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Considering Other Gene Regulation Mechanisms in *Microbispora coralline* : A Novel Idea for Microbisporicin Biosynthesis

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ABSTRACT

Many antibiotics have been used quite for a period of time and for so long that some bacteria have been known to be resistant. Lantibiotics are ribosomally synthesized post-transitionally from *Microbispora corallina* by a modification process of hydroxylation of proline and chlorination of tryptophan amino acid sequence in a coordinated fashion of gene regulation. Lantibiotics are becoming more popular as an antibiotic against Gram-positive and Gram-negative bacteria. Most especially its ability to combat methicillin-resistant *Staphylococcus aureus* (MRSA) infection which has been known to be a nosocomial infection causing microorganism. This review summarizes the potential opportunity in the comprehension of the gene regulation in *Microbispora corallina* for increased production of microbisporin lantibiotics. By considering the mechanistic procedure involved in gene regulation for*Microbispora corallina* at the level of DNA replication, transcription, post-transcription, translation, post-translation will foster increased production of microbisporin antibiotics to fight resistant microbial infection in the future. Exploring the working mechanism of association of cluster of genes such as MibW/MibX/MibR will provide a fertile ground for copious production of microbisporin in *Microbispora corallina.*

INTRODUCTION

Microbispora corallina is Gram-positive bacteria which belong to the family of Actinomycetes whose peptide synthesized products has been known in the treatment of many resistant infections, including methicillin-resistant *Staphylococcus aureus* (MRSA) Gram-positive bacteria. The main aim of this review research study is to understand the nature of gene regulation control in *Microbispora corallina* and its role in the biosynthesis of microbisporicin and some other polypeptides at the various level of gene regulation [1]. The synthesis of enzymes in bacteria follows a double genetic control (Jacob and Monod 1961). Only a few lantibiotics biosynthetic gene clusters derived from actinobacteria have been characterized thus far all of them are chromosomally located (Li and O' Sullivan, 2012). These clusters typically contain genes encoding the precursor peptide, enzymes responsible for a variety of post-translational modification proteins involved in export and immunity with frequent pathway-specific regulatory proteins (Chatterjee et al., 2005; Amison et al;2013). Most substrates formed and their derivatives play a very critical role in the gene regulation of Actinobacteria microorganism. Different levels of gene regulation occur in bacteria. These established levels of gene regulation in prokaryotes occur at the DNA, transcriptional, translational, posttranscriptional, posttranslational levels. The DNA rearrangement has been identified with gene regulation at the DNA level. In-Depth knowledge of this network of gene clusters enables more modification and manipulation for lantibiotic synthesis in *Microbispora corallina* actinobacteria. The purpose of this study is twofold. First, to understand the various gene clusters connection of promoter, regulator, and oppressor that takes part in the control of biosynthesis of lantibiotics in *Microbispora corallina*. Second, to apply this knowledge to enhance the synthesis of microbisporicin antibiotics in *Microbispora* corallina. The topic chosen is gene regulation in actinomycete-this is an area of the field in which earlier researchers have identified MibX and MibW as the sigma/anti-sigma factor complex for regulation of biosynthesis of microbisporicin antibiotics in *Microbispora corallina* (Lorena T. Fernandez-Martinez et al., 2015). Performing genetic manipulations with *bld* genes in Streptomyces coelicolor, it possible to achieve an increased level of antibiotics production in actinomycetes (Ostash, B.O. et al., 2011). With genetic manipulations of MibX/MibW/MibR genes, it is possible to achieve a significant increase in the level of microbisporicin lantibiotics production by *Microsbispora corallina.*

MATERIAL AND METHODS:

A computer-aided search of PubMed and Google scholar was done using a different combination of the keywords.”*Microbispora corallina* biosynthesis”“gene regulation in *Microbispora corallina*,” “Microbispora and antibiotics”, “*Microbispora corallina* and inorganic phosphates”. An initial search was done using gene regulation which showed 112 articles. The articles were analyzed and 86 relevant articles were included in the review. All the studies about the gene regulation in *M. corallina* were analyzed. The aim was to determine various gene regulations in *Microbispora corallina* at the DNA level, transcription level, posttranslational level, translational level and posttranslational level for knowledge manipulation that will enhance more lantibiotic biosynthesis in *Microbispora corallina.*

Principles

Transcriptional level regulation

The regulation at the level of the transcription plays an important role in the biosynthesis of peptide products in *Microbispora corallina* in further maturation of produced peptide products before post-translation modification. The biosynthesis of various and different metabolites are regulated by phosphate in association with catabolite activator protein. Production of these valuable compounds occurs only under phosphate-limiting nutritional conditions. In some few cases as well, evidence has shown that the negative phosphate control is made happen precisely at the transcription level. It has been proposed that phosphate control is used as a mechanism that triggers secondary metabolite biosynthesis when phosphate in the environment is depleted.

