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Activation of cryptic antimicrobial compounds by microbial co-cultures

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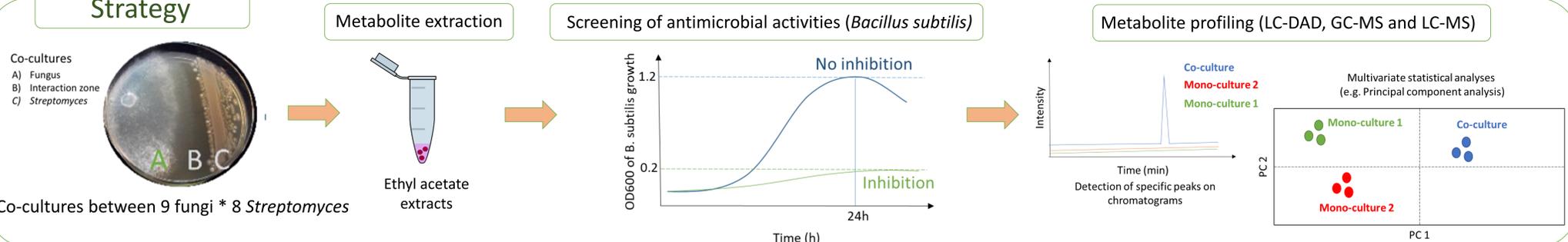
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Introduction

The **emergence** of new **multiresistant bacteria** is nowadays a public health issue and the **discovery of new antibiotics** becomes crucial to overcome this threat. **Bacteria** (mostly actinomycetes *e.g. Streptomyces*) and **fungi** are one of the major **source of antimicrobial compounds** (secondary metabolites). However, **most of the gene clusters coding for these secondary metabolites remain silent** in standard lab conditions. Biotic interactions between microbes in nature constitute a signal to induce the production of specialized metabolites. Thus, **co-cultures** in lab, which mimic these interactions, can induce the production of **cryptic natural products**. The objective of this study is to perform **co-cultures between Streptomyces and fungi (e.g. Schizophyllum commune)** for the **production of new antimicrobial compounds**.

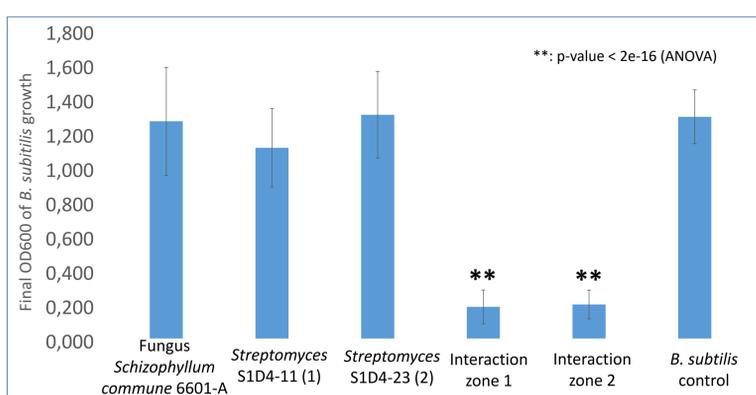
Strategy



Results

Antimicrobial activity during interaction

→ Among 144 co-cultures, 2 models were selected for their antimicrobial activity during interactions



The growth of *B. subtilis* was challenged in presence of ethyl acetate extracts obtained from: control cultures of *Streptomyces* S1D4-11, *Streptomyces* S1D4-23, the fungus *S. commune* 6601A and their interaction zones. The growth of the bacteria in presence of all the single culture extracts was the same than the *B. subtilis* control. Interaction zones inhibited the growth of *B. subtilis*, indicating the presence of an antimicrobial activity not observed in the controls.

Interaction zone 1: interaction between *S. commune* and *Streptomyces* S1D4-11
Interaction zone 2: interaction between *S. commune* and *Streptomyces* S1D4-23

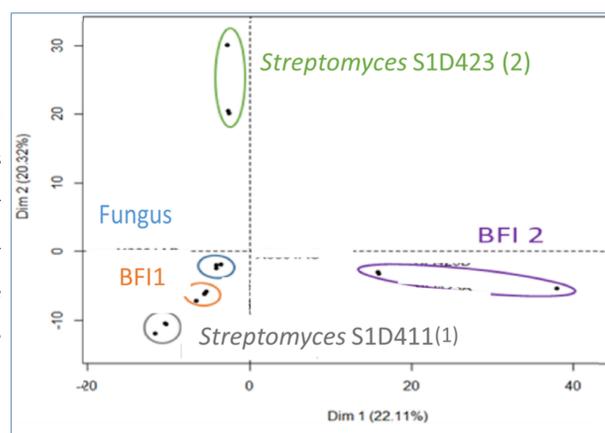
2) Are new metabolites produced during interactions?

