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Innovative Explorations of Microbial Synthetic Biology in Spermidine Production

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Abstract

Spermidine, a polyamine with bioactivities such as anti-aging and cardiovascular protection, holds broad application prospects in the fields of biomedicine and health products. It can delay the aging process by regulating cellular mechanisms and simultaneously exert a positive protective effect on cardiovascular health, thus attracting widespread attention from the industrial community. However, traditional production methods have long restricted the industrialization of spermidine. The chemical synthesis method has issues including insufficient safety of raw materials and catalysts, numerous by-products, low purity, and environmental pollution. The natural extraction method, on the other hand, results in high product costs due to the low content of active ingredients in raw materials and low extraction efficiency, making it difficult to meet market demand. The emergence of microbial synthetic biology technology has brought a new breakthrough to spermidine production. Through metabolic engineering of microbial chassis, optimization of strain performance, and combination with adaptive fermentation processes, the yield and purity of spermidine have been significantly improved. At present, relevant enterprises have promoted industrialization attempts, and costs have been reduced to a certain extent. Nevertheless, challenges still exist in aspects such as strain stability, economics of large-scale production, and industry certification. Continuous technological improvement is required in the future to promote its large-scale application.

Keywords

spermidine, microbial synthetic, biocomputing, metabolic network

1. Introduction

Spermidine is a polyamine endogenously present in human cells, which participates in fundamental physiological processes including cell proliferation and differentiation. In recent years, its potential in the biomedical field has become increasingly prominent. Endowed with core bioactivities such as anti-aging and cardiovascular protection, it is recognized within the industry as “the next 100-billion-level bioactive molecule” and has garnered substantial attention in the research and development of products for chronic disease intervention and functional restoration.

Nevertheless, literature surveys indicate that exorbitant production costs remain a critical constraint to its large-scale application. Conventional production approaches either depend on high-risk chemical feedstocks

or are constrained by the low extraction efficiency of natural raw materials. This leads to prohibitively high prices of end products, rendering them inaccessible for broader application scenarios [1].

Against this backdrop, microbial synthetic biology technology, characterized by its designability, environmental friendliness, and high efficiency, offers a novel avenue to overcome the cost bottleneck. Through the engineering of microbial metabolic pathways, the directed biosynthesis of spermidine can be achieved, circumventing the limitations of traditional processes. This also serves as the core rationale for the initiation of the present study.

2. Dilemmas in Traditional Production Methods

Preliminary research investigations indicate that traditional spermidine production relies on two primary approaches: wheat germ extraction and chemical synthesis.

The former method yields a product with a purity of merely 1% and contains gluten allergens, accompanied by high costs for separation and purification. While the latter method achieves improved purity, its production cost remains persistently high due to complex operational procedures and expensive reagents.

The global spermidine market has long been monopolized by foreign enterprises. For instance, Sigma-Aldrich prices its 100-gram reagent at over ten thousand yuan, which severely restricts the scope of its application.

3. Technological Breakthroughs in Microbial Spermidine Synthesis

3.1 Metabolic Network Reconstruction Driven by Biocomputing

Metabolic network reconstruction driven by biocomputing leverages computational tools such as bioinformatics analysis, metabolic flux simulation, and molecular structure prediction to accurately identify bottleneck nodes in the spermidine synthesis pathway. These nodes include feedback inhibition of rate-limiting enzymes, insufficient precursor supply, and accumulation of product toxicity.

Subsequently, combined with synthetic biology techniques—such as site-directed mutagenesis, gene editing, and gene tandem expression—targeted engineering is performed. Ultimately, a closed-loop metabolic system encompassing “carbon source uptake-precursor synthesis-product generation-secretion and efflux” is constructed.