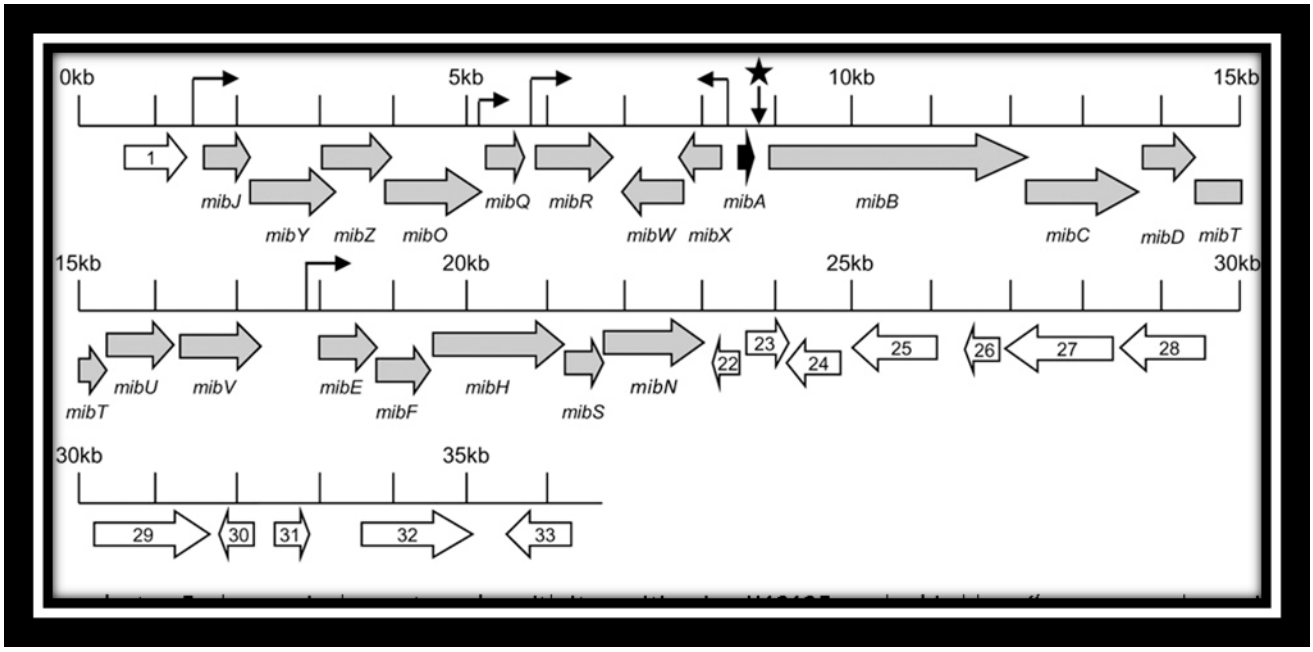

Fig. 1: The microbisporicin biosynthetic gene cluster (Foulstin and Bibb 2010).

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The microorganism cannot proceed at a normal rate (Martin and Demain, 2004). The ability to control and regulate phosphate in the synthesis of secondary metabolites is made to happen at the transcriptional and posttranslational level by antibiotic synthases activity.

Posttranslational level regulation

Microbisprocin lantibiotics, being a peptide containing 19-38 amino acid residues that are synthesized in the ribosome of *Microbispora corallina* with subsequent posttranslational modification confers stability of the residues. The network of cluster genes controls the biosynthesis of microbisporicin by posttranslational modification by chlorination of tryptophan and hydroxylation of proline residues. Different studies have pointed the involvement of tryptophan halogenases in the modification of peptide synthesized in the ribosomal organelle of *Microbispora corallina* and the regulation of specific pathway of gene cluster by an extracytoplasmic function of σ factor-σ factor complex.

