Review

Research and Development of Marine Bio-Organisms - Introduction and Its prospect -

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Abstract A large number of natural products were worldwidely discovered from maine organisms. There are many secondary metabolites produced by maine organisms which showed very strong bio-activities and distinct bio-active mechanisms. In korea, about 350 secondary metabolites including more than 280 novel compounds have been isolated and structually defined. Many researches for developing products such as cosmetics, functional food materials, anti-fouling substances are being performed using distinct activities of marine organisms. Although the research on marine natural products has been remained at its initial or developing stage of drug development, significant progress has been made for isolation, structure determination and bioassay of secondary metabolites.

Key words : Maine organisms, natural products, secondary metabolites

Introduction

Ocean is enormous and provides various different environments such as temperature, light, pressure, salt concentration, therefore tens of millions of living organisms live there. However, we do not fully understand these living organisms and even worse in understanding the physiological function and metabolism of marine bio-organisms.

Based on the differences in their secondary metabolites between land and ocean living organisms, detection and search for chemical substances possessed marine organisms, especially drug, medicine-related materials which have useful bioactivity has begun. This idea became real when nucleoside unknown for land organisms was discovered from the Caribbean Sponge in Early 1950. Later, practical researches for development of drug substances from marine organisms started when anti-cancer substances and antiviral agents (Are-C,1) were discovered from these nucleoside. Coincidentally, the worldwide proclamation of necessity for ocean development and rapid increase of death toll for cancer patient accelerated this trend and development. These trends raised a new area of study, marine natural product chemistry in early 1970 and active researches were performed to develop medicines, specifically, anti-cancer substances from marine lifes in numerous colleges, institutes.

Consequently, more than 13,000 new natural products were discovered from marine organisms worldwide. Despite there are a few promising chemicals as bioactive drugs, developing these chemicals as a drug was delayed and even failed because 1) its structure was complex and it was not able to supply samples by the chemical synthesis. 2) Quantity obtained from marine organisms is not enough, 3) it has very high toxicity. However, approved drugs will be available very soon and the number of clinically tested-medicines increases annually. In addition, there are many secondary metabolites produced by marine organisms which showed very stong bio-activities and distinct bio-active mechanisms. Approximately 350 secondary metabolites including more than 280 novel compounds have been isolated and structurally defined in Korea. These are strong candidates developed for the research chemical reagents, even if not medicines, though. Actually, many marine natural products are being used for research reagents. Many researches for developing products such as cos-

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metics, functional food materials, anti-fouling substances are being performed using distinct activities of marine organisms. Hydrocolloids originated from seaweed were used diversely so long and are being applied to various aspects. Proteins of marine organisms also attracted researchers' attention.

Although the research on marine natural products has been remained at its initial or developing stage of drug development, significant progress has been made for isolation, structure determination and bioassay of secondary metabolites. (Fig.)

Drug Development

Necessity for drug development from marine organisms dramatically increased when rapid increase of death toll for cancer patient showed up, and most active searches and detection efforts were made for anti-cancer substances. This trend now continues and some promising drugs for anti-inflammatory disease, analgesic substances, Alzheimer cures, anticancer agents were discovered. Currently, more than 30 compounds are being tested clinically. (Table.) Conus of the Mollusk, Gastropods recently attracted a lot of researchers' attention. Conus Class uses the unique poisoned arrow to catch foods and stored toxins are released when they pierce their foods. Analysis of Conus Toxin showed it contained many different kinds of peptides carrying various biological activities. several kinds of peptides such as α-conotoxin, μ-conotoxin(acting on Na channel), ω-conotoxin(acting on Ca channel) were isolated from various conus. Some of these conotoxins are being tested clinically as an analgestics and SNX-1000 (ziconitide) is expected to be approved as an analgestic in US in the very near future.

Table. Major marine organisms and substances currently in the clinical-test

Species	compound	disease	stage
Porifera			
Agelas mauritianus	KRN7000[1]	cancer	I
Halichondria okadai	Halichondrin B	cancer	I
Cymbastella sp.	HTI-286[2]	cancer	I
Haliclona sp.	Manzamine A	malaria	II
Petrosia contignata	IPL-567[3]	inflammation	I
Coelenterate			
Pseudopterogorgaia elisabethae	Methopterosin[4]	inflammation, · trauma	I
Nemertinean			
Amphiporus lactifloreus	GST-21[5]	Alzheimer	I
Mollusk			
Dolabella auricularia	Dolastatin 10	cancer	II
D. auricularia	LU-103798[6]	cancer	I
Elysia rufescens	Kahalalide F	cancer	II
Conus magnus	Ziconitide[7]	aches	III
C. catus	AM336[8]	aches	II
C. geographus	CGX-1007[9]	aches	II
C. tulipa	Conantokin-T	aches	II
Ectoprocta			
Bugula meritina	Bryostatin	cancer	II
Protochordate			
Aplidium albicans	Aplydine	cancer	II
Ecteinascidia turbinata	Ecteinascidin 743	cancer	III
Pisces			
Squalus acanthias	Squalamine	cancer	II
shark Cartilage	AE-941[10]	cancer	II
swellfish	Tetrodotoxin	aches et al.	II

