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Identification of candidate genes contributing to
epicolactone biosynthesis in *Epicoccum nigrum*

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RESUMO

BRAGA, R. M. **Identificação de genes possivelmente envolvidos na biossíntese da epicolactona em *Epicoccum nigrum***. 2016. 128 p. Tese (Doutorado em Biotecnologia) - Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2016.

Epicoccum nigrum é um fungo ubíquo conhecido por sua capacidade de produzir vários metabólitos secundários bioativos e pelo seu uso potencial como agente de controle biológico contra vários fitopatógenos. Apesar de muitos compostos com importância biotecnológica produzidos por *E. nigrum* terem sido descritos na literatura, ainda há uma grande lacuna de conhecimento acerca da biossíntese desses compostos e dos genes envolvidos. Entre os compostos produzidos por *E. nigrum*, epicolactona é um policetídeo com um esqueleto de carbono incomum que tem atraído grande interesse acerca da sua síntese. O objetivo desta tese foi identificar e caracterizar genes relacionados à biossíntese da epicolactona em *E. nigrum*. Três mutantes anteriormente gerados por mutagenese aleatória que tiveram a capacidade de produzir epicolactona reduzida ou ausente foram analisados. O T-DNA estava inserido em regiões intergênicas nesses mutantes, assim, os genes próximos ao sítio de inserção foram analisados. Entretanto, a expressão desses genes não foi significativamente diferente do fungo selvagem, indicando que esses genes provavelmente não estão relacionados à biossíntese da epicolactona. É possível que o T-DNA tenha se inserido em uma região regulatória. Usando ferramentas de bioinformática, genes candidatos codificadores de PKSs foram identificados no genoma de *E. nigrum* e seis genes foram selecionados para deleção. A deleção do gene PKSi12 mostrou que os seus produtos estão relacionados à atividade antagonista contra fitopatógenos. A análise química permitiu a identificação putativa dos preditos precursores da epicolactona, epicoccona B e epicoccina, o quais tiveram sua produção afetada no mutante Δ PKSi12. Com base nas evidências fornecidas pelas análises químicas e *in silico*, foi proposta uma possível biossíntese de epicoccona B e epicoccina por *E. nigrum*. Entretanto, ainda há muito a se compreender acerca da biossíntese da epicolactona e são necessários experimentos adicionais para confirmar o papel da PKSi12 na produção de epicoccona B e epicoccina.

Palavras-chave: *Epicoccum nigrum*. Endófito. Epicolactona. Policetídeo. Policetídeo sintase. Biossíntese.

ABSTRACT

BRAGA, R. M. **Identification of candidate genes contributing to epicolactone biosynthesis in *Epicoccum nigrum***. 2016. 128 p. PhD thesis (Biotechnology) - Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2016.

Epicoccum nigrum is a ubiquitous fungus known mainly for its ability to produce numerous bioactive secondary metabolites and for its potential use as a biocontrol agent against various phytopathogens. Although many compounds of biotechnological significance that are produced by *E. nigrum* have been described in the literature, there is still a large gap in the knowledge on their biosynthesis and on the genes involved. Among the bioactive compounds produced by *E. nigrum*, epicolactone is a polyketide with an unusual carbon skeleton; this compound has attracted great interest in terms of its synthesis. The aim of this thesis was to identify and characterize genes related to epicolactone biosynthesis in *E. nigrum*. Three mutants (previously generated by random mutagenesis) that have a reduced or no ability to produce epicolactone were analyzed. The transfer DNA (T-DNA) was inserted in intergenic regions in these mutants; thus, the genes located near the insertion site were analyzed. Their expression was not significantly different from that in the wild type, indicating that they are probably not related to epicolactone biosynthesis. It is possible that the T-DNA was inserted in a regulatory region. Using a genome-mining approach, genes of polyketide synthases (PKSs) were identified in the *E. nigrum* genome, and six candidate genes were selected for targeted gene replacement. Deletion of the *PKSi12* gene showed that its products are related to *E. nigrum*'s inhibitory effects on the growth of fungal phytopathogens. Chemical analysis enabled putative identification of the previously proposed epicolactone precursors—epicoccine and epicoccone B—whose production was altered in the Δ PKSi12 mutant. On the basis of the results of the chemical and *in silico* analyses, a possible biosynthetic pathway for epicoccone B and epicoccine in *E. nigrum* was proposed. There is still a lot to learn about epicolactone biosynthesis, and further experiments are necessary to confirm the role of PKSi12 in the biosynthesis of epicoccone B and epicoccine.

Keywords: *Epicoccum nigrum*. Endophyte. Epicolactone. Polyketide. Polyketide synthase. Biosynthesis.