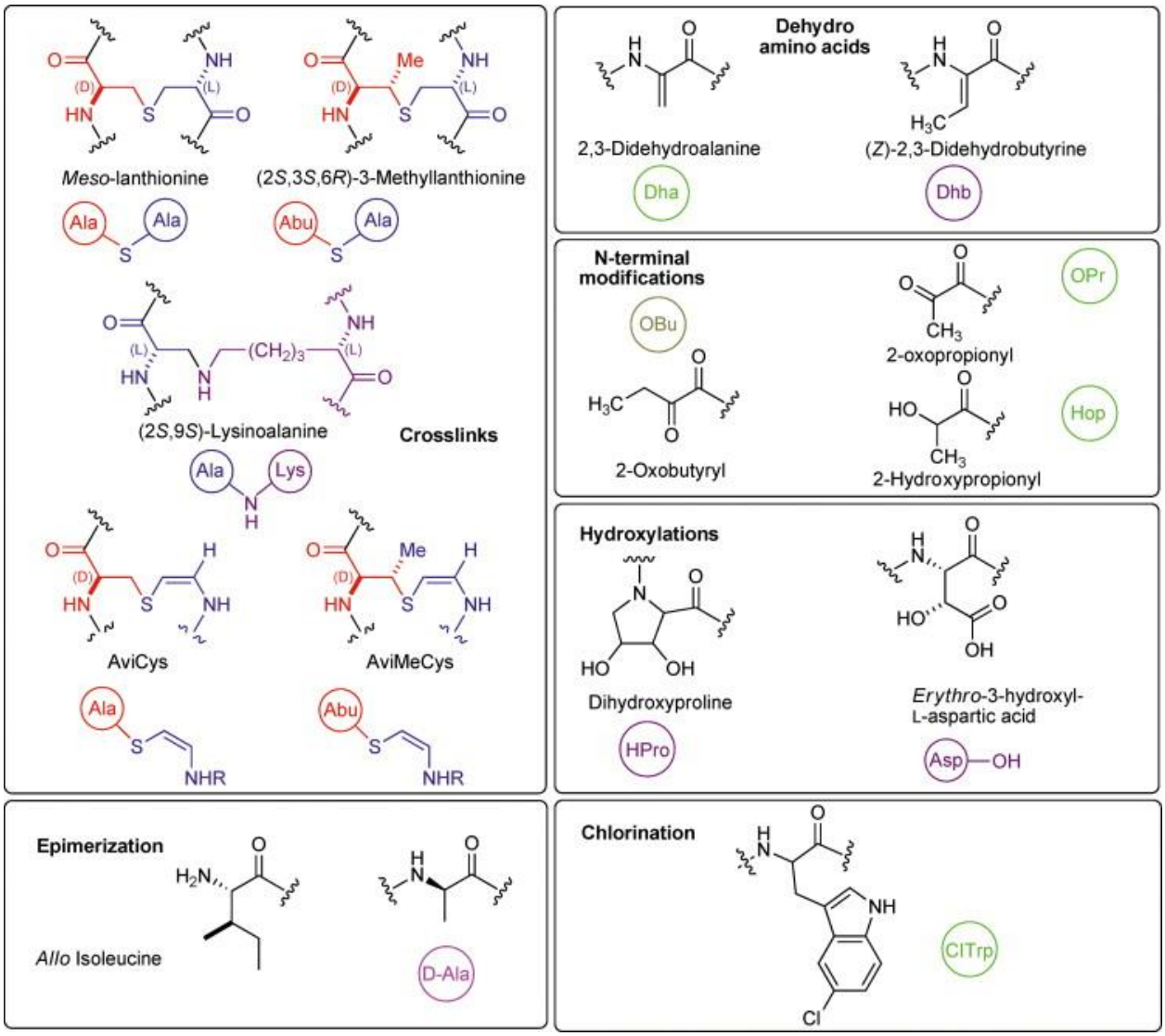

Fig. 2: The posttranslational modification of peptide synthesized by Chlorination and hydroxylation of Tryptophan and Proline respectively.

DISCUSSION:

It has been discovered by researchers that *Microbispora corallina* produced lantibiotics antibiotics which is active against microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). This has been made possible due to autoinduction of regulatory gene MibX, MibW and transcriptor MibR (Fernandez-Martinez L. T. et al., 2015). Understanding of the molecular mechanism of this gene and its manipulative express is an insight into the proliferation of *Microsbispora corallina* for antibiotic production (Rabyk M.V. et al., 2012). The enzymes synthesis in bacteria follows a dual genetic control. However, the structural genes determine the molecular organization of the proteins.

