Elucidating the molecular physiology of lantibiotic NAI-107 production in Microbispora ATCC-PTA-5024

The filamentous actinomycete Microbispora ATCC-PTA-5024 produces the lantibiotic NAI-107, which is an antibiotic peptide effective against multidrug-resistant Gram-positive bacteria. In actinomycetes, antibiotic production is often associated with a physiological differentiation program controlled by a complex regulatory and metabolic network that may be elucidated by the integration of genomic, proteomic and bioinformatic tools. Accordingly, an extensive evaluation of the proteomic changes associated with NAI-107 production was performed on Microbispora ATCC-PTA-5024 by combining two-dimensional difference in gel electrophoresis, mass spectrometry and gene ontology approaches. Microbispora ATCC-PTA-5024 cultivations in a complex medium were characterized by stages of biomass accumulation (A) followed by biomass yield decline (D). NAI-107 production started at 90 h (A stage), reached a maximum at 140 h (D stage) and decreased thereafter. To reveal patterns of differentially represented proteins associated with NAI-107 production onset and maintenance, differential proteomic analyses were carried out on biomass samples collected: i) before (66 h) and during (90 h) NAI-107 production at A stage; ii) during three time-points (117, 140, and 162 h) at D stage characterized by different profiles of NAI-107 yield accumulation (117 and 140 h) and decrement (162 h). Regulatory, metabolic and unknown-function proteins, were identified and functionally clustered, revealing that nutritional signals, regulatory cascades and primary metabolism shift-down trigger the accumulation of protein components involved in nitrogen and phosphate metabolism, cell wall biosynthesis/maturation, lipid metabolism, osmotic stress response, multi-drug resistance, and NAI-107 transport. The stimulating role on physiological differentiation of a TetR-like regulator, originally identified in this study, was confirmed by the construction of an over-expressing strain. Finally, the possible role of cellular response to membrane stability alterations and of multi-drug resistance ABC transporters as additional self-resistance mechanisms toward the lantibiotic was confirmed by proteomic and confocal microscopy experiments on a Microbispora ATCC-PTA-5024 lantibiotic-null producer strain which was exposed to an externally-added amount of NAI-107 during growth. This study provides a net contribution to the elucidation of the regulatory, metabolic and molecular patterns controlling physiological differentiation in Microbispora ATCC-PTA-5024, supporting the relevance of proteomics in revealing protein players of antibiotic biosynthesis in actinomycetes.

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