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Myxobacteria as a Promising Source of Novel Natural Products

Dharmesh Harwani[1]
[1]*Department of Microbiology, Maharaja Ganga Singh University, Bikaner, Rajasthan, India*

Abstract: ***For more than a century bioactive natural products from plants and microorganisms have played a fundamental role in drug discovery. Bacteria have been by far the most innovative and inexhaustible resource for useful metabolites in the past and will certainly remain. Actinomycetes have been screened for several years, while the myxobacteria have been ignored in the past. Actinomycetes (Gram-positive bacteria) and myxobacteria (Gram-negative bacteria) both groups have a number of analogous characters, as they both have a high GC content and huge genetic makeup and they both differentiate by forming resting phase as spores. But in the present time, myxobacteria with many species of* Bacillus*, action my cetes, fungi have also been considered as top producers of secondary metabolites of therapeutic use. Myxobacteria are a group of proteo bacteria which reside mainly in soil and are ubiquitous, soil-dwelling, cellulose decomposers and predatory bacteria. Myxobacteria differ to other bacteria because of their uncommon behaviour during their lifecycle, most notably their ability to move through a thin slime and capable of developing social conduct. Intriguingly, numerous screening efforts have revealed a substantial proportion of the myxobacterial secondary metabolites to have activities against human bacterial and viral infections and cancer. The following brief review is an attempt to discuss history, ecological behaviour and genetics of secondary metabolite production in myxobacteria.***

Keywords: Myxococcales, Gram-negative, Slime bacteria, Antibiotic gene clusters, Therapeutics

I. INTRODUCTION

Myxobacteria areprimarily soil microorganisms. They colonize soil of neutral or slightly alkaline pH,the bark of trees and rotting woods of tropical and subtropical regions[1-4]. Dung of various animals, especially herbivores is an excellent source of myxobacteria. Importantly, aged dung is considered arelatively better source for myxobacterial isolation than the fresh dung and prefer aerobic and mesophilic growth conditions. They are known as auseful source of structurally complex bioactive secondary metabolites making them highly valuable for industrial and pharmaceutical therapeutic applications[5-7]. In the past decade, unusual myxobacterial genera have been unearthed that represent the moderatelyhalophilicas well as thermophilic groups[8-10]. In addition to that, the discovery of the anaerobes[11] and the facultative anaerobes[12]propose that myxobacteria are diverse in nature. These social behavior exhibiting bacteria move by an axonal cellular motion known asgliding[13]. The cells of myxobacteria grow independently but form collective swarms under nutrient scarcity and developtransient structures known as fruiting bodies that can harbor around 10^5 individuals[14]. Cells within these structures become myxospores. During cooperative feeding, individual cells arrange in waves that travel in a rippling motion[13]. When vegetative myxobacteria encounter prey they neutralize them by secreting antibiotics and hydrolytic enzymes[15]. By excreting these enzymes, they are able to lyse other bacteria, yeasts and organic material to assimilate proteins and nucleic acids. Sporulation is triggered by signaling mediated by the cell-cell contact if nutrients are available, and eventually, new swarms are developed upon germination of myxospores[16]. These processesare controlled by myxobacteria by a highly evolved mechanism of extracellular and intracellular signaling involvingmany proteins and metabolitemolecules[17]. The shape of the fruiting bodies varies between species to speciesthat can develop intothe tall and tree-like structurein Stigmatellaaurantica and Chondromycescrocatus to globular formations in Angiococcus and Sorangium species. Even the colour between species differs from yellow, red, brown or black[18-22]. For the classification of the different species of myxobacteria,fruiting bodies and swarming arrangements are commonly considered[23]whichare reminiscent sometimes more of eukaryotic fungi[24].

II. TAXONOMY OF MYXOBACTERIA

The first myxo bacterium, Polyangiumvitellinum was discovered in 1809 by the German botanist H.F. Link but it was characterized as a fungus inaccurately because of the characteristic fungal life cycle[25]. Roland Thaxterin 1892 identified these organisms as bacteria[26]. The myxobacterial G+C content of 67-70%[27,28] differentiates them from the Cytophagales. The genomes of M. xanthus and S. aurantiaca is in the range of ~3.1-3.8 x 10^9 da and about 24-53% larger than the *E. coli* genome[29,30]. Myxobacteria belong to

the δ- Proteobacteria based on their 16S rRNA gene sequence analyses[31-33]and fatty acid and phylogeny correlation[34]and build the order Myxococcales. The order consists of 55 species including 28 genera (Figure 1) and these numbers are expected to increase near in future after the complete portrayal of yet-to-be-identified/published novel isolates from environmental samples[35].