Furthermore, the functionally specialized, genetic determinants, called regulator and operator genes, usually control the rate of protein synthesis through intermediacy cytoplasmic components known as the repressors. The repressors can be inactivated (induction) or activated (repression) by certain metabolites. The complex system of regulation appears to operate directly at the level of the biosynthesis by the gene of a short-lived intermediate or biological messenger which becomes associated with the ribosomes where protein biosynthesis takes place usually. Guanosine tetraphosphate (ppGpp) inhibit stable RNA and causes the synthesis of mRNA (Bremer H. and Ehrenberg M. 1995) [1, 2]. This action is an expression of the relA gene and absence of the relA gene in *Microbispora corallina*. This strongly indicates that guanosine tetraphosphate plays an important role and function in the regulation of the gene of *Microbispora corallina*, (Fernandez-Martinez et al., 2015). The Alpha/Beta family, (also known as AB-superfamily) transport proteins involved in lantibiotic translocation, regulatory proteins controlling lantibiotic biosynthesis and proteins that protect the producing strain from the action of its own lantibiotic. By analysis of their genes and their products, this is giving a greater understanding of the complex mechanisms of the biosynthesis of these unique peptides for a fight against microbial organisms [3, 44]. Importantly, phosphate is regulating the synthesis of different antibiotics and other secondary metabolites that are being produced. Biosynthesis of these valuable compounds occurs only under the limited supply of phosphate. In some cases, there is evidence that is showing a negative phosphate controls is occurring at the transcriptional level. Negatively, the effect exerted by inorganic phosphate on the biosynthesis of secondary metabolites is observed in a wide range of microorganisms, including actinomycetes and probably has a wide significant ecological role. It has been proposed that phosphate control is used as the mechanism to trigger secondary metabolite biosynthesis when phosphate in the environment is depleted and therefore growth of the microorganism cannot proceed at the normal rate (Martin et al). In conditions, when the concentration of phosphate in the culture medium decreases drastically below a threshold level, bacteria, therefore, increase their production of a variety of metabolites that which serve as direct antagonists to another microorganism. Phosphate regulation that occurs in the biosynthesis of secondary metabolites is exerted mostly at the transcriptional and posttranscriptional (antibiotic synthases activity) levels [4, 28]. Microbisporicin is active against Gram-positive bacteria, including vancomycin-resistant enterococci (VRE). It has shown superior efficacy in animal models of multidrug-resistant infections compared with drugs of last resort, linezolid, and vancomycin. In M. corallina, it was proposed that unknown signal, possibly nutrient limitation, activates the positive-

regulator MibR in a growth rate-dependent manner. MibR triggers the expression of the MibABCD-TUV operon, leading to the precursor peptide biosynthesis (mibA), the core peptide proteolysis and export (mibTU). The precursor peptide export would cause the release of σ-MibX through inactivation of the anti-σ factor MibW. Sigma MibX controls, in addition, mibR, genes to confer immunity to microbisporicin (mibFF and mibQ) and genes required for tryptophan chlorination (mibHS) and proline hydroxylatrion (mibo) resulting in the formation and fully processed and active microbisporicin [5]. These gene clusters comprise, besides structural genes, genes encoding modification enzymes and transporters, which have to be tightly regulated to guarantee a fully modified active peptide. The number of regulations involved in the biosynthesis of antimicrobial peptides can vary from one to several regulators at the same time (Onaka et al., 2005). Moreover, the external factors such as nitrogen and carbon sources and temperature, pH, the presence of metal ions, oxygen play a significant role in the production of several known ribosomally post-translationally modified peptides [6]. The gene cluster consist of structural gene lanA that encodes pre peptide, modification gene lanB, C, M, L, labKC encoding enzymes that introduce thioether rings, transporter (lanT) gene that exports modified peptide as well cleaves leader peptide for and extracellular protease (lanP) that removes the leader and immunity gene (lan I (H) and lan FEG that protect the producing bacteria from being harm by its own synthesized product. The regulation of lantibiotics biosynthesis is done either by quorum-sensing or by growth phase-dependent mechanism's (Charterjee et al., 2005). Quorun sensing system consists of a receptor histidine kinase (lanK) and its cognate transcriptional response regulator (lanR) (McAulifee et al. 2001; Bierbaum & Sahl 2009) [7, 8, 9]. There is a growing number being identified from Actinobacteria phylum and some of these exhibit novel modifications leading to increased functional diversity among lantibiotics[11]. To identify secondary metabolite genes clusters, the analysis pipeline antiSMASH was run on the genome, giving an overview of the secondary metabolite potential of this strain. A total of 20 potential clusters genes for secondary metabolites were identified in the *Microbispora* corallina genome, in addition to the mlb cluster gene [12, 13].

CONCLUSION

Majority of the recent analysis of genome and sequencing and experimental research vehemently indicate that a more complex gene regulation network is yet to be explored and discovered. Understanding of these intricate the network in the coordinated gene regulation

will increase the biosynthesis of microbisporicin lantibiotics in *Microbispora corallina*. By giving recognition to the fact that gene regulation for biosynthesis could be explored and be manipulated at the level of DNA, transcriptional, posttranscriptional, translational and posttranslational stage of biosynthesis will foster abundant biosynthesis for microbisporicin lantibiotics production to fight against a fast-growing drug-resistant microorganism. The autogenous regulation of protein and RNA of its own product by a repressor protein that are a target for mRNAs as the initiation codon (AUG) and the single-stranded 5`leader site of action respectively are complex regulatory mechanisms that must be explored adequately in the future research studies for the auto-induction biosynthetic process of microbisporicin lantibiotics.

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Conflict of Interest: None has been declared.

Ethical Approval: Not required

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