Discovery of small molecule bioactive agents from endophytic fungi of the Sonoran Desert

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Abstract

In our search for novel small molecule bioactive agents from endophytic fungi of the Sonoran desert, extracts derived from cultures of some selected endophytic fungal strains have been screened in assays for inhibition of heat shock protein 90 (Hsp90) activity, cancer cell proliferation and migration. *Chaetomium chiversii*, *Chaetomium globosum*, *Fusarium acuminatum* and *Fusarium oxysporum* producing metabolites active in these assays were cultured on large-scale and the derived extracts were subjected to bioactivity-guided fractionation to obtain a variety of natural products with diverse structures, and potential applications in cancer chemotherapeutics. This paper discusses the isolation, characterisation, and biological activity of some selected small molecule metabolites.

Keywords: endophytic fungi, small molecule natural products, isolation, structure elucidation biological activity, cytotoxic agents, cell migration inhibitors; Hsp90 inhibitors

Introduction

The growing body of evidence suggests that endophytic microorganisms represent a huge and largely untapped resource of small molecule natural products with chemical structures that have been optimised by evolution for biological and/or ecological relevance. In their symbiotic association, the macrophyte protects and feeds the endophyte, which 'in return' produces bioactive compounds to enhance the growth and competitiveness of the host and to protect it from herbivores and plant pathogens. Accordingly, some endophytes could be valuable sources of biologically active small molecule metabolites including anticancer agents. This is exemplified by isolation of anticancer drugs such as Taxol™ (paclitaxel) (Stierle *et al.* 1993; Stierle *et al.* 1995; Strobel *et al.* 1996), camptothecin (Puri *et al.* 2005), and podophyllotoxin (Eyberger *et al.* 2006) from endophytic fungal strains.

The possibility that plant-associated microbial diversity is influenced by the diversity of plant species and environmental factors suggests a greater potential for harvesting unique secondary metabolites from endophytic microorganisms found in association with hitherto unexploited floristically diverse plant communities (Gunatilaka 2006). Until now most studies on endophytes of higher plants for bioactive agents have focused on those that occur in northern temperate forests. Adaptations of endophytic communities in plants that grow in extreme habitats, other than arctic or alpine plants, are generally unknown. Desert plants have largely been ignored as a source of endophytes probably due to the assumption that endophyte infection requires humidity. Contrary to this contention, Faeth and co-workers have recently isolated and partially identified over 400 endophytic fungal taxa from Arizona fescue (Schulthess & Faeth 1998), more than 40 morphospecies of endophytic fungi from Emory oak (Faeth & Hammon 1997) and 22 endophyte species from cacti (Suryanarayanan *et al.* 2005) growing in very dry regions of Arizona. It is noteworthy that endophytically established fungi, such as *Hypoxylon* spp. undergo active mycelial development in response to water stress in host organs (Chapela 1989). Even endophytes in agronomic grasses grown under mesic conditions produce metabolites that increase resistance to drought stress (Clay & Holah 1999; Bush *et al.* 1997). It is reasonable to expect that endophytes in plants in xeric habitats should produce even greater diversity of these metabolites.

In our search for novel small molecule bioactive agents from endophytic fungi of the Sonoran desert, we have constructed an endophytic fungal library consisting of over 1000 strains. Extracts derived from cultures of over 600 of these have been screened in assays for inhibition of heat shock protein 90 (Hsp90), cancer cell

Figure 1 Metabolites of *Chaetomium chiversii.*

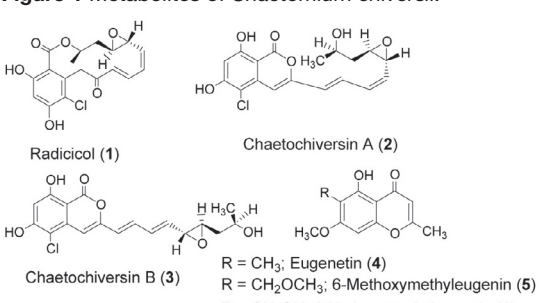

Figure 2 Metabolites of *Chaetomium globosum.*