The engineering work on Saccharomyces cerevisiae conducted by Qin Jiufu’s team [2]serves as a typical practice of this strategy. Its core focuses on three key modules: “enhancement of precursor supply, alleviation of feedback inhibition, and optimization of product transport”. The technical details and implementation process of each module are as follows:

3.1.1 Precursor Supply Enhancement: Systematic Optimization of the Ornithine Synthesis Pathway

Ornithine serves as the core precursor for spermidine synthesis. Specifically, ornithine is decarboxylated to form putrescine, and putrescine then combines with decarboxylated S-adenosylmethionine to generate spermidine. However, the ornithine synthesis pathway (glutamate → ornithine) in Saccharomyces cerevisiae faces two major issues: feedback inhibition of rate-limiting enzymes and insufficient metabolic flux.

The research team achieved a two-fold increase in precursor supply through a three-step strategy of “computational localization - enzyme molecular modification - gene expression regulation”.

3.1.2 Biological Computation for Bottleneck Localization: Identifying Rate-Limiting Enzymes and Regulatory Nodes

First, metabolic flux analysis (MFA) was used to track the flow of carbon source (glucose) in the yeast metabolic network. Detection results showed that the conversion rate of glutamate to ornithine was only 31%, which was much lower than the theoretical value (over 80%). Through enzyme kinetic simulation, the key rate-limiting enzyme in the pathway was identified as N-acetylglutamate kinase (ArgB). The activity of this

enzyme is strongly inhibited by the end product ornithine, with an inhibition constant Ki = 0.32 mM—meaning that even a very low concentration of ornithine can reduce ArgB activity by 50% [3].

Further transcriptome association analysis revealed that glutamate dehydrogenase (encoded by the gdh1 gene) can catalyze the production of glutamate (providing substrates for ornithine synthesis), but its natural expression level is relatively low, resulting in insufficient glutamate supply. Verification via computational tools (e.g., COBRA Toolbox metabolic network model) confirmed that the feedback inhibition of ArgB and the low expression of gdh1 are the core bottlenecks in ornithine synthesis, which require priority modification. Verification via computational tools (e.g., COBRA Toolbox metabolic network model) confirmed that the feedback inhibition of ArgB and the low expression of gdh1 are the core bottlenecks in ornithine synthesis, which require priority modification.

3.1.3 Site-Directed Saturation Mutagenesis for ArgB Modification: Relieving Feedback Inhibition and Enhancing Enzyme Activity

To address the feedback inhibition of ArgB, site-directed saturation mutagenesis was applied to modify the enzyme's "allosteric regulatory domain"—a key region where ornithine binds and inhibits ArgB activity. Mutating critical amino acids in this domain can reduce the enzyme's affinity for ornithine while preserving or even enhancing its catalytic activity. The specific implementation steps are as follows:

First, homology modeling and molecular docking (using the AutoDock Vina tool) were employed to simulate the binding process between ornithine and ArgB. The results revealed that V126 (valine) and F189 (phenylalanine) in ArgB's allosteric regulatory domain are key ornithine-binding sites; the side chains of these two amino acids fix ornithine via hydrophobic interactions and hydrogen bonds, triggering conformational changes in the enzyme and thus inhibiting its activity.

Next, saturation mutagenesis primers were designed and a mutant library was constructed. For the V126 and F189 sites, primers containing degenerate codons were designed (e.g., the "NNS" degenerate codon was used for the V126 site, which can encode 20 natural amino acids, and the same for the F189 site) to ensure all possible amino acid mutations were covered at each site. Using the Saccharomyces cerevisiae argB gene as a template, PCR amplification was performed with the degenerate primers to obtain argB fragments containing the mutation sites. These fragments were then inserted into an expression vector (e.g., pRS426 plasmid) carrying the strong promoter Ptef1 to construct an ArgB mutant library.

Subsequently, the mutant library was transformed into an ArgB-deficient yeast strain (ΔargB), and target mutants were screened through "ornithine-deficient medium screening + enzyme activity determination". In the first step, only strains with normal ArgB activity could grow on medium without ornithine, enabling the initial elimination of inactive mutants. In the second step, ArgB activity in the surviving strains was detected using an enzyme activity assay kit, and the inhibition rate of ornithine on the enzyme was measured via high-performance liquid chromatography (HPLC). Finally, the "V126A/F189L double mutant" was screened out.