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1) Is the metabolite production different during interactions?

PCA revealed specific metabolite profiles during interactions

Principal component analyses were performed from metabolite profiles (biological triplicate) with HPLC-DAD recorded in 5 wavelengths. The global metabolite profiles obtained from the fungus *S. commune* 6601A (Blue circle) and two *Streptomyces* single cultures (grey and green circles) were compared with the respective co-cultures interaction zones of each *Streptomyces* and the fungus *S. commune* (purple and orange circles). The non-overlapping of circles indicates that global metabolite profiles are different in interaction zones than singles cultures.



BFI1: Bacterial-Fungal interaction between *S. commune* and *Streptomyces* S1D4-11
BFI2: Bacterial-Fungal interaction between *S. commune* and *Streptomyces* S1D4-23
→ 100% of the variability was explained with 5 principal components.
→ Analyses were performed only on common peaks between replicates (40%)

GC-MS revealed the production of 10 metabolites during interaction

→ 10 peaks specific of the interactions were identified

- 5 were common for the two interactions
- 3 were specific of the interaction with *Streptomyces* S1D4-23 and 2 with *Streptomyces* S1D4-11

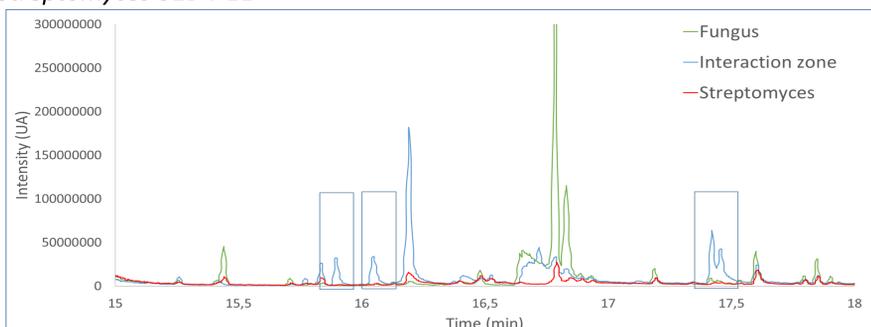


Illustration of the comparison of GC-MS metabolite profiles of one *Streptomyces*, the fungus and their interaction zone. The metabolite profile of *Streptomyces* is in red, the one of the fungus is in green and the interaction zone is in blue. New peaks induced during the interaction are framed by blue rectangles.

LC-MS revealed the production of new metabolites in interaction zones

→ So far, negative mode EICs revealed at least the production of 4 new metabolites in interaction zones between *S. commune* 6601-A and *Streptomyces* S1D4-11

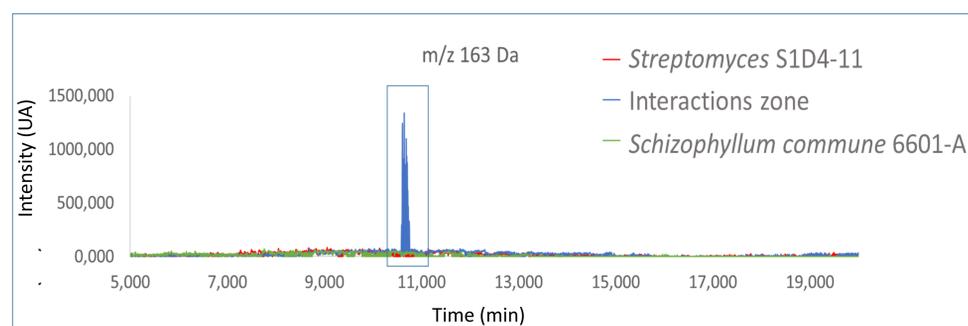


Illustration of the comparison of LC-MS metabolite profiles of one *Streptomyces*, the fungus and their interaction zone for the Extracted-ion chromatograms for m/z 163. The metabolite profile of *Streptomyces* is in red, the one of the fungus is in green and the interaction zone is in blue. The peak at 11 minutes is specific of the interaction.

Conclusions and perspectives

- Two interaction models between *S. commune* and two *Streptomyces* strains showed an induced antimicrobial activity.
- The metabolite profiles of interactions are different from those of single cultures.
- LC-MS and GC-MS peaks, potentially explaining these differences, were identified

➤ Further experiments:

- ✓ To further analyse LC/MS (positive mode/second interaction) and GC/MS
- ✓ To correlate the antimicrobial effect with the production of new compounds
- ✓ To decipher the molecular mechanisms involved during the interactions