Chemical epigenetic remodelling of fungal secondary metabolite biosynthetic genes generates molecular diversity and compounds with anticancer properties

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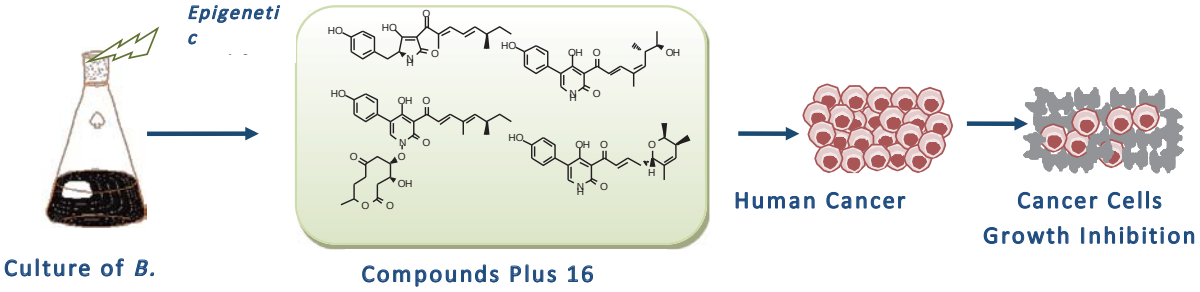
Secondary metabolites from microorganisms are known to be importance source of therapeutic compounds. Genome sequencing projects of filamentous fungi revealed the presence of a myriad of silent secondary metabolite biosynthetic gene clusters which do not yield compounds under conventional fermentation condition. This is suggestive of the fact that fungal secondary metabolite potentials are under-explored. The increasing understanding that non-communicable diseases, in particular cancer, are among the leading cause of human mortality poses a challenge to natural products scientists towards discovery of novel molecular scaffolds for development as new chemotherapeutic agents against cancer. The use of epigenetic approaches are emerging as new strategy of activating silent fungal secondary metabolite genes in order to generate novel metabolites or known compounds that are expressed in lower titres. We have investigated the effect of epigenetic modifiers, 5-azacytidine and Suberoyl bis-hydroxamic acid on insect pathogenic fungi, *Beauveria bassiana CBS*110.25 and its genetically modified strains. This led to upregulation of the 2-pyridone tenellin biosynthetic gene cluster as well as cryptic decanolide polyketide synthase gene, evident from enhanced production of known compounds and biosynthesis of numerous 2-pyridone tenellin-based novel metabolites. Collectively 20 compounds were isolated and identified from these experiments. Tenellin and some other congeners obtained from these experiments were subjected to anticancer screening test against NCI-60 human cancer cell lines. A number of the compounds showed variable potencies and selectivities against the cancer cells. 2-pyridone congeners showed the highest cytostatic and cytotoxic potencies with lowest GI_{50} (50% Growth Inhibition) of 0.0618 μM against Colon Cancer HCT-15 and LC_{50} (50% Lethal Concentration) of 0.828 μM against Melanoma SK-MEL-5 cells respectively. Our investigation highlights the utility of chemical epigenetics as an inexpensive strategy of exploring fungal-based secondary metabolite diversity in search for novel drug candidates as well as the opportunity available to natural products scientists under the Development Therapeutic Program of the National Cancer Institute. We have demonstrated the hitherto unknown potentials of 2-pyridone tenellin and related congeners as cancer chemotherapeutic agents.



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