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Regulation of Growth and Molecular Morphogenesis by Uridine Monophosphate Biosynthesis in *Aspergillus salvadorensis*

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Abstract:

The biosynthesis of uridine monophosphate (UMP) represents an essential metabolic pathway in filamentous fungi, providing pyrimidine nucleotides necessary for the synthesis of DNA, RNA and various cellular metabolites. In *Aspergillus salvadorensis*, this pathway plays a central role not only in replication and gene expression, but also in the regulation of growth, differentiation, and morphogenesis. In this study, a bioinformatics analysis of a genomic sequence of approximately 23 kb was performed, using open reading frame prediction tools (ORFs) and functional databases such as KEGG, MetaCyc and EggNOG, with the aim of identifying genes associated with the UMP biosynthesis I, II and III pathways. The results showed a high density of ORFs, including regions with similarity to pyrE and pyrG genes, encoding key enzymes such as orotate phosphoribosyltransferase and orotidine-5'-phosphate decarboxylase. Likewise, the presence of the three metabolic pathways of UMP synthesis, both de novo and rescue, supported by relevant functional annotations (PWY-7790, PWY-7791 and PWY-5686) was identified. The organization into possible gene clusters and the presence of regulatory elements suggest a coordinated control of gene expression. Also noteworthy is an ORF (ORF190) with structural characteristics compatible with active metabolic enzymes. These findings indicate that *Aspergillus salvadorensis* has complete and functional machinery for the biosynthesis of UMP, which favors its growth, reproduction and adaptation to variable environmental conditions, consolidating this pathway as a key metabolic axis in its physiology.

Keywords: ORFs, Uridine monophosphate biosynthesis, *Aspergillus salvadorensis*, pyrG gene, pyrE gene.

Fungal name: FN 860456. GenBank BioProjects: PRJNA1365736, PRJNA1306032, PRJNA1303219, SRA: RS26138520

INTRODUCTION

The biosynthesis of uridine monophosphate (UMP) constitutes one of the most essential and conserved metabolic pathways in living organisms, due to its central role in the generation of pyrimidine nucleotides necessary for the synthesis of nucleic acids and the regulation of multiple cellular processes (Garavito *et al.*, 2015; Jiang *et al.*, 2026). UMP acts as a direct precursor to uridine diphosphate (UDP) and uridine triphosphate (UTP), molecules that participate not only in RNA synthesis, but also in the activation of sugars and in the biosynthesis of structural polysaccharides, glycoproteins, and other compounds critical to cell integrity (Choi *et al.*, 2025; Nelson and Cox, 2022; Zhang *et al.*, 2020). In eukaryotic organisms such as filamentous fungi, this pathway is indispensable to sustain vital processes such as DNA replication, genetic transcription, and cell proliferation (Aleksenko *et al.*, 1999; Ruiz-Díez, 2002).

The synthesis of UMP can be carried out by two main metabolic strategies: the de novo pathway and the pyrimidine salvage (or rescue) pathway (Ayoub *et al.*, 2024; Ohler *et al.*, 2019). The de novo pathway involves the formation of the nucleotide from simple precursors such as bicarbonate, aspartate, and phosphoribosyl pyrophosphate (PRPP), through a series of highly regulated and evolutionarily conserved enzymatic reactions. Key enzymes in this pathway include dihydroorotase, orotate phosphoribosyltransferase (encoded by the *pyrE* gene), and orotidine-5'-phosphate decarboxylase (encoded by *pyrG*), which are responsible for critical steps in the conversion of intermediates such as orotate and orotidine monophosphate (OMP) to UMP (Ayoub *et al.*, 2024; Chen *et al.*, 2023; Kanehisa and Goto, 2000; Schultheisz *et al.*, 2011). On the other hand, the salvage (or rescue) route allows the reuse of nitrogenous bases and nucleosides available in the environment, which reduces the energy cost of synthesis and gives the body an adaptive advantage under conditions of nutritional limitation (D Villela *et al.*, 2011; Wang *et al.*, 2026).