III. ANTIBIOTIC SIGNALING AND MICROBIAL PREDATION

It has long been speculated that secondary metabolites play a competitive advantage to the producer by inhibiting the growth of nearby microorganism/s in the vicinity. The conception is consistently receiving various arguments[36,37] because the concentration of antibiotics that act as antimicrobials is usually very high. Therefore, it is unclear that how microorganisms could produce an effective antibiotic concentration high enough to kill their competitors in the soil environment. Subsequently, it has been published that antibiotics at sub-lethal concentrations act as signaling molecules and could significantly alter microbial gene expression[38,39]. Myxobacteria have interesting properties of predation and are also known as producers of the useful class of bioactive secondary metabolites[40]. Predation involves their ability to glide and establish stable prey contact and killing which involves both secreted diffusible molecules and direct cell to cell contact[41]. The killed preys are digested into smaller molecules for consumption. Till date very little is known about the molecular mechanism of predation which has already been described long ago[42]. About 20% of myxobacterial secondary metabolites have antibiotic activity[43] hence, a possible role between antimicrobial production and microbial predation exists[44]. On the other hand, actinomycetes, an inexhaustible producer of secondary metabolites are not known to pray other microbes and are not considered predatory. The small metabolite molecules produced from myxobacteria targeting bacteria and fungi are around 29% and 54% respectively and their higher exponential production strengthens the notion that myxobacteria secondary metabolites are exploited in predation[14]. Interestingly, a large number of these metabolite molecules have been found bioactive against human pathogens suggesting that many of these metabolites target evolutionarily conserved processes or metabolic pathway or structural features[45-47].