For the verification of mutant efficacy, results showed that after modification, the feedback inhibition coefficient of ArgB toward ornithine decreased from 0.32 to 0.07—meaning a much higher concentration of ornithine is required to inhibit enzyme activity, and the inhibitory effect is reduced by over 80%. Additionally, the specific enzyme activity (catalytic efficiency per unit mass of enzyme) of the mutant ArgB increased by 1.8 times, indicating that the same amount of enzyme can catalyze more glutamate to produce ornithine.

3.1.4 Gene Tandem Expression: Enhancing the Conversion Rate of Glutamate to Ornithine

To address the issue of insufficient glutamate supply, the "mutant argB gene" and "glutamate dehydrogenase gene (gdh1)" were subjected to tandem expression with the following specific design: the constitutive promoter Ptef1— the one with the highest activity in Saccharomyces cerevisiae and the promoter of translation elongation factor 1α— was selected to ensure efficient transcription of both genes; the mutant argB and gdh1 were tandemly linked via Overlap Extension PCR without inserting a terminator in between, which ensures both genes are transcribed on the same mRNA; the tandem gene fragment was inserted into a yeast integrative vector (e.g., pUG6) and integrated into the rDNA locus (a multi-copy site enabling high-copy gene expression) of the yeast genome through homologous recombination. After modification, the intracellular conversion rate of glutamate to ornithine increased from 31% to 68%, and metabolic flux analysis showed that

the flux of the ornithine synthesis pathway reached 12.6 mmol/(g·h), providing an adequate precursor for spermidine synthesis [4].

3.2 Multi-level Relief of Feedback Inhibition: Breaking the "Product Inhibition Curse" in Spermidine Synthesis

In the spermidine synthesis pathway, in addition to the feedback inhibition from the precursor ornithine, the end product spermidine inhibits synthesis through two mechanisms: ① directly inhibiting the key enzyme S-adenosylmethionine decarboxylase (SpeD); ② forming "metabolic coupling inhibition" with SAM synthetase (Sam2) (SpeD activity depends on S-adenosylmethionine (SAM) generated by Sam2, while spermidine inhibits both simultaneously). The research team completely relieved this inhibition through a multi-level strategy combining "molecular structure simulation-guided mutagenesis and epigenetic regulation". The specific process is as follows:

Bioinformatics calculations identified the inhibition sites of SpeD. The three-dimensional structure of SpeD was resolved using X-ray Crystallography (with a resolution of 2.3 Å), and combined with molecular dynamics simulations (using GROMACS software), the binding mechanism between spermidine and SpeD was clarified: spermidine binds to the "pocket adjacent to the active center" of SpeD through hydrogen bonds and electrostatic interactions, causing conformational changes in the active center that prevent substrate SAM from binding. Y213 (tyrosine) and R267 (arginine) within the pocket are key binding sites — the hydroxyl group of Y213 forms a hydrogen bond with the amino group of spermidine, and the guanidino group of R267 forms an electrostatic interaction with the carboxyl group of spermidine.

Alanine Scanning Mutagenesis was used to screen for inhibition-resistant mutants: this technique replaces candidate sites such as Y213 and R267 one by one with alanine (which has a methyl side chain and no hydrogen bond/electrostatic interaction capabilities) to evaluate the impact of mutations on enzyme activity and inhibition sensitivity. Mutant construction: Site-directed mutagenesis primers were designed for each site, PCR amplified the speD mutant genes, and inserted into expression vectors containing the Ptef1 promoter.

Functional verification: Enzyme activities of each mutant were measured under different spermidine concentrations (0.1-5 mM): the wild-type SpeD showed 50% enzyme activity reduction at 0.15 mM spermidine (Ki=0.15 mM); the Y213A mutant (Y213 replaced with alanine) had a Ki increased to 2.3 mM (requiring 15-fold higher spermidine concentration for enzyme inhibition) while retaining 92% of its enzyme activity (not significantly inactivated by the mutation); although the R267A mutant also relieved inhibition, it only retained 40% of enzyme activity. Therefore, the Y213A mutant was ultimately selected [5].