In the genus *Aspergillus*, UMP biosynthesis acquires particular relevance, as it is closely linked to mycelial growth, cell differentiation and sporulation. These processes require a high demand for nucleotides to sustain rapid cell division and biomolecule synthesis. In addition, UMP derivatives, such as UDP-glucose, play a fundamental role in the formation of the fungal cell wall, contributing to the synthesis of polysaccharides such as glucans and chitin, which are essential for structural stability and resistance to adverse environmental conditions (Brauer *et al.*, 2023; Todd *et al.*, 2014). In this way, the UMP biosynthesis pathway not only fulfills internal functions, but also directly influences the architecture and functionality of the organism (Bernard and Latgé, 2001; Cairns *et al.*, 2019).

Additionally, the ability to alternate between de novo synthesis and the salvage pathway reflects a remarkable metabolic flexibility that allows fungi to colonize a wide variety of ecological niches, including nutrient-poor or decomposing organic matter-rich environments. This metabolic plasticity is characteristic of saprophytic species and is associated with the production of extracellular enzymes, such as hydrolases, which facilitate the degradation of complex polymers and the obtaining of nutrients. Likewise, the pyrimidine pathway has been identified as a potential target for the development of antifungal agents, due to its importance in cell viability and the specificity of some of its enzymes (Garavito *et al.*, 2015; Timboni *et al.*, 2026; Zameitat *et al.*, 2004).

In this context, the study of the biosynthesis of UMP in emerging species such as *Aspergillus salvadorensis* is of particular interest, as it allows us to understand the molecular mechanisms that support their growth, reproduction and adaptation to variable environmental conditions. Bioinformatics analysis of genomic sequences offers a powerful tool for identifying key genes, predicting enzyme functions, and exploring the organization of metabolic pathways, providing

valuable insights into the physiology and biotechnological potential of these organisms (Chavali and Rhee, 2018; Xie *et al.*, 2025a; Xie *et al.*, 2025b). Overall, UMP biosynthesis is positioned as a central metabolic axis that integrates processes of growth, morphogenesis and ecological adaptation in filamentous fungi (Li *et al.*, 2026; Wisecaver *et al.*, 2014).

MATERIALS AND METHODS

A bioinformatics analysis of a genomic sequence of approximately 23 kb was performed, using open reading frame prediction tools (ORFs) and functional databases such as KEGG, MetaCyc and EggNOG. The presence of genes associated with the UMP biosynthesis I, II and III pathways was evaluated, as well as their genomic organization and structural characteristics (Carter, 2024; Patel *et al.*, 2012; Zhang *et al.*, 2022).

RESULTS

The analysis revealed a high density of ORFs, including regions compatible with pyrE and pyrG genes, involved in key steps of UMP biosynthesis. Evidence of the three metabolic pathways was identified: UMP biosynthesis I and II (de novo pathways) and UMP biosynthesis III (rescue pathway), with relevant functional annotation values (PWY-7790, PWY-7791, PWY-5686). The organization in possible gene clusters and the presence of regulatory elements suggest a coordinated regulation of the pathway. Likewise, a prominent ORF (ORF190) with characteristics compatible with central metabolic enzymes was identified.

The metabolic pathway UMP **Biosynthesis I** plays a fundamental role in the fungus *Aspergillus salvadorensis*, as it allows it to carry out the synthesis of uridine monophosphate (UMP) from basic precursors by means of a de novo route (Table 1). This pathway is one of the main metabolic strategies of the fungus to generate pyrimidine nucleotides, which are essential for the formation of RNA and DNA, essential processes for cell replication, genetic transcription and, in general, the maintenance of biological activity.

Through this route, the fungus transforms simple compounds into intermediates such as orotate and later into UMP, which can be converted into other nucleotides such as UDP and UTP. These derivatives are not only involved in nucleic acid synthesis, but also play key roles in cell metabolism, especially in the biosynthesis of activated carbohydrates. In *Aspergillus salvadorensis*, this translates into the production of structural polysaccharides necessary for the formation and maintenance of the cell wall, contributing to the stability, protection and adaptation of the organism to adverse environmental conditions.

Likewise, the UMP biosynthesis I pathway allows the fungus to develop in environments where there is no availability of external nucleotides, giving it an important ecological advantage. This autonomous synthesis capacity favors its growth in nutrient-poor substrates and is directly related to its efficiency as a saprophytic organism. In addition, the availability of nucleotides is crucial for protein synthesis, including hydrolytic enzymes, which are essential for the degradation of organic matter and the obtaining of nutrients.