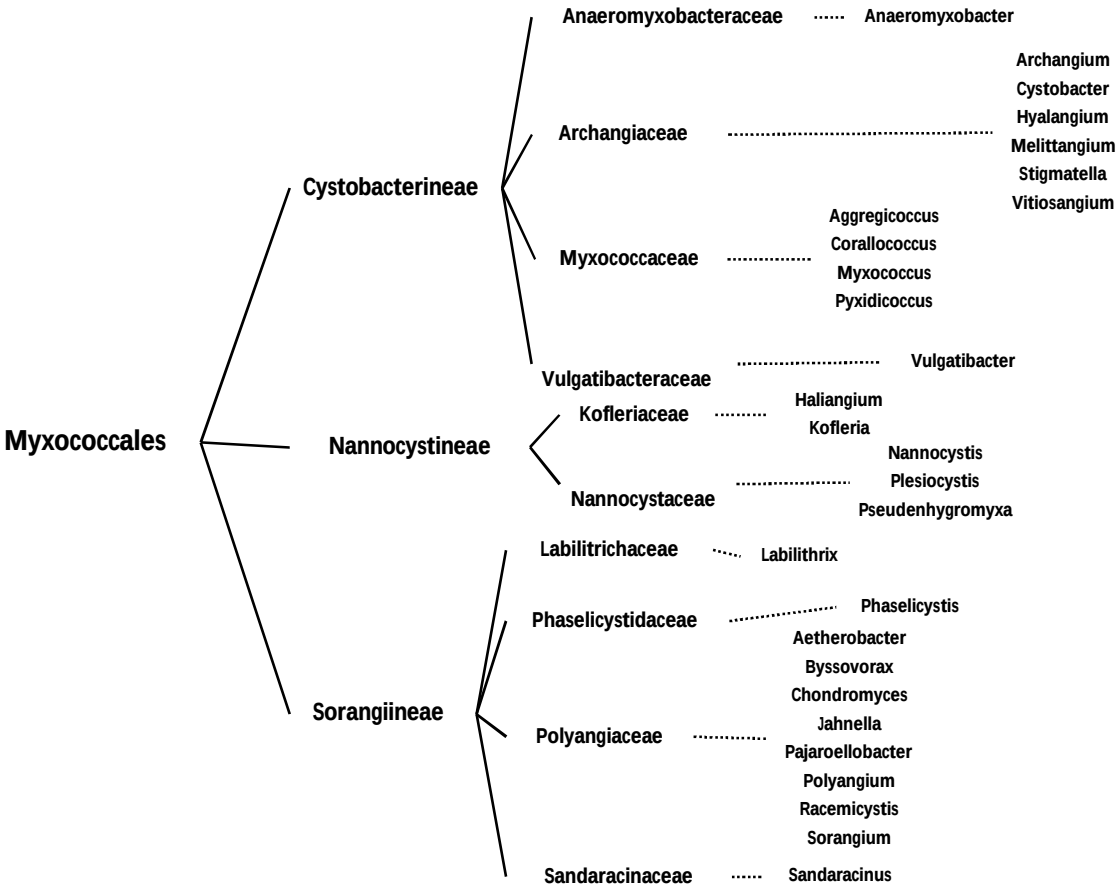

Fig. 1: Taxonomy of Myxobacteria

IV. GENE CLUSTERS FOR SECONDARY METABOLITE PRODUCTION IN MYXOBACTERIA

The largest bacterial genome reported till date belongs to Sorangiumcellulosum (~13.000 base pairs) with around 20 secondary metabolite genetic loci[18]. Another myxobacterium, Myxococcusxanthus has around 18 secondary metabolite gene clusters roughly equals to around 9% of its genome[48]relative to the actinomycete sp. with around 6% of genes exploited in the production of secondary metabolite[49,50]. Because of having large genomic circuit involved in natural product formation and diverse existence in nature, myxobacteria seems to be an immense reservoir ofexploration and exploitation for yet to be identified metabolites of therapeutic use. Moreover, myxobacterial secondary metabolites exhibita huge diversity of novelchemical scaffolds(40%) such as hybrids of polyketides and non-ribosomal peptides which have not been observed to be produced by other bacteria[23,51,52]. Furthermore, as compared to the products derived from actinomycetes, most metabolites from myxobacteria are not glycosylated[53]. Some of the examples in this category include inhibitors of mitochondrial respiration, microtubule assembly, carboxylase and polymerase inhibitors and small molecules interfering in eukaryotic protein synthesis[40].Considering these enormous genomes with the abilities to produce important bioactivities of therapeutic use, myxobacterial species from the natural environment may pave the path near in future to unearth solutions for deadly microbial pathogens and will certainly add new dimensions to fight back with multidrug-resistant pathogens[35,40].

V. ANTIBIOTICS FROM MYXOBACTERIA

Oxford[54] had shown that excreted molecules secreted by Myxococcusvirescens were inhibitory to Staphylococcus aureus. Several reports on antibiotic activities are then published from myxobacterial speciesbut intriguingly no substance was isolated[55-57]. The speculation that myxobacteria could not be grown in liquid mediumprevailed until Peterson et al.[58] demonstrated that some strains of Polyangium produce myxinantibiotic at the end of the logarithmic growth phase. Noren and Odhan[59] isolated iso-branched fatty acids from Myxococcusxanthus which inhibited the germination of Fusarium species. The first complete structure of antibioticambruticin from myxobacteria was elucidated in 1977[60]. Since that time the search for new antibiotics from myxobacteria is continued. In addition to the antibacterial, antiviral and antifungal, myxobacterial metabolites act as antitumor drugs and exhibit insulin-sensitizingand immune regulatory characteristics[40,61-63].Additionally, antimalarial, antihypertensive, antihypercholesterolemic, antidiabetic and insulin-sensitizing characteristics can also be attributed to myxobacterial metabolites[64-66]. Another significant capability of myxobacteria is the production of polyunsaturated fatty acids like eicosaoentaenoic acid and docosahexaenoic acid[67]. More than hundred novelchemical scaffolds have been discovered from myxobacteria[68,69].The myxobacterial compounds with the highest application in pharmaceutical industry are epothilones A and B from Sorangiumcellulosum[70]. Other than epothilones, the common medication for breast cancer was taxanes, anthracyclines and capecetabine, which because of an over-expression of efflux pumps in cancer patients, could be removed very easily from the targeted cancer cell[71-72]. As an effective alternative to the chemotherapies usingtaxanes and anthracyclines, a semi-synthetic epothilone derivative ixabepilone was developed for monotherapy of patients at different stages of breast cancer[73]. As compare to the other available pharmaceutics, ixabepilone is least affected by multidrug-resistant mechanisms and thus assist in elimination of the tumor more effectively[74]. Today, modified versions of these compounds are tested in clinical trials against various types of cancer. Apart from that, during the last few years some very promising compounds have also been described from different species of myxobacteria showing diverse biological activities (Table 1). These include, antibiotics disciformycin A and B isolated from Pyxidicoccusfallax which have been found to be bioactive against Gram-positive bacteria including MRSA strains[75]. Corallopyronin A, from Corallococcuscoralloides was described to be a promising compound against filarial nematodes causing lymphaticfilariasis and onchocerciasis[76.77]. Nannocystin A was isolated from Nannocystis sp.[78]which act as aninhibitor of the eukaryotic translation elongation factor 1α. The compound has an overlapping binding site with the compound didemnin B (anticancer). The chemical derivates of didemnin B has reached in phase two clinical trials[79]. The macrolide Chlorotonil A was isolated from Soranguimcellulosum strainwhich exhibits pronouncedantimalarial activity[80]. The compound isolated from Cystobactervelatus, cystobactamidesexhibitspotent inhibitory effects against pathogenic Gram-negativeE. coli, A. baumannii and P. aeruginosastrains[81].