3.3 CRISPR-dCas9 Epigenetic Regulation: Relieving Metabolic Coupling Between SpeD and Sam2

S-adenosylmethionine synthetase (Sam2) is responsible for generating S-adenosylmethionine (SAM), the substrate of SpeD. However, spermidine inhibits the transcription of the sam2 gene through an "unknown regulatory pathway", leading to insufficient SAM supply and subsequent indirect inhibition of SpeD activity (metabolic coupling inhibition). The research team employed the CRISPR-dCas9 system (inactivated Cas9 with no DNA cleavage activity, serving only as a "targeting vector") for epigenetic regulation to relieve this coupling, with details as follows:

3.3.1 Target Selection: Promoter Regulatory Region of the Sam2 Gene

Chromatin Immunoprecipitation Sequencing (ChIP-seq) revealed that spermidine induces transcriptional repressors (e.g., Mig1) to bind to the -300~-200 bp region of the sam2 promoter, thereby inhibiting transcription. Consequently, this region was selected as the targeting site for dCas9.

3.3.2 Construction of the CRISPR-dCas9 Activation System

sgRNA design: Based on the targeting region of the sam2 promoter, 2 sgRNAs (to ensure targeting specificity) were designed and cloned into a vector containing the U6 promoter (a dedicated promoter for sgRNA).

dCas9 fused with activator: dCas9 was fused with a transcriptional activator of Saccharomyces cerevisiae (e.g., Gal4 activation domain) to construct a "dCas9-activator" expression cassette. This cassette is controlled by the Pgal1 promoter and can be induced to express by galactose.

Transformation and induction: The sgRNA vector and the dCas9-activator vector were co-transformed into yeast strains. After adding galactose to induce expression, the dCas9-activator binds to the inhibitory region of the sam2 promoter in a targeted manner, competitively displacing transcriptional repressors and recruiting transcriptional machinery (e.g., RNA polymerase) to promote sam2 transcription.

3.3.3 Effect of Modification

The mRNA expression level of the sam2 gene increased by 2.5-fold, and the production rate of decarboxylated SAM (the substrate of SpeD) increased by 2.1-fold. When the intracellular spermidine concentration reached 1.8 g/L (far exceeding the inhibition threshold of 1.2 g/L in traditional processes), no synthesis stagnation was observed, completely relieving the metabolic coupling inhibition.

3.4 Enhancement of Product Transport System: Constructing a "Synthesis-Transport Coupling" Module to Alleviate Product Toxicity

Intracellular accumulation of spermidine exerts toxicity on yeast cells (e.g., disrupting cell membrane integrity and inhibiting the respiratory chain). In traditional processes, when the intracellular concentration exceeds 1.2 g/L, the cell growth rate decreases by 50%. The research team achieved efficient extracellular secretion of spermidine through the strategy of "transporter screening - signal peptide optimization - coupling module design", with the specific process as follows:

3.4.1 Screening of Specific Transporters via Comparative Transcriptomics

Transporters associated with spermidine synthesis were screened using comparative transcriptomic analysis (RNA-seq): the experimental group was set as a "high-spermidine-producing strain" (with optimized precursors and relieved feedback inhibition) and the control group as a wild-type strain; transcriptomic data of the two groups were analyzed by the DESeq2 tool, which revealed that the mRNA levels of three transporters (Tpo2, Tpo3, Qdr2) were significantly upregulated in the experimental group, with Pearson correlation coefficients of 0.89, 0.76, and 0.68 respectively, highly consistent with the expression trend of the spermidine synthesis gene speE; for functional verification, overexpression strains of the three transporters were constructed by inserting the tpo2, tpo3, and qdr2 genes into vectors containing the Ptef1 promoter respectively, and the spermidine concentration in the fermentation supernatant was detected via HPLC— the Tpo2-overexpressing strain showed an extracellular secretion level 4.2 times that of the control group and the highest transport specificity for spermidine (its transport efficiency was 2.7 times that of putrescine and 1.3 times that of spermine), thus confirming Tpo2 as an "efficient and specific spermidine efflux transporter".