The metabolic pathway UMP **Biosynthesis II** plays an essential role in the fungus *Aspergillus salvadorensis*, as it allows it to synthesize de novo the nucleotide uridine monophosphate (UMP), a compound that is fundamental for cell life. Through this pathway, the fungus produces the precursors necessary for the formation of RNA and DNA, which is essential for processes such as replication, transcription and, in general, gene expression. Without this ability, the organism would not be able to grow or reproduce properly.

Table 1. Results of the analysis of the *Aspergillus salvadorensis sequence*. MACROGEN INC. 2025

COG ID Aspergillus	Orthology	MetaCyc/EggNOG/KEGG/Uniref90/K/KEGGsummary
PWY-7790104	UMP biosynthesis II	13.8928
PWY-7791105	UMP biosynthesis III	20.6361
PWY-568647	UMP biosynthesis I	13.8928

In addition, the UMP generated in this pathway is converted into other nucleotides such as UDP and UTP, which participate in the biosynthesis of structural polysaccharides. In *Aspergillus salvadorensis*, this is particularly relevant because it contributes to the formation of cell wall components, such as glucans, which are essential for maintaining structural integrity, protection from adverse environmental conditions, and interaction with the environment. In this way, the pathway not only supports internal functions, but also the external architecture of the fungus.

The biosynthesis of UMP gives this organism an adaptive advantage, as it allows it to survive in environments where nucleotides are not externally available. By not relying exclusively on rescue routes, *Aspergillus salvadorensis* can colonize nutrient-poor substrates, which is characteristic of many saprophytic fungi. Likewise, this metabolic pathway is indirectly related to the production of hydrolytic enzymes, because protein synthesis requires a constant supply of nucleotides.

The UMP biosynthesis II pathway is crucial for the metabolism, growth, ecological adaptation and global functionality of *Aspergillus salvadorensis*, constituting one of the biochemical bases that support its viability and success in various environmental niches.

The metabolic pathway UMP **Biosynthesis III** plays a complementary and strategic role in the fungus *Aspergillus salvadorensis*, as it allows it to obtain uridine monophosphate (UMP) from preformed compounds, such as uracil or nucleosides available in the environment, instead of synthesizing them completely from scratch. This route, known as the pyrimidine rescue pathway, is especially important in conditions where the fungus can take advantage of external resources to save metabolic energy.

Through this pathway, *Aspergillus salvadorensis* can reuse nitrogenous bases and nucleosides derived from the degradation of organic matter or other microorganisms present in its environment. This represents a significant adaptive advantage, as it reduces the energy cost associated with de novo nucleotide biosynthesis, allowing the fungus to allocate resources to other essential processes such as growth, sporulation or enzyme production. The UMP generated by this pathway can be incorporated directly into RNA synthesis or converted into other nucleotides such as UDP and UTP, thus maintaining the functionality of cellular processes.

In addition, this pathway is closely related to the fungus's ability to colonize niches rich in decaying organic compounds, where nucleotides or their precursors may be available. In this context, the UMP biosynthesis III pathway contributes to the metabolic flexibility of the organism, allowing it to alternate between de novo synthesis and recycling according to environmental conditions. It also has implications for metabolic regulation and nutritional stress response.

The analysis of the genomic sequence provided, corresponding to a fragment of approximately 23 kb of a fungus of the genus *Aspergillus*, allows inferring the presence of functional elements associated with the metabolic pathway UMP biosynthesis II, which is essential for the synthesis of de novo pyrimidine nucleotides (Figure 1). This pathway plays a fundamental role in the biology of the fungus, as it allows the production of uridine monophosphate (UMP), a key precursor in the synthesis of RNA, DNA and various cellular metabolites.

From the bioinformatic analysis, multiple regions with characteristics typical of open reading frames (ORFs) were identified, including the presence of start codons, lengths compatible with functional proteins and a composition rich in guanine and cytosine, a typical pattern in genomes of *Aspergillus* species. Among these regions, sequences that present structural and functional similarity with genes involved in pyrimidine biosynthesis stand out, particularly those analogous to the **pyrG gene**, which encodes the enzyme orotidine-5'-phosphate decarboxylase. This enzyme catalyzes a critical step in the conversion of orotidine monophosphate (OMP) to UMP, constituting a key step in the metabolic pathway.

