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Progress in Microbial Production of Prodigiosin

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Abstract

Prodigiosin is the secondary metabolites from *Actinomycetes*, *Serratia*, etc. It has many biological activities, including anti-bacterial, anti-fungal and anti-tumor. Recently, lots of researches reveal that prodigiosin has great potential for applications in cancer treatment, so the research of prodigiosin attracts increasing attention.

Keywords: Prodigiosin; Biological activity; Anti-tumor

Introduction

Prodigiosin (PG), its molecular formula is $C_{20}H_{25}N_3O$, molecular weight is 323.1968 g/mol. Its skeleton is characterized by a large conjugated system containing a methyl tri pyrrole ring, in which two rings are directly linked, and the third one is a ring structure connected through a methyl group [1]. Prodigiosin is a typical alkaloid secondary metabolite produced by *Serratia*, *marine bacteria*, *Actinomycetes*, etc.

PG is a general term for natural red pigments. It is used as an ecological dye with good color fastness and dye uptake, and expected to promote technological transformation of the traditional dye industry and even the textile industry. Recent studies have also found that due to the photosensitivity of prodigiosin, it can be used as an additive to sunscreens and other cosmetics to reduce the damage of ultraviolet rays to the skin. Therefore, prodigiosin has a wide range of application prospects and market value in the fields of medicine, environmental treatment, textile dyes and even cosmetics.

Anticancer effect of prodigiosin

The research mainly focuses on PG's anti-cancer mechanism in apoptosis, cell cycle blocking, anti-infection and transfer. Montaner et al. demonstrated that PG can induce apoptosis in human gastric cancer and colon adenocarcinoma cells, and it has a rapid inhibitory effect on the proliferation of hematopoietic cancer cells [2]. Zheng et al. showed that PG has an inhibitory effect on the metastasis of pancreatic cancer cells [3].

Sruthy et al. found that prodigiosin can inhibit the proliferation of human bladder adenocarcinoma cell 8889 at a lower concentration and induce the apoptosis of membranous adenocarcinoma cells, which has a specific effect on tumor cells [4].

It indicates that PG has targeted effect of anti-tumor cell proliferation. With the deepening of research, it has been found that the low concentration of prodigiosin can inhibit the growth of algae or kill algae cells in marine red tides and freshwater blooms without secondary pollution.

Synthetic mechanism of prodigiosin

Nowadays, studies on the molecular level of prodigiosin have focused on key enzyme genes. Xie et al. studied that prodigiosin can significantly inhibit the replication of BmNPV genomic DNA [5]. Chawrai et al. studied the enzymatic properties of prodigiosin condensing enzyme (PigC) in the prodigiosin synthesis pathway [6].

Venil et al. found that the synthesis of prodigiosin of *S. marcescens* is regulated by the transcriptional regulatory factors PigS and PigP [7]. Xu et al. studied the differential expression of proteome of *Serratia marcescens* under different fermentation temperatures (28˚C and 37˚C) and explored the reason why *Serratia marcescens* synthetic prodigiosin is influenced by temperature [8].

Quorum sensing is a system in which bacteria control gene expression according to changes in their own cell density. The basic principle is that bacteria sense a certain kind of signal molecule secreted in their reproductive process [9].

When the signal molecule reaches a certain threshold, the bacteria will initiate the expression of certain genes. Studies show that the process of synthesizing prodigiosin by *Serratia spp* strain S39006 is regulated by a quorum-sensing system consisting of two genes: *SmaI* and *SmaR* [10].

The role of *SmaI* is to synthesize signal molecules N-acyl Homoserine Lactones (AHLs). When the cell density is low, the concentration of AHLs is low, and *SmaR* binds to the pig gene cluster, thereby inhibiting the transcription of the gene cluster with the growth of cells and the concentration of AHLs continuously increases.

When the concentration of AHLs reaches a certain value, by inhibiting the activity of the *SmaR*-binding DNA, the pig gene cluster would be transcribed and the cells begin to synthesize prodigiosin. During the synthesis of prodigiosin by *S. marcescens* SS-1, SpnI and SpnR constitute the quorum sensing system [11].

Optimization of fermentation conditions of synthetic prodigiosin

In order to reduce the cost while increasing the yield of prodigiosin during the fermentation of bacteria, it is very important to screen suitable medium components and determine the optimal amount of

medium. There are two main purposes for optimizing the prodigiosin producing bacteria culture medium: the first one is to increase the production of prodigiosin [12] and the second one is to increase the ability of the strain to produce prodigiosin [13]. The former is mainly achieved by screening the optimum carbon, nitrogen source and trace elements of the culture medium, the latter is mainly achieved by adding prodigiosin synthesized precursor substances or precursor analogues to the culture medium. The carbon source also has a certain influence on the metabolism of prodigiosin.

Production of prodigiosin by microbial fermentation is mainly the production of prodigiosin in shake flasks or bioreactors. In the fermentation process, various factors such as inoculation time, culture time, culture temperature, shaking speed, dissolved oxygen and other factors have an important influence on the production of prodigiosin. Therefore, the selection of the appropriate fermentation process parameters can effectively improve the production of prodigiosin.

Conclusion

This article reviews the current research status of microbial prodigiosin and optimization of fermentation conditions for prodigiosin producing strains. It provides theoretical basis for the construction of high-yield prodigiosin strains, and lays a theoretical foundation for further exploration of the mechanism on the synthesis of prodigiosin. In order to increase the production of prodigiosin and reduce cost, there are several effective ways:

(i) Breeding of high-yield strains: Highly-producing strains of prodigiosin in nature are mainly concentrated in *Serratia*.

(ii) Temperature is a key factor effects the production of prodigiosin: In-depth study of the key enzymes that effect the production of prodigiosin by temperature regulation, increasing the activity of key enzymes affected by temperature is beneficial to the production of prodigiosin.

(iii) Genetic engineering breeding: By genetic engineering, the PG synthesis gene cluster can be cloned into *E. coli* to further study the mechanism of PG synthesis regulation. Fermentation and extraction processes optimization: Response surface methodology is used to optimize the precursors (amino acids) of the metabolic pathways of the strain's biosynthetic prodigiosin, and based on this, the optimal fermentation conditions such as rotation speed, pH, and temperature are clarified.

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