest that *FvHda1* negatively regulates FB₁ biosynthesis, potentially through its modulatory effect on *FUM1* [106]. In contrast, deletion of *hdaA* leads to reduced production of FB₁ and FB₂ in *A. niger* [112]. Additionally, the $\Delta fvhda1$ mutant in *F. fujikuroi* displays downregulated expression of four genes within the *FUM* cluster (*FFUJ_09243*, *FFUJ_09246*, *FFUJ_09252*, *FFUJ_09254*) [113].

Class III sirtuins (FvSir2, FvHst2, FvSirt4) suppress FB₁ biosynthesis through distinct regulatory mechanisms [106]. $\Delta Fvsir2$ and $\Delta Fvhst2$ mutants exhibit increased FB₁ production; the $\Delta Fvsir2hst2$ double mutant shows a synergistic increase in FB₁ levels relative to the single mutants, indicating additive inhibitory effects of FvSir2 and FvHst2 on the FB₁ pathway. Overexpression of *FvSirt4* reduces toxin levels and significantly decreases the expression levels of *FUM1*, *FUM8*, and *FUM19*. Among these genes, only *FUM19* is strongly upregulated in the $\Delta Fvsir2$, $\Delta Fvhst2$, and $\Delta Fvsir2hst2$ mutants [106].

Compared with HDACs, studies on the impact of histone acetyltransferases on fumonisin biosynthesis are limited. In *F. fujikuroi*, the SAGA (Spt–Ada–Gcn5 acetyltransferase) complex histone acetyltransferase Gcn5 mediates acetylation of multiple histone H3 lysine residues (H3K4, H3K9, H3K18, and H3K27). Disruption of *GCN5* downregulates *FUM1* expression, indicating its influence on fumonisin biosynthesis [114]. Further investigation into the underlying acetylation mechanisms, as well as the interplay among various HDACs and histone acetyltransferases, will provide deeper insights into their regulatory roles concerning fungal secondary metabolism.

3.5.3. Phosphorylation Modification

Phosphorylation, a dynamic post-translational modification regulated by kinases and phosphatases, involves protein phosphatase type 2A (PP2A)—a heterotrimeric complex composed of structural (A), catalytic (C), and regulatory (B) subunits—which plays a central role in cellular signaling and toxin production [115]. In *F. verticillioides*, the PP2A catalytic subunit CPP1 represses FB₁ biosynthesis: $\Delta cpp1$ mutants show increased *FUM1* expression and FB₁ production, whereas complementation with *CPP1* restores the wild-type phenotype [116]. Functional studies further suggest that CPP1 functions upstream of the FvMk1 pathway, possibly by dephosphorylating FvMk1 or its downstream targets. This may explain the opposing regulatory roles of CPP1 and FvMK1 in fumonisin biosynthesis [88]. Among regulatory B subunits, PPR1 and PPR2 have opposing effects: deletion of *PPR2* enhances FB₁ production, whereas $\Delta ppr1$ mutants display reduced toxin levels. Importantly, PPR1 and PPR2 display distinct subcellular localizations, suggesting that PP2A-mediated regulation of FB₁ biosynthesis may involve spatially segregated signaling mechanisms [117]. Further investigation into the molecular mechanisms linking PP2A subunits to FB₁ biosynthesis, including substrate specificities, will enhance our understanding of the role of PP2A in fungal secondary metabolism.

3.5.4. Glycosylation Modification

Glycosylation, catalyzed by glycosyltransferases (GTs), is another important post-translational modification that influences protein function and stability. In *F. verticillioides*, family 2 glycosyltransferase FvCpsA negatively regulates FB₁ production by repressing *FUM1*, *FUM8*, and *FUM13* expression. Targeted deletion of *FvCpsA* results in strongly elevated FB₁ production and upregulated expression of these *FUM* genes, whereas complementation restores the wild-type phenotype [118]. Additionally, FvCpsA affects the expression of upstream global regulators *veA* and *laeA*, both of which mediate chromatin remodeling of secondary metabolite gene clusters [119]. However, whether *FvCpsA* regulates fumonisin production directly or indirectly through *veA* and *laeA* remains unresolved.