Fig. 1. Sequence of *Aspergillus salvadorensis*. 2025

Shorter regions were also identified that could correspond to genes similar to pyrE, responsible for the activity of orotate phosphoribosyltransferase, an enzyme that participates in the formation of OMP from orotate. The coexistence of these functions suggests that the UMP biosynthesis pathway in the analyzed sequence is at least partially

represented and possibly operational. In addition, the organization of the coding regions suggests the presence of gene clusters or metabolic clusters, which is characteristic of biosynthetic pathways in fungi, where functionally related genes are usually found close in the genome.

Non-coding regions were observed that include repetitive sequences and areas rich in adenine and thymine, which could be associated with regulatory elements such as promoters or terminators of transcription. These elements suggest a level of transcriptional control that would allow the regulation of the pathway in response to environmental conditions or metabolic needs of the organism.

These findings indicate that the strain analyzed has the necessary genetic machinery to carry out the biosynthesis of UMP autonomously, which implies that the fungus is capable of synthesizing nucleotides without depending on external sources of pyrimidines. This ability is crucial for their growth, proliferation, and adaptation to various environments, especially in conditions where nutrients are limited. In addition, the functionality of this pathway has important implications in processes such as the production of hydrolytic enzymes, previously observed in this organism, as well as in its potential resistance to antifungal compounds that act on essential metabolic pathways.

It is important to note that, although the analysis performed provides solid evidence based on sequence patterns and structural characteristics, definitive confirmation of the identity and function of these genes requires complementary studies, such as comparisons with databases using tools such as BLAST, protein domain analysis, and experimental validation.

The sequence analyzed, with an approximate length of 23 kb, is sufficiently extensive to allow a reliable functional analysis in a fungus of the genus Aspergillus. From its evaluation, a clear interpretation was obtained about the presence of genes associated with the metabolic pathway UMP biosynthesis I,II,III observing consistent evidence of components involved in the biosynthesis of pyrimidine nucleotides.

The sequence analysis using ORFfinder reveals a high density of open reading frames (ORFs), suggesting a metabolically active genomic region potentially involved in essential biosynthetic pathways (Figure 2). Among these, ORF190 is the most suitable of the others identified, with a length of 172 amino acids, it stands out as a relevant functional candidate due to its size and composition, characteristics consistent with enzymes involved in central pathways of nucleotide metabolism.

The biosynthesis of uridine monophosphate (UMP), this region could be associated with key enzymes of the de novo pathway of pyrimidines, such as dihydroorotase, orotate phosphoribosyltransferase or UMP synthase. The presence of multiple ORFs in different frames and strands suggests a compact genetic organization, typical of fungi such as *Aspergillus salvadorensis*, where functionally related genes can be found close or even partially overlapping, facilitating coordinated regulation.

The partial protein sequence of ORF190 shows a significant proportion of hydrophobic residues and potentially structural regions, which is indicative of stable, possibly cytosolic, enzymatic proteins involved in biosynthetic processes. Since UMP is an essential precursor for the synthesis of RNA, DNA (via conversion to dTMP) and metabolic cofactors, any gene associated with its production has a direct impact on cell proliferation, spore germination and adaptation to variable environmental conditions.

