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Bioinformatics Approach in Natural Products Discovery: A Cautionary Tale

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In the past decade, the focus of drug discovery has shifted from the traditional natural product research to synthetic medicinal chemistry approach. However, many are reverting back to using natural products resources, but this time taking advantage of the booming area of genome sequencing. Using bioinformatics, many novel compounds have been isolated, even from the "unculturable" microbes. However, not all genes can be translated into proteins, and not all proteins are active. Two polyketide synthase genes, *MgPKS2* and *MgPKS8*, from the plant pathogen fungus *Mycosphaerella graminicola* were selected using bioinformatics approach, and were cloned and transformed into a heterologous host, *Aspergillus oryzae* M-2-3. The genes were linked with the enhanced green fluorescent protein (*eGFP*) to detect formation of protein. The transformed *MgPKS2* did not show the formation of the polyketide synthase enzyme but *MgPKS8* did. The most possible reason for the negative result of *MgPKS2* is incorrect intron splicing in *Aspergillus oryzae* M-2-3. *MgPKS8* transformants were extracted and checked for production of new metabolites using LC-MS. However, none was detected. Some of the possible reasons for these results are the productions of new metabolites were below the detection level or, the polyketide need a special starter unit for biosynthesis or, incorrect protein folding. These results showed that this emerging method of natural product research has many hidden difficulties that should be shared amongst the natural product community.

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