Current Journal of Applied Science and Technology

31(1): 1-5, 2018; Article no.CJAST.45867
ISSN: 2457-1024
(Past name: British Journal of Applied Science & Technology, Past ISSN: 2231-0843, NLM ID: 101664541)

The Role of the Global Regulator of Secondary Metabolism LaeA in Different Fungi

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CJAST/2018/45867

Mini-review Article

Received 05 November 2018
Accepted 28 November 2018
Published 08 December 2018

ABSTRACT

Secondary metabolites are natural bioactive products produced by bacteria, fungi and plants. It can be categorised as the deleterious mycotoxins, cytotoxic carcinogenic compounds or the beneficial antibiotics, fungicides, insecticides and antitumor metabolites. The increasing number of genome sequencing has shown that the fungal genome is a rich source of genes involved in secondary metabolism. Fungal secondary metabolism has, therefore, become an important topic of research around the globe. The genes involved in secondary metabolism are usually found in clusters in the genome. Secondary metabolites have been known to play important role in the development and pathogenesis of the fungus. To understand the role of secondary metabolites in pathogenesis it is important to study the mechanism of the global regulators of metabolism. Understanding the mechanism of action of the global regulators would help in increasing the production of beneficial metabolites and decreasing the production of deleterious metabolites. It would also provide an insight into the production of metabolites. One such global regulator of secondary metabolism is LaeA. The focus of this review is to provide an overview of the role played by LaeA across different fungi.

Keywords: Secondary metabolites; global regulator; pathogenesis; beneficial; deleterious.

1. INTRODUCTION

Secondary metabolites are low molecular weight organic compounds that are not directly required for the growth and reproduction of the producing organism. It plays a role in the defence of the organism [1,2]. Secondary metabolites are associated with the sporulation process of the

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Note: Special issue with selected papers presented in National Conference on Biotechnological Initiatives for Crop Improvement (BICI 2018), December 08-09, 2018, Organized by Bihar Agricultural University, Sabour, Bhagalpur - 813210 (Bihar), India. Conference organizing committee and Guest Editorial Board completed peer-review of this manuscript.

fungus. It is required for the niche specialisation and has its use in the pharmaceutical and biotechnological industry [3,4]. Secondary metabolite production commences in the late growth phase that is in the stationary or resting phase [5]. Fungal genome shows good potential for the secondary metabolite genes. For example, *Aspergillus nidulans* is able to produce 32 polyketides, 14 non-ribosomal peptides and 2 indole alkaloids [6,7]. Therefore there is an increasing research on fungal secondary metabolism across the globe. LaeA (loss of AflR function) was first identified in *Aspergillus nidulans* through complementation of a sterigmatocystin mutant [8]. After its discovery, several homologues of it was found in several other species. LaeA is found conserved in filamentous fungi but is absent in *Saccharomyces cerevisiae*, an important finding as this fungus is devoid of secondary metabolites [8]. This review aims to study the role LaeA plays across several fungi.

2. STRUCTURE

LaeA is a nuclear protein and has a methyltransferase domain. This 375 amino acid protein has a conserved S-adenosylmethionine binding site. It has one intron and 3 putative AflR binding sites one in the promoter and 2 in the encoding region [8]. Till date, no substrate has been found for the methyltransferase activity of LaeA. It is known to automethylate at a methionine residue near the SAM-binding site [9].

2.1 LaeA in *Aspergillus sp.*

LaeA is a regulator of secondary metabolism in *Aspergillus sp.* where it has been first reported. In *A.nidulans* it is required for sterigmatocystin, penicillin biosynthesis as well as expression of the Lovastatin (LOV) gene cluster. In *A. terreus*, it also helps in LOV expression [8]. Overexpression of *LaeA* in *A. terreus* leads to increased production of itaconic acid [10]. In *A fumigatus* it helps in the synthesis of gliotoxin, fumagillin, fumagatin, helvolic acid and mycelia pigments. Deletion of *LaeA* in *A fumigatus* has a decreased rate of fatal infections in the murine model [11]. In *A flavus* overexpression of *LaeA* overproduced several metabolites including aflatoxin, cyclopiazonic acid, kojic acid, oryzaechlorin and asperfuran. Mutants produced less lipase activity and were unable to colonise peanut and maize seed. There was decreased conidial production and loss of sclerotia [12]. *A carbonarius* produces ochratoxin A in grapes wine or juices. *LaeA* null mutants showed a decreased Ochratoxin A and conidial production [13]. LaeA in *A oryzae* regulates Kojic acid synthesis gene [14]. LaeA in *A niger* helps in citric acid production [15]. In *Aspergillus fumisynnematus* overexpression of the *laeA* gene resulted in increased production of cyclopiazonic acid and decreased pigment, conidia and shorter conidial head chains [16].