1 GENERAL INTRODUCTION

Epicoccum nigrum is a dothideomycete fungus widespread in ambient air, in soil, and on decaying vegetation; this fungus can lead an endophytic lifestyle and is commonly isolated from diverse plant tissues. *E. nigrum* is mainly known for its ability to produce many bioactive secondary metabolites and for its potential use as a biocontrol agent against many phytopathogens. Among the bioactive compounds produced by *E. nigrum*, epicolactone is a polyketide with an unusual carbon skeleton. This compound has antimicrobial activity and was first isolated from *E. nigrum* P16, the strain used in the present study. Because of its unique and complex structure, epicolactone has aroused a lot of interest in relation to its synthesis. Studies on its biomimetic synthesis and actual biosynthesis have attracted considerable attention from the chemical-synthesis community.

The *E. nigrum* P16 strain was isolated from sugarcane leaves and shows *in vitro* inhibitory activity against sugarcane phytopathogens. This strain is also capable of increasing the sugarcane root system biomass. The genome of *E. nigrum* P16 was sequenced and has been assembled and annotated by our research group; these data allow for studies on genes and possible metabolic pathways related to biosynthesis of secondary metabolites. Although many compounds of biotechnological importance produced by *E. nigrum* have been described in the literature, there is still a large gap in the knowledge on their biosynthesis and on the genes involved. In this sense, identification and characterization of genes involved in the biosynthesis of secondary metabolites in *E. nigrum* can contribute to the discovery of new enzymatic functions and to genetic engineering studies. This knowledge will help to expand the pool of potential polyketide drugs and to synthesize new non-native compounds with improved characteristics.

On the other hand, the polyketide epicolactone produced by *E. nigrum* has an antimicrobial activity and complex structure. Although there are studies describing the biomimetic synthesis of epicolactone and the possible actual biosynthetic pathway, there are no *in vivo* studies on its biosynthesis, and no genes related to its biosynthesis have been identified to date. In addition, the knowledge about the secondary metabolites produced by *E. nigrum* can contribute to the understanding of the ecological

relations of this fungus, such as the plant-endophyte relation and its antagonistic activity in the host plant.

Therefore, the aim of the present study was to identify and characterize genes contributing to epicolactone biosynthesis in *E. nigrum*. Three *E. nigrum* mutants (generated by random mutagenesis) that have a reduced (or no) ability to produce epicolactone were analyzed. Mutants P16-17, P16-47set, and P16-91 were obtained in a previous study by our research group. The genes located near the transfer DNA (T-DNA) insertion site were annotated and analyzed. In addition, gene expression of two polyketide synthase (PKS) genes located in the same gene cluster (and suggested to be possibly related to epicolactone biosynthesis) was also evaluated. These results are described in chapter 3 “Analysis of epicolactone-deficient *Epicoccum nigrum* mutants P16-17, P16-47set, and P16-91 and screening of a mutant library.”

Chapter 4, “Genome mining in *Epicoccum nigrum* reveals a gene cluster associated with antagonistic activity and probably involved in epicolactone biosynthesis,” describes the diversity of PKS gene clusters in *E. nigrum* and generation and analysis of PKS deletion mutants. Bioinformatic tools were used to identify PKS-encoding genes in the *E. nigrum* genome and to select six genes that could be related to epicolactone biosynthesis. A protocol for targeted gene replacement in *E. nigrum* was successfully established, and PKS deletion mutants were generated and analyzed.

OVERALL CONCLUSIONS

Two approaches were used in this study to identify the genes involved in epicolactone biosynthesis: 1) analysis of epicolactone-deficient mutants obtained previously by random mutagenesis and 2) genome mining of candidate genes followed by targeted gene replacement. With the first approach, it was found that the T-DNA got inserted into intergenic regions, and the expression of the genes located near the insertion was not significantly affected in the mutants, suggesting that the T-DNA was probably inserted into a regulatory region. With the second approach, five NR-PKSs that are known to synthesize mono- or polycyclic aromatic compounds were selected for targeted gene replacement. In November 2014, Ellerbrock et al. published a hypothetical biosynthetic pathway for epicolactone; this scheme guided the present study toward identification of an orsellinic acid synthase or a synthase of an orsellinic-acid derivative because the predicted epicolactone precursors (epicoccone B and epicoccine) are believed to derive from orsellinic acid.

Deletion of the *PKSi12* gene showed that PKSi12 is related to antagonistic action of *E. nigrum* on fungal phytopathogens. Chemical analysis enabled putative identification of epicoccine and epicoccone B, whose production was altered in the Δ PKSi12 mutant. According to the results of the chemical and *in silico* analyses, a hypothetical biosynthetic pathway for epicoccone B and epicoccine in *E. nigrum* was proposed. Nonetheless, there is still a lot to learn about epicolactone biosynthesis, and further research is needed to confirm the function of PKSi12 in the biosynthesis of epicoccone B and epicoccine.

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