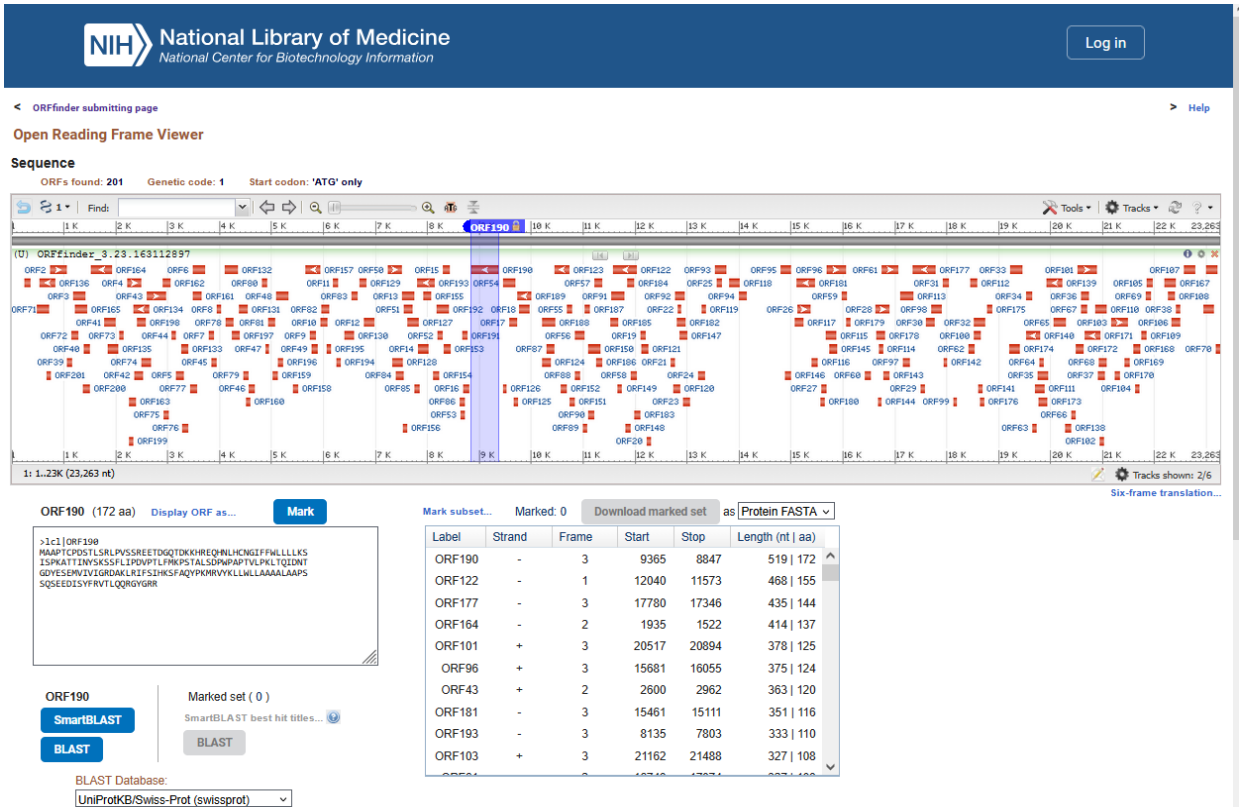

Fig. 2. ORFs analysis of the *Aspergillus salvadorensis sequence*. NIH ORFs 2025

The abundance of ORFs in this region could reflect functional redundancy or specialization in response to environmental stress, allowing the organism to modulate nucleotide production based on nutrient availability or external signals. This is particularly relevant in filamentous fungi, where the regulation of pyrimidine metabolism is closely linked to mycelial growth and reproductive efficiency.

The evidence suggests that the analyzed region is not only involved in the biosynthesis of uridine monophosphate, but is also part of a broader metabolic network that underpins the growth, cell division, and adaptive capacity of *Aspergillus salvadorensis* in its ecological environment.

The data presented in figure (3) showed that multiple regions were identified with typical characteristics of genes involved in this pathway, particularly open reading frames (ORFs) of considerable length that have ATG-like start codons, a guanine- and cytosine-rich composition typical of *Aspergillus* species, and sizes compatible with functional proteins. Within these regions, segments that show structural similarity to pyrG-like genes, which encode the enzyme orotidine-5'-phosphate decarboxylase, stand out. This enzyme is essential in the conversion of orotidine monophosphate (OMP) to uridine monophosphate (UMP), constituting one of the key steps of the pathway.

Additionally, shorter regions were detected that could correspond to pyrE-type genes, associated with the activity of phosphoribosyltransferase orotate, an enzyme that catalyzes the formation of OMP from orotate, a previous step in the biosynthetic pathway. The presence of these elements suggests that the sequence contains at least part of the enzyme assembly necessary for the synthesis of UMP.

