Targeted Genome Mining of Anticancer Natural Products

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Abstract:
Recent advancements in bioinformatics and next-generation sequencing have revolutionized natural product drug discovery, enabling the identification of cryptic, or 'hidden' biosynthetic gene clusters (BGCs) and providing a growing, untapped reservoir of medicinal potential. Large datasets of compiled genomic data thus warrant research optimizing the *in silico* prioritization of natural products with translational potential. Despite their chemical diversity, core biosynthetic machinery and resistance markers are often genetically conserved within BGCs encoding bioactive natural products. Therefore, we can harness the chemical potential encoded within microbial genomes by prioritizing molecules with a targeted mechanism of action. In this study, we focus on the widely distributed Vicinal Oxygen Chelate (VOC) protein fold as a tool for identifying anticancer natural products. Our research shows that VOCs are multifunctional proteins that prevent reduction of redox-active molecules, thereby preventing redox cycling and formation of harmful reactive oxygen species. Reductive activation is a common mechanism of action for anticancer natural products, and VOCs may provide self-protection to microorganisms producing these molecules as evidenced by the fact that VOCs are found in BGCs encoding FDA-approved anticancer natural products with mechanisms of action involving reductive activation (ex: doxorubicin, mitomycin, and the enediynes). *This information further supports the ubiquity, redox association, and translational potential of this protein fold in predicting anticancer activity.* Moreover, VOCs are found in over 38,000 cryptic BGCs, some of which are capable of preventing redox cycling *in vitro*-- highlighting the broad and largely unexplored redox activity of VOCs in bacteria. *Our central hypothesis is that VOCs are present in BGCs that encode redox active, anticancer natural products.* To explore this hypothesis, we will express, purify, and assess the cytotoxicity of a metabolite encoded in a cryptic BGC with a functional VOC, establishing a *proof-of-concept* model for VOC-targeted genome mining. In addition, we will employ VOC structural models as a molecular handle to develop an *in silico* genome mining pipeline. By prioritizing the discovery of natural products with proven anticancer potential, this research may significantly impact human health, accelerating the development of new cancer therapies and expanding the arsenal of available treatment options.