3.4.2 Signal Peptide Optimization: Enhancing the Secretion Efficiency of Tpo2

Tpo2 is a membrane protein, and its N-terminal native signal peptide guides the protein to localize to the cell membrane but with relatively low efficiency. To optimize its localization efficiency, the research team replaced the native signal peptide: they selected the α-factor signal peptide— which has the highest secretion efficiency in Saccharomyces cerevisiae, is naturally used for secretory proteins such as invertase, and can efficiently guide proteins to the cell membrane via the endoplasmic reticulum-Golgi pathway— then replaced Tpo2's native signal peptide with this 19-amino-acid α-factor signal peptide by PCR to construct the "α-factor signal peptide-Tpo2" fusion gene; efficacy verification via fluorescent labeling (GFP fusion) showed that after optimization, Tpo2's localization efficiency on the cell membrane increased by 2.3-fold, the extracellular secretion rate of spermidine increased by 3.7-fold, and the intracellular accumulation decreased by 42%.

3.4.3 Design of the "Synthesis-Transport Coupling" Module: Achieving Dynamic Balance

To avoid "mismatch between synthesis rate and transport rate" (e.g., intracellular accumulation caused by faster synthesis than transport, or raw material waste caused by faster transport than synthesis), the research team designed a gene tandem module mediated by a self-cleaving peptide. The module structure involves tandemly connecting the spermidine synthase gene (speE, responsible for spermidine production) with the optimized tpo2 gene via the P2A self-cleaving peptide (derived from foot-and-mouth disease virus, which

automatically cleaves into two independent proteins after translation) to form the "speE-P2A-tpo2" cassette. For promoter control, the inducible promoter Pgal10 (repressed by glucose and induced by galactose) is used to ensure the module is only activated during the spermidine synthesis phase. As for the dynamic balance mechanism, when the spermidine synthesis rate increases (with enhanced speE expression), tpo2 achieves "equivalent expression" through the synchronous translation and cleavage of P2A, and the transport system is activated simultaneously to ensure timely extracellular efflux of the product; conversely, when the synthesis rate decreases, the transport rate also decreases accordingly to avoid energy waste.

3.5 Verification of Synergistic Effects: Testing the Industrial Potential in a 5L Fermenter

After modifying the above three modules (precursor optimization, feedback derepression, and transport enhancement), the research team verified their synergistic effects through 5L fed-batch fermentation. The specific parameters and results are as follows: For fermentation conditions, glucose was used as the sole carbon source (initial concentration of 40 g/L, maintained at 5-10 g/L via feeding), pH was controlled at 6.0, dissolved oxygen was maintained at 30%, and the fermentation cycle was 36 hours. Key results showed that the spermidine yield reached 2.3 g/L, the raw material cost was reduced by 68% compared with the traditional process (which requires exogenous addition of methionine and putrescine), and the product yield was increased to 0.057 g/g glucose. The core innovation lies in the construction of a closed-loop metabolic network of "carbon source uptake → glutamic acid → ornithine → spermidine → extracellular secretion"; all synthesis units rely on the yeast's own metabolism without any exogenous precursors, completely solving the cost and efficiency problems of the traditional process.

4. Discovery of the Extracellular Secretion Mechanism

In the innovation of the spermidine production process, the Qin Jiufu team not only achieved a breakthrough in metabolic network reconstruction but also accomplished a leap from the traditional model to an innovative system in the extraction and purification stage. Through bioinformatics-driven mining and application of transporters, the team transformed the spermidine extraction model from "juice squeezing"-like cell disruption extraction to "tap water collection"-like continuous secretion collection. This revolutionized the downstream process and brought comprehensive optimizations in impurity removal rate, production cost, and production efficiency.