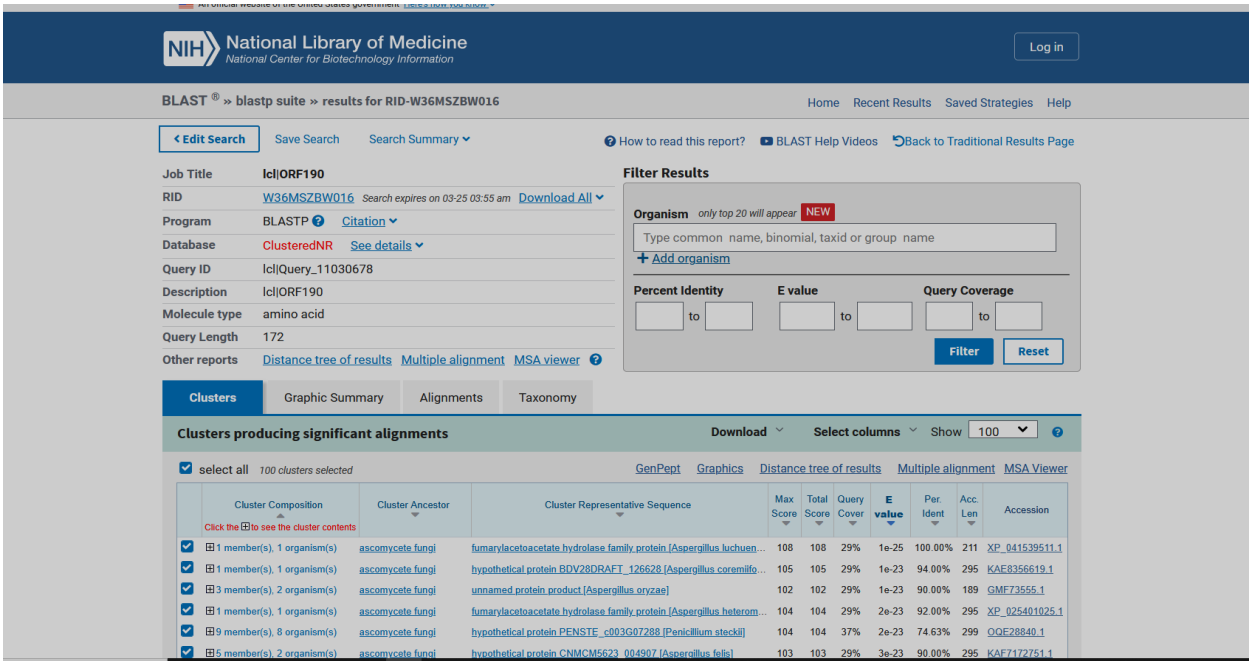

Fig. 3. Cluster of ORFs genes of the *Aspergillus salvadorensis* sequence. BLAST NIH.2025

The organization of the sequence also reveals a pattern consistent with primary fungal metabolism, as clusters of coding regions are observed that could form gene clusters. This type of organization is common in fungi, where genes involved in the same metabolic pathway are usually located close to each other, facilitating their coordinated regulation.

Non-coding regions characterized by repetitive sequences and areas rich in adenine and thymine were identified, which could function as regulatory elements, including promoters or terminators of transcription. This indicates the possible existence of genetic regulatory mechanisms that control the expression of genes involved in the pathway.

Biologically, these findings suggest that, in the probably analyzed strain *Aspergillus salvadorensis*, the UMP biosynthesis pathway is functional or nearly complete. This implies that the fungus has the ability to synthesize nucleotides de novo, without depending on external sources of uracil, which favors its growth in environments with limited availability of nutrients. Likewise, this metabolic capacity is closely related to the production of enzymes, such as previously identified hydrolases, since protein synthesis requires a constant supply of nucleotides. In addition, the pyrimidine pathway is relevant in antifungal resistance studies, since several of its enzymes are potential drug targets.

It is important to consider that this analysis is based on sequence patterns and bioinformatic criteria, so although the evidence is strong, definitive confirmation requires complementary studies, such as comparisons using tools such as BLAST, protein domain analysis (e.g., Pfam or InterPro), and experimental validations.

The representation of bioinformatics databases such as KEGG, MetaCyc and EggNOG indicates that the analysis is supported by reliable functional annotations, while the identification of specific pathways (UMP biosynthesis I, II and III) confirms the coexistence of multiple complementary metabolic mechanisms. Taken together, the image not only summarizes the complexity of UMP biosynthesis, but also highlights its importance in the adaptation, growth, and ecological success of *Aspergillus salvadorensis*.

DISCUSSION

The biosynthesis of uridine monophosphate (UMP) is an essential metabolic pathway in eukaryotic organisms such as *Aspergillus salvadorensis*, as it provides the necessary precursors for the synthesis of nucleic acids and other nucleotide-derived metabolites. The analysis of the genomic region using ORFfinder shows a remarkable density of open reading frames, suggesting a functionally active organization associated with critical metabolic pathways. In particular, the identification of ORFs such as ORF190, with structural characteristics compatible with enzymatic proteins, allows us to infer their possible participation in the de novo pathway of pyrimidines, where enzymes such as UMP synthase play a determining role in the conversion of orotate to UMP, a key step in the production of pyrimidine nucleotides (Moffatt and Ashihara, 2002; Nelson and Cox, 2022).

