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Progress of research on prodigiosin

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Abstract: Prodigiosin is a natural red pigment derived primarily from secondary metabolites of microorganisms, especially Serratia marcescens. Prodigiosin has been proven to have antitumor, antibacterial, antimalaria, anti-insect, antialgae, and immunosuppressive activities, and is gaining increasing important in the global market because of its great potential application value in clinical medicine development, environmental treatment, preparation of food additives, and so on. This paper reviews the progress of the research on prodigiosin.

Keywords: Prodigiosin; Secondary metabolite; Bioactivity.

1. Introduction

Prodigiosin is a red microbial pigment with a tripyrrole ring structure with the molecular formula C20H25N3O[1-3]. It is mainly produced by Serratia marcescens [4-5], Pseudomonas, actinomycetes and some marine bacteria [6-8]. Prodigiosin, which is red under acidic and neutral conditions and yellow under alkaline conditions [9-10], is a biologically active secondary metabolite with many medicinal uses and has important roles in antibacterial [13-14], algaecidal, anticancer, antimalarial, anti-inflammatory [15-16], antidiabetic and immunomodulatory properties.

2. Biosynthesis of prodigiosin

As a result of the wide range of bioactivity of prodiginines, many studies on prodiginines biosynthesis have been reported in the past decades. Through a set of analysis which includes homology detection among enzymes, repressing the genes to identify its function, analysis of intermediate metabolites, and complementation experiments, the pathways and regulatory mechanisms for prodigiosin production in S. marcescens and S.coelicolor are now clear [17,18]. Two key intermediates, 2-methyl-3-n-amylpyrrole (MAP)and 4-methoxy-2,2′-bipyrrole-5-carbaldehyde (MBC), are synthesized by bifurcated pathway.

In S. marcescens and S. coelicolor, the biosynthesis of MBC begins with the activation of L-proline as a thioester and is subsequently converted to the pyrrole ring A of prodigiosin. In the upcoming steps, C2 unit provided by malonyl CoA, C2N unit provided by serine, and methyl group provided by S-adenosylmethionine successively combine with pyrrole ring A to form MBC. In S. marcescens, MAP is formed in a three-step reaction from the initial precursor, 2-octenoyl CoA, which was formed by the combination of 2-octenal and pyruvate. Finally, MBC and MAP are condensed by enzyme to form prodigiosin.

In different bacteria species, the gene clusters involved in prodigiosin synthesis vary greatly. For example, the Pig cluster and the Red cluster are responsible for the biosynthesis of prodigiosin in Serratia sp. and Streptomyces sp., respectively [17,19]. Other clusters include Hap cluster from H. chejuensis and Tam cluster from Pseudoalteromonas tunicata. The Pig clusters of S.marcescens has a certain degree of genomic modularization. The Pig B,Pig D, Pig E gene encodes the protein for biosynthesis of MAP, and PigC is involved in the final step of condensation of MAP with MBC to form prodigiosin. The rest of the Pig cluster, containing Pig A and Pig F–Pig N, encodes proteins that are directly or indirectly involved in MBC biosynthesis.

It is worth noting that the synthesis pathway of MBC is highly conserved. All clusters have a specific set of genes that are homologous to each of the enzymes involved in the formation of MBC in S. marcescens, suggesting that MBC biosynthesis was a common pathway. However, the biosynthetic pathway of MAP is completely different. For instance, none of the proteins involved in MAP biosynthesis in S. marcescens had close homologs in the Red cluster. In addition, Pig C homologs were found in all clusters such as Red H, Hap C, Tam Q.

3. Bioactivity of prodigiosin

Increased attention on the red pigments and their derivatives is due to their inherent bioactivity against several strains of bacteria, algae, larva, and parasites [21,22]. They are also well-known for their higher immunomodulating capability and cytotoxicity against cancerous cells . Being a pigment, the prime activity expected from these molecules is their anti-oxidant capability.

