Understanding the evolutionary origins of bacterial natural products with immunosuppressant properties

Wenfa Ng

Unaffiliated researcher, Singapore, Email: ngwenfa771@hotmail.com

Abstract

Actinobacteria and streptomyces are known to produce a variety of natural products, some of which confer antibiotic or immunosuppressive activities. While it is understandable that microbes develop the ability to synthesize molecules such as antibiotics that attack other competing microbes, but why would a secondary metabolite (natural product) synthesized by a microbe confer immunosuppressive activities? Was the capability to synthesize such a molecule endowed by evolution in the context of enabling microbes to develop resistance to immune cells of the human body? Or did the capability come from the need to colonize human body surfaces or gut to gain a survival niche for the microbe? Given that actinobacteria and streptomyces are soil microbes not usually associated with human body surfaces, could their biosynthetic capability for particular immunosuppressants arise from horizontal gene transfer from bacteria that colonize human body surfaces and subsequently develop the ability to synthesize the pertinent compounds through evolution? An alternate line of thinking on this issue touches on the possibility that microbes could encounter analogs of immuno-active molecules in their natural environment. Such molecules might elicit undesired physiological effects on the microbes, which place a selection pressure on microbes to develop countermeasures to the immuno-active molecules through mutations. Hence, through evolution, microbes could have developed the capability to synthesize secondary metabolites able to bind analogs of immuno-active molecules and help sequester them or quench their bioactivity. Subsequent profiling of such secondary metabolites in drug discovery efforts could have uncovered compounds with immunosuppressant activity which are originally developed for counteracting analogs of immuno-active molecules in the environment. It has to be recognized that analogs of immuno-active compounds remain somewhat dissimilar to immune compounds secreted by human immune cells, but they likely share common motifs for protein-secondary metabolite interactions. Direct evidence of the evolution of natural products with immunosuppressant activities could only be obtained from challenging suitable bacterial species with immuno-active molecules. Long cultivation experiments with multiple generations may result in the evolution of biosynthetic gene clusters for the synthesis of natural products able to sequester or quench immuno-active molecules. But, on the another hand, understanding relative binding affinities between a library of natural products and immuno-active molecules from humans would suggest drug candidates and their biosynthetic gene clusters. Subsequent phylogenetic analysis of cluster genes with their homologs from other species may yield insights into the evolution of genes and their putative function.

Keywords: biosynthetic gene clusters, actinobacteria, streptomyces, *Bacillus subtilis*, *Pseudomonas aeruginosa*, immuno-active molecules, natural products, secondary metabolites, evolution, selection pressure,

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Subject areas: biotechnology, biochemistry, microbiology, genomics, bioinformatics,

Conflicts of interest

The author declares no conflicts of interest.

Funding

No funding was used in this work.

PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.27774v1 | CC BY 4.0 Open Access | rec: 2 Jun 2019, publ: 2 Jun 2019