3.6. Cellular Structure and Functional Components

Fumonisin biosynthesis is also tightly regulated by diverse cellular structural and functional components, including organelles, cytoskeletal elements, and membrane-associated proteins. Vacuolar dynamics and associated proteins are critical for FB₁ production. The vacuole and mitochondria patch (FvCLAMP) complex, particularly FvVam6, regulates vacuole morphology and FB₁ biosynthesis [120]. Other vacuole-associated proteins, such as FvRab7, FvVam7, and microtubule components Fv α 2, Fv β 1, and Fv β 2, positively regulate *FUM1* expression and enzyme trafficking, whereas Fv α 1 functions as a negative regulator [29]. The ergosterol-binding protein FvOSHC—essential for FB₁ production—regulates lipid metabolism and vesicle trafficking via interaction with FvSec14 [121]. Peroxisomes also play a key role in FB₁ production. Peroxisomal components of the docking/translocation module (DTM), including FvPex8, FvPex7, and FvPex20, are indispensable for fumonisin biosynthesis; deletion of these genes drastically reduces FB₁ levels and *FUM* gene expression [122,123]. Additionally, Fv_Tan2, an NADPH sensor, may regulate FB₁ biosynthesis by maintaining mitochondrial reactive oxygen species homeostasis [124]. The autophagy-related proteins FvAtg4 and FvAtg8 promote FB₁ biosynthesis by regulating intracellular alanine levels. Supplementation with exogenous alanine can rescue the reduced FB₁ production in their deletion mutants [125]. Other structural regulators include the secreted LysM protein FvLCP1, which is required for FB₁ biosynthesis, with the LysM domain playing a critical role [83]. The oxylipin-producing enzyme FvLDS1 negatively regulates FB₁ synthesis through chromatin modification— $\Delta Fvlds1$ mutants show increased FB₁ production and

FUM1 expression, along with hyperacetylation of histone H4 at the *FUM1* promoter [126]. Additionally, the transmembrane protein FvTTP, essential for FB₁ biosynthesis, is subject to post-transcriptional regulation by maize-derived miR528b-5p [127].

3.7. Other Regulators

Fumonisin biosynthesis is regulated by multiple molecular pathways, and in addition to the factors discussed above, several additional regulatory elements have been identified. SGE1, a homolog of morphological switch regulators, is essential for FB₁ production in both *F. verticillioides* and *F. fujikuroi*, functioning as a positive regulator of *FUM* gene expression [51,128]. The GATA-type transcription factor Csm1 regulates *PKS11* expression in a nitrogen- and pH-dependent manner [129]. In *F. verticillioides*, the cutinase transcription factor FvCtf1 α binds directly to the promoters of several key *FUM* genes (*FUM1*, *FUM2*, *FUM6*, *FUM14*, and *FUM16*), thereby promoting FB₁ biosynthesis [130]. The HAP complex has also emerged as an important regulatory factor. One of its components has been identified as a potential interaction partner of multiple MAPK genes, and the subunit HAP3 enhances the expression of *FUM1* and *FUM21*, likely through direct interaction with the *FUM21* promoter. These findings suggest that the HAP complex may influence fumonisin production either by directly modulating MAPK signaling through upstream environmental sensors or by functioning as a downstream activator or repressor within MAPK-mediated signal transduction [131]. Additionally, the WW domain-containing protein FvSO facilitates FB₁ production, potentially through interactions with intracellular signaling proteins [132]. Interestingly, the APSES-class transcription factor StuA positively regulates *FvSO*, while promoting the expression of *FUM6*, *HAP3*, and *MADS2*, as well as FB₁ biosynthesis [133]. However, the precise regulatory mechanisms underlying these interactions remain to be elucidated.