In the stage of bioinformatics screening and functional verification of transporters, the team established a multi-dimensional screening system. Based on the Saccharomyces cerevisiae genome database, 23 candidate members belonging to the polyamine transporter family (PAT) were first screened from 127 potential transporters through sequence homology analysis (with an E-value threshold set at 1e-5). Subsequently, using co-expression analysis of transcriptome data, it was found that when the expression of the spermidine synthesis gene speE was upregulated, the mRNA levels of three transporters—Tpo2, Tpo3, and Qdr2—increased synchronously (Pearson correlation coefficients were 0.89, 0.76, and 0.68, respectively). To verify their functions, the team constructed overexpression strains of these three genes and detected the spermidine concentration in the fermentation supernatant via high-performance liquid chromatography (HPLC). The results showed that the extracellular secretion of the Tpo2-overexpressing strain was the highest, reaching 4.2 times that of the control group. Moreover, its transport specificity experiment indicated that the transport efficiency of this protein for spermidine was 2.7 times that of putrescine and 1.3 times that of spermine, confirming it as a high-efficiency and specific spermidine efflux transporter.

This innovation in the extraction model brought significant process advantages. The traditional "juice squeezing"-like process requires cell disruption via high-pressure homogenization or ultrasonic treatment (with a disruption rate of approximately 85%). While releasing intracellular products, it also introduces impurities such as cell debris, nucleic acids, and proteins into the extract, significantly increasing the load of subsequent purification steps (e.g., ion exchange chromatography, gel filtration). Comparative data showed that the concentration of protein impurities in the extract of the traditional process was as high as 12.6 g/L, whereas after adopting the Tpo2-mediated "tap water collection" model, the concentration of protein impurities in the fermentation supernatant was only 0.8 g/L, representing a 93.6% increase in impurity removal rate. This change reduced the number of purification steps from 4 to 2 (only requiring nanofiltration decolorization and

crystallization), which not only shortened the process cycle (from 24 hours to 8 hours) but also reduced the purification cost by 62%.

In addition, the continuous secretion model also achieved a leap in production efficiency. The traditional process is limited by the cell growth cycle and requires centralized harvesting when cells reach the stationary phase, with the problem of product accumulation inhibition (when the intracellular spermidine concentration exceeds 1.2 g/L, the cell growth rate decreases by 50%). In contrast, the "tap water collection" model maintains the intracellular spermidine concentration stably at 0.3–0.5 g/L through real-time product efflux, relieving the inhibitory effect. Cells can maintain the metabolic activity of the logarithmic growth phase, enabling continuous fed-batch fermentation. Practical operation data showed that the fermentation productivity under this model reached 0.064 g/(L·h), which was 106% higher than the 0.031 g/(L·h) of traditional batch fermentation. Furthermore, the fermentation cycle could be extended to 72 hours without a significant decrease in productivity, significantly improving equipment utilization.

The innovation of the Qin Jiufu team is not only a breakthrough at the technical level but also establishes a green production model integrating "synthesis-secretion-purification". By combining bioinformatics screening with metabolic engineering modification, the team realized the transformation of products from intracellular accumulation to continuous extracellular secretion. This provides a highly valuable reference paradigm for the extraction processes of other microbial secondary metabolites, especially demonstrating great application potential in reducing industrial production costs and improving product purity [5].

5. Conclusion

In summary, spermidine, as a natural polyamine in the human body, has become a highly promising "100-billion-level bioactive molecule" in the biomedical field due to its prominent activities in anti-aging, cardiovascular protection, and other areas. It also demonstrates significant value in the research and development of chronic disease intervention and functional repair products. However, its large-scale application has long been hindered by the drawbacks of traditional production methods—high-risk chemical synthesis and low-efficiency natural extraction together drive up costs, making it difficult for products to achieve widespread use.

Microbial synthetic biology technology, with the advantages of designability, environmental friendliness, and high efficiency, enables the targeted synthesis of spermidine by modifying microbial metabolic pathways. This effectively avoids the shortcomings of traditional processes and provides a key solution to break through the cost bottleneck. This technical route not only meets the industrialization needs of spermidine but also confirms the necessity of this study starting from "solving application pain points," laying a core direction for subsequent research on large-scale production and application of spermidine.

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