[1]Agelasphin Derivative; [2]Contignasterol Derivative; [3]Hemiasterlin Derivative; [4]Pseudopterosin Derivative; [5]Anabaseine Derivative; [6]Dolastatin 15 Derivative; [7]w-Conotoxin CVⅡA; [8]w-Conotoxin CVID; [9]contulakin-G; [10]Shark cartilage extracts.

Chemical Research Reagents

Animal and plant toxins were widely used as research reagents (pharmacological reagents) in neurological physiology area so long. In mid 1960, since tetrodotoxin from swellfish was discovered to inhibit the intracellular input of Na ion by specifically repressing the Na channel, various researches using toxins were done in different areas including the neuro-transmission mechanism. Subsequently, significant amount of new informations for neurological physiology were obtained. Discovery of these chemical reagents greatly contributed to the academic progresses. It is obvious that if a compound discovered in which any specific enzyme and its receptors interact, information regarding their live interactions between specific enzymes and receptors are likely studied vastly and accumulated easily. The demands for these specific reagents are very high. One good example for this is discovery of PP(protein phosphatase) inhibitors type1, and 2A, Okadaic acid and CalyculinA. These compounds were originally isolated as a cellular toxin from Sponges, when their reaction mechanisms of enzyme inhibition were revealed, physiological mechanisms of protein phosporic acidization and dephosphoric acidization were discovered and finally led to reveal the information of intercellular communication, muscle contraction, oncogenesis. Chemical reagents already showed significant industrial importances. Most of physiologically-active substances posses remarkably high bio-activities, and distinct chemical structures and they likely will be used to study their interaction mechanisms.

The Others

Marine Biotechnology is a new subject in which specific functions of marine organisms are studied and are applied for the large amount of foods and useful substances production. Recently, restriction for use of organic tin(Sn) type antifouling-agents such as TBT and TBTO led the researches for development of environment-friendly anti-fouling agents very active worldwide. In addition, cement substances secreted from periphyton such as Sea mussel and Oysters attaching them to the bottom of sea rocks attracted a lot of attentions from Scientists. Specific enzymes carried by marine organisms were utilized as research purposes so long and recently fluorescent proteins such as green fluorescent proteins derived from Coelenterates also came under notice. Studies have been focused on brown algae, coelenterates, and sponges. Recently marine microbes have been emerged as new sources of bio-active compounds.

Future Prospects

Most important point in utilizing useful compounds possessed by the marine organisms as medicines is how to supply them in large quantities. In developing anti-cancer substances, for example, few substances were developed to the clinical-test stage, because complex structures and quantities available prevented scientists to fully investigate the severity of their toxicity even though they showed strong activities. Actually, collecting several hundred Kgs, or a few tons of marine organisms and extracting anti-cancer substances could cause severe ecological problems. Without solving this problem, development of medicines from marine organisms will be fruitless and that is major obstacles in marine Biotechnology. Peptides such as Dolastatin 10, dehydrodi demnin B, Glycolipid such as KRN7000 and several promising substances isolated from sponges are good examples for this. Recently, Aquacultures solved this kind of problems arisen from Halichonndrin B which was discovered from *Halichondria okadai* and showed strong anti-cancer activity and low toxicity, but its complex structures prevented the chemical synthesis of these substances. Aquacultural researches are actively performed to harvest in a large quantities for several promising drug candidates such as bryostatin 1 isolated from *Bugula neritina*, ecteinascidin from *Ecteinascidia tubinata, Laminaria japonica.*

In addition, efficient means are being studied to increase a mount of supply for β-carotene, astaxanthin, DHA, EPA: β-carotene, astaxanthin are produced by incubation of microalgae, large quantity of EPA and DHA might be produced by fermentation of marine bacteria recently discovered. Recently, It was demonstrated that the symbiotic bacteria produced strong anti-cancer substances discovered by Japanese Sponge, *Theonella swinhoei* and its synthetic gene is cloned successfully. Therefore, when this cloned synthetic gene is expressed in *E.coli*, mass production of these anti-cancer substances is possible. Actually, this method is more reliable compared to production on a large scale by the aquacultures and will be used more often. Currently, it is impossible to incubate this kind of bacteria, but possible to produce useful substances originated from marine organisms by fermentation.