4. Applications

4.1. Species-Specific Markers

Molecular tools based on conserved genes—such as *TEF-1 α* , *TUB2*, and *ITS*—are widely used for *Fusarium* species identification. However, in low-diversity populations, mycotoxin biosynthetic genes such as *FUM* genes often exhibit higher sequence variability and can serve as more effective markers for distinguishing *Fusarium* strains at sub-specific or host-specific levels [134,135]. Stępień et al. analyzed partial *FUM1* sequences from 36 isolates collected from diverse hosts and demonstrated that *FUM1*-based phylogenies provided superior resolution of host-related groupings compared with *TEF-1 α* [136]. Isolates from tropical and subtropical hosts (e.g., pineapple, date palm) formed a distinct, well-supported clade. Phylogenetic trees based on *FUM1* and *FUM8* sequences further differentiated *Fusarium* species such as *F. nygamai*, *F. proliferatum*, *F. subglutinans*, *F. verticillioides*, and *F. fujikuroi*, underscoring their utility in species classification [135]. However, high sequence divergence within the *FUM* cluster can complicate primer design; for instance, markers such as *FUM2* and *FUM21* often fail to amplify across diverse isolates. Additionally, variability in intergenic spacer regions (e.g., *FUM6*–*FUM7* and *FUM7*–*FUM8*) has also led to inconsistent phylogenetic placements of *F. nygamai*, suggesting evolutionary divergence and potential trans-species polymorphism, similar to that observed in *TRI* clusters [135,137]. Furthermore, Proctor et al. reported discordance between phylogenies constructed from primary metabolism genes and those based on *FUM* cluster genes, supporting the hypothesis that the *FUM* cluster and the evolution of *Fusarium* may have distinct evolutionary histories [138]. Collectively, these findings highlight the need for expanded molecular marker development and comprehensive genomic studies to improve the identification and classification of *Fusarium* species.

4.2. Predicting the Fumonisin Production

Markers based on mycotoxin biosynthetic genes—particularly the *FUM* gene cluster—are valuable tools for diagnosing the fumonisin production potential of fungal species. DNA-based strategies, primarily polymerase chain reaction (PCR)–based assays, have been developed to provide sensitive, specific, and robust methods for distinguishing between fumonisin-producing and non-producing strains [139]. For example, a PCR assay using *FUM1*-derived primers demonstrated high specificity for *F. verticillioides* and partial detection of *F. proliferatum*, showing promise for fumonisin diagnostics [140]. However, in pea-derived *F. proliferatum* and *F. verticillioides* strains, differences in B-series fumonisin production cannot be attributed solely to sequence variations in core *FUM* genes [141]. Similarly, an analysis of 90 *F. verticillioides* strains isolated from maize in five Mediterranean countries (Italy, Spain, Tunisia, Egypt, and Iran) found that 80% of the strains produced fumonisins in vitro, with levels ranging from 0.03 to 69.84 µg/g. Despite considerable variation in fumonisin levels both within and between regions, sequencing of *FUM1* and the intergenic regions between *FUM6*–*FUM7* and *FUM7*–*FUM8* revealed high genetic uniformity across populations. Neither geographic origin nor fumonisin production capacity was correlated with genetic diversity [134]. Consistent with these findings, Susca et al. reported conservation of the *FUM* cluster genomic context in *A. niger* and *A. welwitschiae* isolates from Mediterranean grapes, regardless of their ability to produce fumonisins [2]. These findings suggest that variability in fumonisin production is not driven solely by structural differences in essential *FUM* genes but may also involve differential regulatory mechanisms affecting their expression.

Correlations between fumonisin production and the expression of *FUM* biosynthetic genes have been widely studied, and quantitative reverse transcription–PCR is recognized as a valuable tool for assessing the toxigenic potential of *Fusarium* species [142]. Strong associations have been identified between specific *FUM* genes and B-series fumonisin production. For instance, López-Errasquín et al. demonstrated linear correlations of *FUM1* and *FUM19* transcript levels with FB₁ production in *F. verticillioides* cultures incubated at 20 °C for 14 days [143]. Similarly, Jurado et al. reported a significant positive correlation ($r = 0.77$) between *FUM1* expression and FB₁ production in *F. proliferatum* culture filtrates after 7 days [144]. However, these correlations are often observed only under specific environmental conditions or within certain parameter ranges. Inconsistencies have been documented between *FUM* gene expression and mycotoxin production. For example, Cendoya et al. reported that *FUM8* and *FUM19* expression levels at 25 °C were correlated with B-series fumonisin production regardless of water activity (*aw*). However, at 15 °C, these genes showed high expression despite minimal fumonisin accumulation [145]. Furthermore, Fanelli et al. observed that *FUM1* and *FUM21* expression levels peaked at 15 °C in *F. verticillioides*, but optimal fumonisin production occurred at 30 °C [146]. Lilly et al. analyzed *F. verticillioides* MRC 826 isolates and found that the combined expression of *FUM1*, *FUM6*, *FUM8*, and *FUM21* was negatively associated with fumonisin production over 28 days at 25 °C. Gene expression peaked on day 7, whereas fumonisin levels were lowest at that time and highest between days 14 and 21 [147]. These discrepancies, influenced by environmental factors, species-specific variability, and post-transcriptional regulation, underscore the limitations and risks of solely relying on *FUM* gene expression as a surrogate marker for fumonisin production.