3.1. Antimicrobial activity

In antimicrobial approaches, numerous pathogens have been tested and have shown growth inhibition or even programmed cell death characteristics. Research regarding the interaction between microbiota and an amphibian host implies assistance from S. marcescens against Batrachochytrium dendrobatidis via production of prodigiosin . According to the application of antifungal function, PG has been used for preventing red tide [25–26]. Collecting the known detailed mechanisms, the induction of ROS and inhibition of microcystin production (a group of small toxic cyclin peptides believed to respond to nutrient stress) are major reactions and cause the leakage of the plasma membrane. Interestingly, PG is also an antioxidant for which the potency of antioxidation activity is at least ten-times higher than that of a-tocopherol [28,29]. How PG triggers oxidative stress and prevents ROS scavenging is still

unknown. While combined with N-myristoyltyrosine, the IC50 of PG against Corynebacterium glutamicum can drop from 1.6 μg/mL to 5 ng/mL. Furthermore, PG induced the cell apoptosis of Bombyx mori nucleopolyhedrovirus infected silkworm cells but not normal cells in the same species, indicating that PG possesses antiviral activities. Taken together, PG is suitable for food additives owing to antimicrobial activities and its bright-red color.

3.2. Antimalarial activity

Malaria is a mosquito-borne infectious disease, which is transmitted by Plasmodium through the bite of Anopheles mosquitoes. Gerber et al. for the first time reported the anti-malarial activity of prodiginines. They found methylcyclodecylprodigiosin extended the lifespan of mice infected with Plasmodium berghei, but other prodiginines either had no therapeutic effect or showed toxicity to mice. Another study reported that cycloprodigiosin was an effective anti-malarial drug against P. berghei, with an IC50 of 11 nM. Its performance in anti-malarial test was even much better than the traditional antimalarial drugs, chloroquine, and its derivatives. In addition, four new prodiginine derivatives were synthesized and tested against four different sources of P. falciparum, and only isoheptylprodigiosin and 2-methyl-3-butyl prodigiosin exhibited strong inhibition activities.

Interestingly, prodiginines were also proven to be effective mosquitoicides, which have considerable potential in the biological control of mosquito larval populations by killing intermediate carriers and blocking the transmission route of Plasmodium sp. The research found that prodigiosin showed strong inhibition against early stage II of Aedes aegypti and Anopheles stephensi with a LC50 of 14 ± 1.2 μg/mL and 19.7 ± 1.12 μg/mL, respectively. The prodigiosin could inhibit H+-V-ATPase to decrease the pH in midgut and cecum of the fourth-stage larvae of A. aegypti. A drop in pH leads to reduced nutrient uptake and death of A. aegypti larvae. Besides, prodigiosin showed a good performance against mosquito larvae by the combining with other compounds or bacteria extracts. For example, prodigiosin could work as a photoprotectant to enhance the killing effect of Bacillus thuringiensis BtSV2 on A. stephensi stage IV larvae, and S. marcescens could inhibit A. aegypti by producing a combination of prodigiosin and other secondary metabolites like serratamolides .

3.3. Immunosuppressive activity

The inhibition of the cell cycle is a unique property of prodigiosin, which is found and established at non-apoptotic doses, like an immunosuppressant. Prodigiosin has been found to reduce graft versus host disease (GvHD). For this, no remarkable sign of toxicity was found in mouse models. In addition to that, prodigiosin also has another important effect, which is the delay in the progression of autoimmune diabetes. Literature reported that prevention of GvHD and collagen-induced arthritis (which were very common) was successfully carried out in mouse model. Undecylprodigiosin, metacyclo prodigiosin, and cycloprodigiosin all are different forms of prodigiosin-inhibited proliferation of T cells. Yet, various levels of in vivo toxicity were reported .

4. Conclusion

So prodigiosin was found as a significant pigment, which belongs to a family of natural red dye. It was found in various types of bacteria, but first, it was isolated from Serratia marcescens and also had unique pyrrolyl pyrromethane structures. It has several functions such as anti-fungal, anti-bacterial, anti-malarial, and anti-cancer activities and catalyzes the progression of apoptosis which means programmed cell death in different cancer cell lines.

To gain an in-depth understanding of the biosynthetic pathway of prodiginines, finding key factors that stimulate compound production is necessary. Finally, it is the question of compound stability. The prodiginines are very easy to be photolyzed, which largely limits their applications. Therefore, more efforts should be made to increase the chemical stability of prodiginines without losing their bioactivity.

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