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Gene Clusters from Plants to Microbes: Their Role in Specialized Metabolism and Drug Development

Chakraborty P*

Kalpana Chawla Centre for Space and Nanosciences, Indian Institute of Chemical Biology, India

***Corresponding author:** Prasanta Chakraborty, Kalpana Chawla Centre for Space and Nanosciences, Indian Institute of Chemical Biology, India, Tel: +91-332416 7786; Email: prasanta3274@yahoo.in

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Editorial

Most of the drugs we use as anticancer agents, anti-infective agents, heart protective and antidiabetic are secondary metabolites of plants or microbes or derived from natural products. Plant or microbe genomics research and their gene clusters can find many unknown enzymes/new metabolic pathways [1,2] and thus it is believed that this field of research has far greater potential to produce specialized metabolites than was thought from classic bioactivity screens. Genomic research of fruit plants, crops, medicinal plants give information's about gene clusters which helps to identify gene-metabolite linkage. These important metabolites are used as either plant defense or as medicines for human use. There are now examples in which many genes encoding certain plant natural product pathways are grouped together in biosynthetic gene clusters. Analysis of a draft genome sequence of a medicinal plant Catharanthus roseus shows partial clustering of genes encoding monterpenoid indole alkaloid(MIA) biosynthetic pathway of anticancer vinblastine, vincristine. With the help of bacterial artificial chromosome (BAC) Kellner, et al. showed seven small clusters each contained two to three genes encoding enzymatic pathways of vinblastine/vincristine. In opium poppy (Papaver somniferum), a gene-cluster for the synthesis of noscapine, an anticancer drug has recently been discovered. This cluster contains 10-genes encoding five distinct classes of enzymes including first committed step for biosynthetic pathway of noscapine. In cucumber (Cucumis sativus) , five genes are clustered, encoding enzymes required for the biosynthesis of cucurbitacins (triterpenoids). In another fruit plant, tomato (Solanum lycopersicum) genes for the synthesis of steroidal glycoalkaloid alpha-tomatine are clustered and the genes encoded dioxygenase and sugar transferases. In rice crops, Oryza sativa, diterpenes, momilactones and phytocassanes pathway genes were characterized as clusters [3,4].

Biosynthetic gene-clusters (BGCs), responsible for small molecule production of microbes often does not reside within discrete localized section of microbial genome and hence they are termed as BGCs. Various biosynthetic microbial products are being isolated including antifungal, antibacterial, antiviral, cytotoxic and immunosuppressive agents. In spite of having huge potential of BGCs of microbes towards the production of specialized metabolites, the research in this area has been hampered as because many biosynthetic gene clusters are not expressed, remain silent in laboratory cultures. Different approaches including thermal stress, chemicals, bacterial co-cultures, fungal-bacteria co-cultures, synthetic biology approaches are taken for the elicitation of natural products from silent BGCs [5]. Recent genome sequencing approaches of bacteria shows that the next generation of bioactive molecules will probably come from biosynthetic gene-clusters. Analysis of the sequenced genomes of actinomycetes, the group of bacteria responsible for over 50% of all antibiotics, has demonstrated that great majority of biosynthetic gene-clusters, the sets of genes responsible for production of bioactive compounds remain inactive or silent, and the reasons for this type of behaviour not very clear. A recent study involving activation of two silent gene clusters of pathogenic model of bacteria , Burkholderia thailandensis shows that when elicitor antibiotic used at low concentrations they act as

inducers of secondary metabolism[6]. The interesting point is that certain elicitor acts as a global activator of secondary metabolism and induces several biosynthetic pathways and thus provides access to the vast array of silent molecules found in bacteria.

Thus systematic analysis of plant and microbe genomes, and increased knowledge of metabolic biosynthetic gene clusters- assembly, regulation and architecture will be key factors in expediting discovery of many drugs or drug-like molecules.

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