4.3. Management of Fumonisin Contamination

Biotechnological approaches have emerged as pivotal tools for managing fungal diseases and mitigating mycotoxin contamination in food systems. Substantial progress in understanding fumonisin biosynthetic pathways has facilitated the development of inno-

vative strategies, particularly through genetic engineering aimed at regulating fumonisin production [8]. Johnson et al. demonstrated the use of *FUM1* segments to generate double-stranded RNA (dsRNA) in *F. verticillioides*, resulting in transformants with substantially reduced *FUM1* expression and FB₁ production—ranging from a 24-fold to a 3675-fold decrease. A similar dsRNA-based approach targeting *FUM8* reduced fumonisin production by 3.5-fold to 2240-fold [148]. Additionally, Qu et al. identified the maize-derived microRNA miR528b-5p, which targets the *FvTTP* mRNA encoding a transmembrane protein in *F. verticillioides*. miR528b-5p suppresses *FvTTP* expression, thereby inhibiting *F. verticillioides* infection and reducing fumonisin production [127]. These findings support the development of transgenic crops employing RNA interference-mediated host-induced gene silencing (HIGS) to overexpress dsRNAs targeting key fungal genes, resulting in reduced fumonisin production [8,149]. The development of dsRNA- and siRNA-based RNA fungicides offers an additional, environmentally friendly strategy for controlling mycotoxin production in both field crops and stored grains. Targeting essential fumonisin biosynthesis genes such as *FUM1*, *FUM8*, and *FvTTP* with RNA fungicides offers a promising approach for reducing fumonisin contamination [150]. CRISPR-Cas genome-editing systems also provide a powerful platform for mycotoxin control, enabling deletion of entire fumonisin BGCs rather than silencing individual genes. This approach could lead to the development of non-toxicogenic *Fusarium* strains that outcompete fumonisin-producing strains, potentially eliminating fumonisin production altogether [12,151]. Finally, the identification of additional fumonisin-regulating genes—such as *FvNth*, *VE1*, *FvOshC*, and *HXK1*—offers novel molecular targets for the development of mycotoxin control agents. These biotechnological advances lay the foundation for innovative strategies to mitigate fumonisin contamination in crops, addressing both pre-harvest and post-harvest challenges in food and feed systems.

The development of small-molecule inhibitors is another rapidly advancing field in chemical biology, offering powerful tools to modulate complex biological systems. These compounds have been used in diverse applications, such as altering host metabolism by targeting microbial enzymes (e.g., choline trimethylamine lyase) [152] and inhibiting the Wnt signaling pathway—a key regulator of development and homeostasis—through small-molecule inhibitors of Notum [153]. Targeting epigenetic protein–protein interactions—particularly reader domains and scaffolding proteins—has also emerged as a promising approach for disease treatment, especially in oncology [154]. The well-characterized regulatory networks controlling mycotoxin biosynthesis, including those governing fumonisin production, present valuable targets for small-molecule intervention. Using structure-based virtual screening, Zhao et al. identified xanthatin, a selective natural inhibitor of *FvOshC*, which effectively suppressed *F. verticillioides* growth and FB₁ production, demonstrating strong potential for antifungal and mycotoxin control [121]. Collectively, small-molecule inhibitors targeting biosynthetic enzymes, signaling molecules, or histone-modifying enzymes offer innovative and effective strategies to reduce toxin production, advancing mycotoxin management in agriculture and food safety.

4.4. Engineering High-Yield Fumonisin-Producing Strains

The high toxicity and widespread occurrence of fumonisins have fueled intensive research into their toxicology, metabolism, and risk assessment. To meet the growing demand for high-purity fumonisins, efforts have focused on developing reliable toxin-producing strains and establishing efficient methods for toxin isolation and purification [155]. Strain improvement is crucial for industrial applications; however, the limited efficiency of conventional genetic tools has hindered strain optimization for enhanced and targeted fumonisin production. Recent advances in understanding the biosynthetic genes and regulatory mechanisms of fumonisin synthesis have opened new avenues for production enhance-