From a biochemical perspective, the UMP synthesis pathway is highly conserved and regulated, reflecting its importance in cellular homeostasis. In filamentous fungi, this pathway not only underpins DNA replication and RNA transcription, but is also closely linked to mycelial growth, sporulation, and environmental stress response processes. The presence of multiple ORFs in different reading frames within the analyzed region could indicate the existence of genes coding for helper enzymes, transporters or regulatory factors that modulate the efficiency of nucleotide biosynthesis, allowing an adaptive response to variations in nutrient availability (Dong *et al.*, 2025; Kanehisa and Goto, 2000; Wright *et al.*, 2022).

Likewise, the possible redundancy or functional diversification of the identified genes suggests an evolutionary strategy aimed at guaranteeing metabolic continuity under adverse conditions. In this sense, studies in species of the genus *Aspergillus* have shown that the regulation of the pyrimidine pathway can be influenced by epigenetic mechanisms and by the interaction with other metabolic pathways, such as nitrogen and carbon metabolism, which optimizes the allocation of cellular resources (Todd *et al.*, 2014). This metabolic integration allows the organism to adjust its growth and reproduction rate based on environmental cues, favoring its survival in changing ecological niches (Wu *et al.*, 2023).

The structure of the proteins encoded by the identified ORFs, characterized by the presence of hydrophobic regions and conserved domains, suggests stable and efficient enzymatic functionality. This is consistent with the role of enzymes in the UMP pathway, which require high specificity and fine-regulation to maintain the balance between nucleotide synthesis and consumption. In addition, subcellular compartmentalization of these enzymes may contribute to metabolic efficiency, facilitating the channeling of intermediates and reducing metabolite loss (Bar-Peled and Kory, 2022; Yao *et al.*, 2023; Zameitat *et al.*, 2004).

Evidence derived from genomic analysis suggests that the studied region plays a central role in the biosynthesis of uridine monophosphate and, therefore, in the overall physiology of *Aspergillus salvadorensis*. The high density of ORFs and their possible functional relationship with the pyrimidine pathway reflect a genomic organization aimed at maximizing the metabolic efficiency and adaptive capacity of the organism. This integrated approach between genomic structure, enzyme function and metabolic regulation allows us to understand how UMP biosynthesis not only supports basic processes such as cell replication, but also contributes to the ecological plasticity and evolutionary success of filamentous fungi.

CONCLUSION

The sequence studied presents evidence consistent with the presence of genes involved in the UMP biosynthesis pathway, which supports the metabolic capacity of the fungus for nucleotide synthesis and reinforces its biological

viability and adaptive potential within its ecological niche.

The UMP biosynthesis I pathway in *Aspergillus salvadorensis* is key to sustaining its basic metabolism, allowing its growth and reproduction, facilitating the construction of its cellular structure and ensuring its adaptation to various environments. This metabolic pathway is therefore an essential component of its biological viability and ecological success.

The sequence presents robust evidence of genes associated with the UMP biosynthesis II pathway, including pyrG-like elements with a higher degree of certainty and possible regions corresponding to pyrE, as well as a genomic organization consistent with fungal metabolic pathways. This supports the fact that the organism has an active nucleotide metabolism, which gives it biological viability and adaptive capacity within its environment.

The UMP biosynthesis III pathway allows *Aspergillus salvadorensis* to optimize the use of available resources, improve its energy efficiency and adapt to different environmental conditions, complementing the de novo biosynthesis pathways and reinforcing its survival capacity and ecological competitiveness.

The results indicate that *Aspergillus salvadorensis* possesses a complete and functional metabolic machinery for the biosynthesis of UMP, which supports its growth, reproduction and morphological plasticity. The integration of de novo and rescue routes gives the fungus an adaptive advantage in environments with variable nutrient availability, consolidating the biosynthesis of UMP as a central axis in its physiology and ecological success.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

GENERATIVE AI STATEMENT

This study used Generative AI tools in data re-organization. We confirm that all AI-assisted processes were critically reviewed by the author's to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the author's.

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