Screening and characterization of microbial inhibitors against eukaryotic protein phosphatases (PP1 and PP2A)

Abstract

Aim: To identify novel microbial inhibitors of protein phosphatase 1 (PP1).

Methods and Results: 750 actinomycetes and 408 microfungi were isolated from Sabah forest soils and screened for production of potential PP1 inhibitors using an in vivo screening system, in which candidate inhibitors were identified through mimicking the properties of PP1-deficient yeast cells. Acetone extracts of two fungi, H9318 (Penicillium) and H9978 (non-Penicillium) identified in this way showed inhibitory activity towards both mammalian PP1 and PP2A in an in vitro phosphatase assay, while extract from H7520 (Streptomyces) inhibited PP2A but not PP1. Consistently, using a drug-induced haploinsufficiency test, strains with either reduced PP1 or PP2A function were hypersensitive to H9318 and H9978 extracts whereas only the latter strain showed hypersensitivity to H7250 extract. H9318 extract was fractionated using RP-HPLC into two active peaks (S1 and S2). A yeast strain with reduced PP1 function showed hypersensitivity to fraction S2 whereas a strain with reduced PP2A function was hypersensitive to fraction S1. However, S1 and S2 inhibited both PP1 and PP2A activities to a similar extent.

Conclusion: Three candidate PP inhibitors have been identified. Significance and Impact of the Study : Further development may generate useful research tools and ultimately therapeutic agents.