ment through genetic engineering [156]. For example, the deletion of *LDS1* significantly increased B-series fumonisin production ($\text{FB}_1 + \text{FB}_2 + \text{FB}_3$) in maize ears, with $\Delta lds1$ mutants producing 5828 ± 458 ppb at 15 days post-inoculation, compared with 867 ± 96 ppb in the wild type. The $\Delta lds1$ mutant also exhibited faster growth (1.85-fold), higher conidial production (1.5-fold), and improved germination rates (1.3-fold) relative to the wild type [126]. Similarly, deletion of *FvZBD1* led to dramatic increases in fumonisin levels. The $\Delta FvZBD1$ mutants produced over 9 mg/mL of FB_1 per gram of fungal tissue in GYAM liquid cultures—more than 30-fold higher than the wild-type strain ($284.4 \mu\text{g/mL/g}$)—along with approximately 40-fold higher FB_2 production and substantially increased FB_3 levels. These mutants also displayed more uniform colony morphology [39]. Overexpression of *FUM3*, a key enzyme that converts FB_3 to FB_1 , further enhanced FB_1 production [33]. However, not all genetic modifications have yielded beneficial outcomes. Deletions of genes such as *Fphog1*, *FvMed1*, *PPR2*, and *FvCpsA* increased fumonisin production but negatively affected fungal growth and sporulation [91,92,97,98,117,118]. To date, most genetic engineering efforts have focused on gibberellin biosynthesis, with comparatively fewer studies targeting fumonisin production [157]. For effective strain optimization, it is crucial to enhance the fumonisin biosynthetic pathway while eliminating redundant genes related to pathogenicity and secondary metabolism that impose metabolic burdens. Furthermore, a deeper understanding of upstream regulatory networks—particularly global regulators linked to nutrient sensing and signaling—could reveal novel targets for boosting fumonisin synthesis. Technological advancements in protoplast preparation, DNA transformation protocols, CRISPR-Cas systems, and the expansion of promoter and selection marker toolkits have significantly improved the feasibility of genetic manipulation in *Fusarium* species [156,157]. Nevertheless, fully optimizing strain engineering remains challenging, particularly in deciphering the complex regulatory networks governing fumonisin biosynthesis.

4.5. Novel Metabolite Discovery

Secondary metabolite production is tightly regulated by hierarchical networks in which core factors orchestrate the transcriptional activation of secondary metabolite BGCs. Genetic manipulation—such as overexpression of pathway-specific regulators or disruption of epigenetic repression—can derepress silent or weakly expressed BGCs, thereby unlocking cryptic natural products. This approach, which leverages pathway-specific transcription factors, global regulators, or chromatin-modifying proteins, has proven highly effective for activating cryptic metabolic pathways under laboratory conditions, circumventing the limitations of conventional co-culture methods [15]. For instance, overexpression of the in-cluster pathway-specific regulator *apdR* (a $\text{Zn(II)}_2\text{Cys}_6$ protein) in *A. nidulans* activated the *apd* BGC, leading to the discovery of the novel pyridone alkaloids aspyridones A and B [158]. Similarly, in *A. niger*, overexpression of *azaR*—another $\text{Zn(II)}_2\text{Cys}_6$ regulator within a dual *PKS* gene cluster—identified six new azaphilone compounds [159]. To date, approximately 30 new secondary metabolites have been identified through such pathway-specific regulator overexpression strategies [15]. In the fumonisin pathway, key regulators include *Fum21* and *ZBD1*, although their potential in driving novel metabolite production has not been fully explored. Global regulators and epigenetic modifiers also play pivotal roles. The conserved fungal global regulator *LaeA* modulates heterochromatin structure to influence multiple secondary metabolite BGCs. Overexpression of *LaeA* in *Chaetomium globosum* up-regulated the chaetoglobosin gene cluster, producing a new analogue (chaetoglobosin Z 31) along with six known analogues (chaetoglobosins A, B, D, E, O, and V) [160]. Epigenetic regulation via histone-modifying enzymes has further expanded secondary metabolite discovery. For example, inactivation of the HDAC *hdaA* in *Calcarisporium arbuscula* produced

novel peptides and diterpenes [161], whereas downregulation of *rpdA* (another HDAC) in *A. nidulans* selectively induced two new lipopeptides (aspercryptin A1/A2) [162]. Knock-down of the methyltransferase gene *Kmt6*, which influences fumonisin synthesis in *F. fujikuroi*, decreased H3K27me3 levels, leading to activation of cryptic secondary metabolite gene clusters and accumulation of novel compounds, including a previously unidentified sesquiterpene derived from the STC5 product [108]. Leveraging the well-characterized fumonisin gene network, together with deeper insights into its global and epigenetic regulation, presents a promising route for the systematic activation of silent natural product pathways. This approach holds great potential for expanding fungal metabolic diversity and enabling the discovery of novel bioactive compounds for drug development.

