

Bacteria-induced natural product formation in the fungus *Aspergillus nidulans* requires Saga/Ada-mediated histone acetylation.

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Abstract

Sequence analyses of fungal genomes have revealed that the potential of fungi to produce secondary metabolites is greatly underestimated. In fact, most gene clusters coding for the biosynthesis of antibiotics, toxins, or pigments are silent under standard laboratory conditions. Hence, it is one of the major challenges in microbiology to uncover the mechanisms required for pathway activation. Recently, we discovered that intimate physical interaction of the important model fungus *Aspergillus nidulans* with the soil-dwelling bacterium *Streptomyces rapamycinicus* specifically activated silent fungal secondary metabolism genes, resulting in the production of the archetypal polyketide orsellinic acid and its derivatives. Here, we report that the streptomycete triggers modification of fungal histones. Deletion analysis of 36 of 40 acetyltransferases, including histone acetyltransferases (HATs) of *A. nidulans*, demonstrated that the Saga/Ada complex containing the HAT GcnE and the AdaB protein is required for induction of the orsellinic acid gene

cluster by the bacterium. We also showed that Saga/Ada plays a major role for specific induction of other biosynthesis gene clusters, such as sterigmatocystin, terrequinone, and penicillin. Chromatin immunoprecipitation showed that the Saga/Ada-dependent increase of histone 3 acetylation at lysine 9 and 14 occurs during interaction of fungus and bacterium. Furthermore, the production of secondary metabolites in *A. nidulans* is accompanied by a global increase in H3K14 acetylation. Increased H3K9 acetylation, however, was only found within gene clusters. This report provides previously undescribed evidence of Saga/Ada dependent histone acetylation triggered by prokaryotes.

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