Table 2: Important Myxobacterial Compounds and their Biological Activities

Compound	Activity	Mode of action	Species	References
Mbruticin	Antifungal	Interfere with high osmolarity glycerol	S. cellulosum	[60]

		(HOG) signaling pathway		
Myxothiazol	Antifungal	Inhibits electron transport	M. fulvus	[92]
Myxovirescin	Antibacterial	Inhibition of signal peptidase	M. virescens	[93]
Myxovalargin	Antibacterial	Inhibits of protein synthesis and damages cell membranes	M. fulvus	[76,94]
Aurachins	Antibacterial	NADH oxidation	S. aurantiaca	[95]
Sorangicin	Antibacterial	Inhibits RNA polymerase	S. cellulosum	[96]
Rhizopodin	Cytostatic	Alteration of protein phosphorilation	M. stipitatus	[97]
Crocacin	Antibacterial	Inhibits electron transport	C. crocatus	[98]
Stigmatellin	Antibacterial	Inhibits electron transport	S. aurantiaca	[98]
Ripostatin	Antibacterial	Inhibits RNA polymerase	S. cellulosum	[99]
Chrondramide	Antifungal/ cytostatic	Interfere with actin polymerisation	C. crocatus	[100]
Epothilones	Cytotoxic	Inhibition of microtubule function	S. cellulosum	[101]
Cystothiazol	Antifungal/ cytostatic	inhibits submitochondrial NADH oxidation	C. fuscus	[102]
Melithiazols	Antibacterial	inhibit NADH oxidation	M. lichenicola, A.gephyra	[103]
Etnangien	Antibacterial	Inhibits nucleic acid polymerases	S. cellulosum	[104]
Cystobactamids	Antibacterial	Inhibit type II topoisomerase	Cystobacter sp.	[81]
Disciformycins	Antibacterial	not been identified	P. fallax	[75]
Soraphens	Antifungal, antiviral, cancerocidal, immuno-regulatory, insulin sensitizing	Inhibit acetyl-CoA carboxylase	S. cellulosum	[61,62,65,66,105,106]

VI. CONCLUSION

Understanding the biology of natural products from myxobacteria may lead to discover much needed novel chemical scaffolds of bioactive antimicrobials. Moreover, understanding of natural products can be exploited in the laboratory to evolve strains with improved yieldand potencies[82,83]. The biological significance of secondary metabolite production in bacteria is largely remained elusive. In the case of antibioticsan obvious role exists, that in natural environment antibiotics confer a competitive advantage to the producer by inhibiting the growth of nearby competitor. More recently, thenotion has been criticized as presented above[37]. Myxobacteria bacteria are a promising source forexploration of novel antibiotics because the genes encoding the production of secondary metabolites have consistently been found to be overrepresented in theirgenomes. Because of this reason speculations can

also be made that myxobacteria can sense their external environment to regulate the expression of genes involved in antibiotic production and thus production and appropriate secretion of antibiotics. In contrast, the biological role of antibiotics produced by genus Streptomyces remains a puzzle to some extent. However, one possible explanation could be given that that antibiotic molecules produced in vicinity could serve as intercellular signals[84]. In other cases, the biological function of antibiotics has been clearly demarcated[39]. Regarding the available information on the chemistry of myxobacteria, it seems likely that every strain has the potential to produce at least a single class of natural products with potent antimicrobial activity. The discovery of chemical relatives such as gulmirecins and disciformycins in different strains of Pyxidicoccusfallax supports this idea of species-specific antibiotics[85] . Interestingly, the higher production of myxovirescins and corallopyronins in Myxococcusxan thus and Corallococcuscoralloides suggests a positive correlation between taxonomy and secondary metabolism[86,87]. Finally, the understanding of antibiotic regulation and its secretion into a given environment may lead to the identification of potentmyxo bacterial strains which may produce much needed secondary metabolites of therapeutic use[55].To exploitmyxo bacteria more fully to discover novel antibiotics, new technologies such as cloning of antibiotic genes and expression of complex molecular structures inheterologous organisms, *in silico* tools to predict targets and nanoparticles mediated delivery strategies will definitely play a crucial role in the future[88-91].