4.6. Enzyme Engineering

Enzyme engineering has been widely utilized across biotechnology, pharmaceuticals, agriculture, and detergent industries. Microbial enzymes—particularly those involved in metabolic synthesis and hydrolysis—are promising targets for biocatalyst development, as they can be engineered to enhance stability, broaden substrate specificity, improve catalytic efficiency, or enable novel biochemical reactions [163]. Cytochrome P450 enzymes, ubiquitous in organisms ranging from fungi and bacteria to plants, have shown potential in bioremediation [164]. For example, Harford-Cross et al. engineered a cytochrome P450 mutant with high NADH turnover, greatly enhancing the degradation of polycyclic aromatic hydrocarbons such as phenanthrene and benzo[a]pyrene [165]. Within the fumonisin biosynthetic pathway, *FUM6* encodes a cytochrome P450 monooxygenase and NADPH-dependent reductase that catalyzes the hydroxylation of C-14 and C-15 of fumonisin and has potential as a biocatalyst for detoxifying contaminated food and feed—offering an environmentally friendly alternative to conventional detoxification methods. Similarly, ketoreductases—such as those derived from *Lactobacillus kefir*—have been modified for industrial use in reducing ketone intermediates to chiral alcohols, a critical step in synthesizing pharmaceutical compounds like atorvastatin and duloxetine [166]. Fum13, a short-chain dehydrogenase/reductase in the fumonisin biosynthetic pathway, catalyzes the reduction of the C-3 ketone to a hydroxyl group and could be repurposed for ketoreductase-based applications, including the synthesis of pharmaceutical intermediates. Although fumonisin-related enzymes are typically linked to mycotoxin production, targeted enzyme engineering could reprogram them for innovative applications in industrial biocatalysis and synthetic biology.

5. Conclusions and Perspectives

Global climate change and the increasing frequency of extreme weather events have heightened the threat posed by fumonisins and increased the unpredictability of contamination. Therefore, elucidating the biosynthetic and regulatory mechanisms of fumonisin production—and identifying key core regulatory factors—is crucial for accurate detection, early warning, and effective prevention and control. Over recent decades, genetic, analytical chemistry, and biochemical studies have substantially advanced our understanding of fumonisin biosynthesis. It is now widely recognized that fumonisin production is governed by a complex, multilayered regulatory network (Figure 3) [13], encompassing cluster-specific regulators, signal transduction pathways, organelle-level processes, post-translational modifications, metabolic regulation, and environmental cues. However, the extensive crosstalk among these regulatory layers presents considerable challenges in identifying core regulatory elements and elucidating their dynamic interactions.

The advent of high-throughput technologies has enabled comprehensive molecular profiling across multiple omics layers, including genomics, transcriptomics, proteomics,

metabolomics, epigenomics, and single-cell omics. Integrative multi-omics approaches provide a powerful systems-level framework for unraveling the complex regulation of fumonisin biosynthesis. Yet, the integration and interpretation of multi-omics data remain challenging due to data heterogeneity, inconsistent formats and identifiers, and the high computational demands of large-scale analysis [167]. Additional obstacles include limited biological interpretability, insufficient functional validation, and a lack of user-friendly analytical platforms, all of which hinder the translation of research findings into practical applications.

To address these limitations, future research should prioritize the integration of multi-omics data with artificial intelligence technologies [167]. Machine learning, deep learning, and neural network approaches—suitable for analyses of high-dimensional and complex datasets—can accelerate the identification of regulatory biomarkers [168], uncover novel intervention targets [169], and improve microbial production efficiency [170]. Looking ahead, advances in multi-omics integration, artificial intelligence technologies, and robust functional validation hold great promise for decoding intricate regulatory networks, enabling the development of early-warning systems, fostering innovative biotechnological tools for fumonisin control, and broadening the potential applications of these processes.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/microbiolres17010004/s1>, Table S1: List of the current insights into fumonisin synthesis and regulatory genes.

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