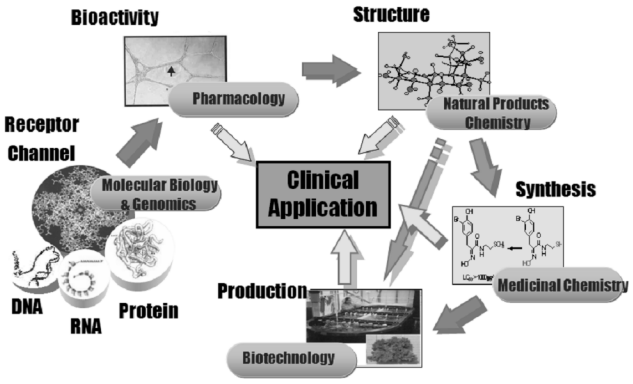

Fig. Drug development of marine natural products: multi-disciplinary approach(courtesy from Dr. J. Shin).

We in Korea have plenty of unutilized resources such as Seaweed, Sponges, efficient industrialization of these organisms is very important in creating new businesses. Research direction and scopes are gradually expanding to more industry-oriented purpose. Marine organisms provides highly new, useful resources such as developing medicines, but most critical thing is how to utilize these substances.

References

1. Anderson L. 1995. *New Scient.* **148**, 5.
2. Bajpai P. and Bajpai P. K. 1993. Eicosapentaenoic acid (EPA) production from microorganisms: a review. *J. Biotechnol.* **30(2)**, 161-183.
3. Blunt J. W., Copp B. R., Munro M. H., Northcote P. T., Prinsep M. R. 2004. Marine natural products. *Nat. Prod. Rep.* **21(1)**, 1-49.
4. Davidson S. K. and Haygood M. G. 1999. Identification of sibling species of the bryozoan *Bugula neritina* that produce different anticancer bryostatins and harbor distinct strains of the bacterial symbiont "Candidatus Endobugula sertula". *Biol. Bull.* **196(3)**, 273-280.
5. Duckworth A. and Battershill C. 2003. *Aquaculture* **212**, 311.
6. Faulkner D. J. 2002. Marine natural products. *Nat. Prod. Rep.* **19(1)**, 1-48.
7. Fusetani N. 2004. Biofouling and antifouling. *Nat. Prod. Rep.* **21(1)**, 94-104.
8. Haefner B. 2003. Drugs from the deep: marine natural products as drug candidates. *Drug Discov. Today* **8(12)**, 536-544.
9. Hildebrand M., Waggoner L. E., Liu H., Sudek S., Allen S., Anderson C., Sherman D. H., and Haygood M. 2004. bryA: an unusual modular polyketide synthase gene from the uncultivated bacterial symbiont of the marine bryozoan *Bugula neritina*. *Chem. Biol.* **11(11)**, 1543-1552.
10. Ireland C. M. *et al.* 1993. Marine Biotechnology, Vol.1. p.1, Plenum, New York.
11. Jordan M. A. and Wilson L. 2004. Microtubules as a target for anticancer drugs. *Nat. Rev. Cancer* **4(4)**, 253-265.
12. Livett B. G., Gayler K. R., and Khalil Z. 2004. Drugs from the sea: conopeptides as potential therapeutics. *Curr. Med. Chem.* **11(13)**, 1715-1723.
13. McGovern P. E. and Michel R. H. 1990. *Acc. Chem. Res.* **23**, 152.
14. Mendola D. 2003. *Biomol. Eng.* **20**, 441.
15. Munro M. H., Blunt J. W., Dumdei E. J., Hickford S. J., Lill R. E., Li S., Battershill C. N., and Duckworth A. R. 1999. The discovery and development of marine compounds with pharmaceutical potential. *J. Biotechnol.* **70(1-3)**, 15-25.
16. Piel J., Hui D., Wen G., Butzke D., Platzer M., Fusetani N., and Matsunaga S. 2004. Antitumor polyketide biosynthesis by an uncultivated bacterial symbiont of the marine sponge *Theonella swinhoei*. *Proc. Natl. Acad. Sci. U.S.A.* **101(46)**, 16222-16227.
17. Shu Y. Z. 1998. Recent natural products based drug development: a pharmaceutical industry perspective. *J. Nat. Prod.* **61(8)**, 1053-1071.
18. Tangley L. 1996. *BioScience* **46**, 245.
19. Terlau H. and Olivera B. M. 2004. Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol. Rev.* **84(1)**, 41-68.
20. Tremblay J. F. 2000. *Chem. Eng. News* **78**, 31.
21. Yano Y., Nakayama A., and Yoshida K. 1997. Distribution of polyunsaturated fatty acids in bacteria present in intestines of deep-sea fish and shallow-sea poikilothermic animals. *Appl. Environ. Microbiol.* **63(7)**, 2572-2577.