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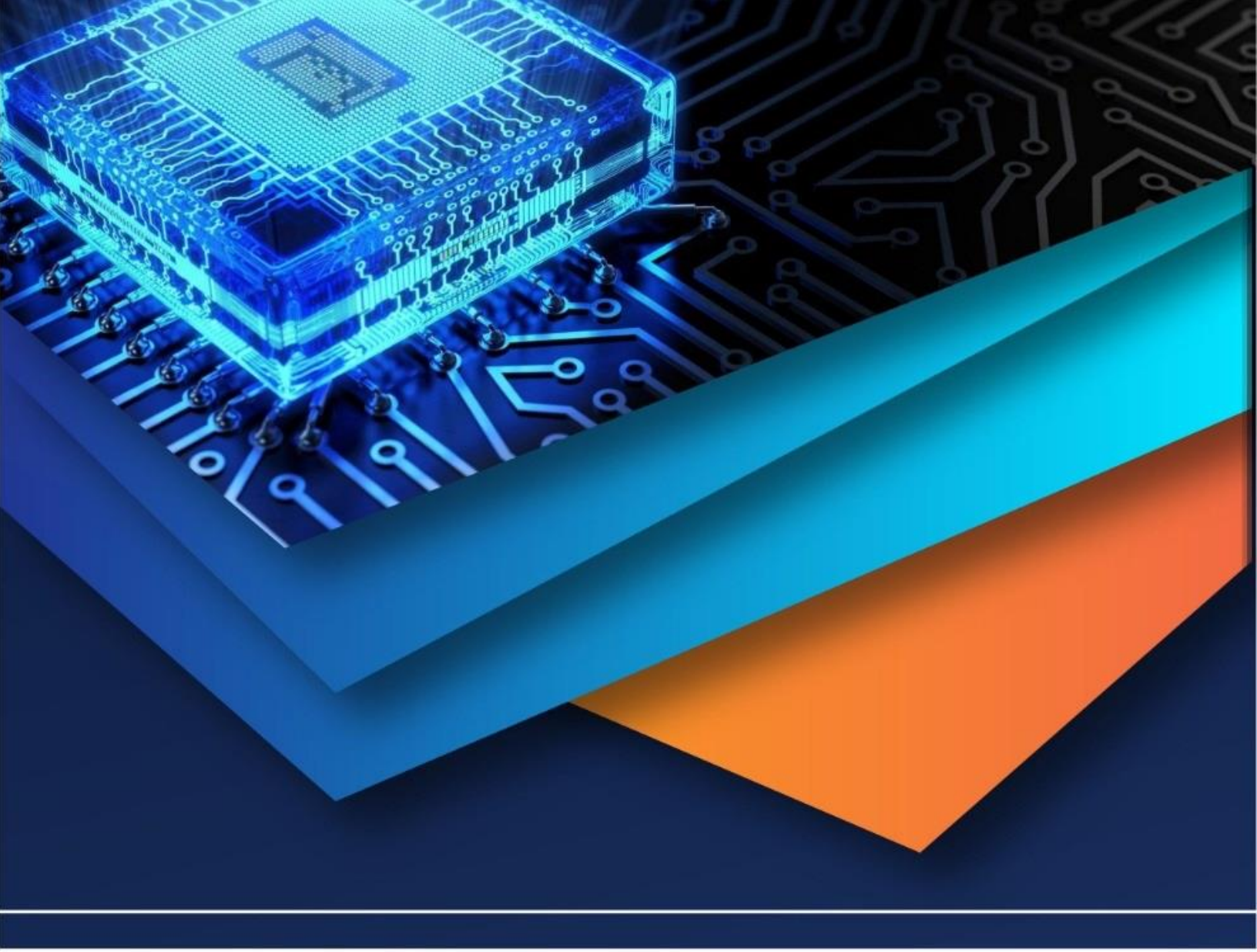

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