MICROBISPORA sp. ATCC-PTA-5024 PROTEOME ANALYSIS: UNRAVELING THE MOLECULAR PHYSIOLOGY OF LANTIBIOTIC PRODUCTION

Giuseppe Gallo[a], Emilia Palazzotto[a], Giovanni Renzone[b], Anna Giardina[a], Rosa Alduina[a], Paolo Monciardini[c], Tilmann Weber[d], Roberta Pozzi[d], Evi Stegmann[d], Margherita Sosio[c], Andrea Scaloni[b] and Anna Maria Puglia[a].

[a]Molecular Microbiology and Biotechnology laboratory, STEBICEF department ,University of Palermo, Viale delle Scienze, ed. 16, 90128 Palermo.
[b]Proteomic and Mass Spectrometry laboratory, ISPAAM,CNR, via Argine 1085, 80147 Napoli.
[c]NAICONS, Via Fantoli 16/15, 20138 Milano.
[d]Interfaculty Institute of Microbiology and Infection Medicine, Eberhard Karls University of Tübingen, Auf der Morgenstelle 28, 72076 Tübingen (Germany).
giumir@msn.com
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Introduction. The actinomycete *Microbispora* sp. ATCC-PTA-5024 produces the lantibiotic NAI-107 [1] which has been attracting the attention as a potential drug candidate. In fact, NAI-107 is active against vancomycin-resistant Gram-positive pathogens and its in vivo efficacy was confirmed using animal models [2]. Although NAI-107 has a high potential as a therapeutic drug, the producer strain is only poorly characterized. Thus, high throughput studies may give some insights in order to investigate biochemical capability, metabolic pathways and regulation of NAI-107 production. Therefore, a comprehensive proteomic-based study was performed to unravel changes in global protein expression by comparing (Fig. 1):
A) *Microbispora* wild type (WT) strain during producing and not-producing growth stages;
B) WT and two *Microbispora* mutant strains, a super producer (SP) and a null mutant (NP) for production, respectively.

Methods. For biomass collection and proteome analyses, all *Microbispora* strains were cultivated using a rich medium containing glucose. For A analysis, Wt strain was sampled several times during growth at rapid growth and decline stages. For B comparison, biomass samples were harvested at mid-rapid growth-phase, coinciding with NAI-107 production on-set in Wt and SP. Differential proteome analysis was carried-out using 2D Fluorescence Difference Gel Electrophoresis (2D-DIGE) and mass spectrometry (MS) procedures. [4].

Results. Differential proteome analysis, coupled with gene ontology classification, revealed differential regulation for pleiotropic regulators, stress response factors (mainly oxidative) and proteins involved in many cell processes (like lantibiotic resistance and cell-wall biosynthesis) and metabolic pathways (such as central carbon amino acid metabolism). In particular, amino sugar, nitrogen, phosphate and sulphur metabolism, oxidative stress and antibiotic resistance response are positively regulated while amino acid, nucleotide and energy metabolism negatively correlated to NAI-107 production. Thus, proteomics revealed a differential regulation of anabolic and catabolic processes putatively aimed to support antibiotic production and biomass accumulation.

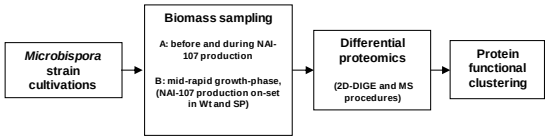

Fig.1 Proteomics analysis work-flow for *Microbispora* strains

Conclusions. These data, giving clues on *Microbispora* sp. metabolic and biochemical capability, showed differentially regulated proteins that could play a key role on molecular and cellular processes associated to biomass and lantibiotic biosynthesis. Thus the results can be used as a background to improve fermentation strategies or to design rational genetic engineering experiments aimed to increase lantibiotic yield production.

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References.

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