Title: Self-resistance mechanisms in *Streptomyces olindensis* show response to antitumorals Doxorubicin and Cosmomycin D.

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Abstract:

Streptomyces produce various bioactive natural products and possess resistance systems for these metabolites, which are co-regulated with antibiotic biosynthesis genes. Antibiotic producer microorganisms require one or more self-resistance determinants to survival during antibiotic production. The effectors of these mechanisms are proteins that inactivate the antibiotic, facilitate its export, or modify the host to render it insensitive to the molecule. *Streptomyces olindensis* DAUFPE 5622 produces the antitumoral Cosmomycin D part of the anthracycline family, widely studied such as production, toxicity, structural analysis, chemical proprieties, interaction DNA–anthracycline, biosynthesis and genome sequencing. In this study we show resistance genes in Cosmomycin D biosynthetic cluster provide self-resistance, including an ATP-dependent efflux pump for transporting drug, resistance to the cell through excisional repair of DNA and response to hydroxyl radicals. We cloned and expressed the resistance genes from *Streptomyces olindensis* in *Streptomyces albus* anthracycline sensitive host, containing expression plasmid PEM4A with constitutive promoter ermE*p. We evaluated the capacity of resistance with different concentrations of anthracyclines Cosmomycin D and commercial Doxorubicin widely used for the treatment of human cancers. The expression of each resistance components increments the response to anthracyclines in recombinant *Streptomyces albus*. Finally we could be assisted and discuss different active strategies for this drugs in actinobacteria. Indeed, introduction of multicopies of resistance genes probably act positively into the production of antibiotics containing efficient efflux pumps and detoxification systems for secondary metabolites.

Key Words: Self-resistance, *Streptomyces,* Cosmomycin D, Doxorubicin, Resistance systems, Expression host