2.2 LaeA in *Monascus sp*.

Overexpression of the ortholog of the *laeA* gene in *M pilosus* showed increased production of monacolin K, a cholesterol-lowering agent. It also increased pigment production. *Monascus* species is used as fermentative fungi in Asia and the overexpression of *LaeA* can improve functional food production [17]. Null mutants of *LaeA* in *M rubber* have shown decreased production of metabolites and pigments [18].

2.3 LaeA in *Alternaria sp*.

LaeA positively regulates host-specific toxins biosynthesis, pathogenicity, growth and differentiation in *A. alternata. Knockout mutants of LaeA showed decreased virulence in the host plant along with reduced sporulation and hyphal growth* [19].

2.4 *LaeA in Penicillium sp.*

Overexpression of LaeA in P chrysogenum showed 25% increase in penicillin production. Mutants showed defects in penicillin production as well as in sporulation and pigmentation [20]. In *Penicillium citrinum* LaeA played critical roles in ML-236B production, a polyketide which exhibits a potent inhibitory effect on the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase [21,22] by controlling the expression of *mlcR*, the pathway-specific activator gene for ML-236B biosynthesis [23]. LaeA in *P expansum* regulates several secondary metabolite genes including the mycotoxin patulin gene cluster. Mutants show a loss in virulence [24]. LaeA in *P oxalicum* helps in regulating the expression of cellulase and β-xylosidase gene, especially when transcription activator gene (*clrB* or *xlnR*) was overexpressed or transcription repressor gene (*creA*) was deleted. It affected glycoside hydrolase gene expression in the later phases of prolonged batch cultures [25].

2.5 Lae1 in *Trichoderma sp.*

Overexpression of *Lae1* in *T reesei* resulted in increased cellulose gene expression whereas deletion mutants showed complete loss of expression of all seven cellulases, β-glucosidases and xylanases [26]. Deletion of *Lae1* in *T atroviride* leads to a 50% decrease in conidiation whereas conidiation increases to 30-50% in the overexpression strains. In the dark, the null mutants do not sporulate whereas the Lae1-over expressing strains sporulate as the wild-type. Deletion of Lae1 also reduces the ability of the fungus to defend against another fungus. This is due to the reduced expression of proteases, polyketide synthases and small cystein-rich secreted protein [27].

2.6 Lae1 in *Fusarium sp.*

Mutants of *Lae1* resulted in reduced expression of gene clusters responsible for the synthesis of the secondary metabolites bikaverin, fumonisins,fusaric acid in *F. Verticillioides* [28]. LaeA in *F graminearum* helps in the production of tricothecenes. It also controls sexual development and virulence [29].

2.7 LaeA in *Cochliobolus sp*.

Lae1 mutants of *C heterostrophus* showed a reduced level of T- toxins in dark compared to the wild-type as well as reduced aerial hyphal growth. Mutants also showed increased melanin synthesis and sporulation [30].

2.8 LaeA in *Botrytis cinerea*

LaeA regulates the production of oxalic acid in *B cinerea* and to cope with oxidative stress conditions [31].

2.9 LaeA in *Dothistroma septosporum*

Null mutants of *LaeA* in pine needle pathogen *D septosporum* leads to enhanced production of dothistromin, a polyketide virulence factor. The mutants also showed reduced asexual sporulation and germination [32].

2.10 LaeA in *Chaetomium globosum*

Overexpression of *LaeA* in *Chaetomium globosum* CBS148.51 up-regulated expression of the chaetoglobosin gene cluster and resulted in the isolation of a new cytochalasan, chaetoglobosin Z (1), together with six known analogues, chaetoglobosins A (2), B (3), D (4), E (5), O (6), and V (7) [33].

2.11 LaeA in *Magnaporthe oryzae*

Blast disease caused by *Magnaporthe oryzae* is a major constraint to rice production not only in India but is considered as the most destructive fungal pathogen of rice worldwide. LaeA has been immensely studied in various filamentous fungi for over a decade but it has not been characterised in *M.oryzae*. In fact, hardly anything is known about secondary metabolism in this fungus in detail. To study the role of secondary metabolites and LaeA in *M.oryzae* we have developed several mutants. *LaeA* plays a role in melanin synthesis, sporulation and pathogenesis in *M oryzae* indicating that the role of this global regulator is also conserved in this filamentous fungi. LaeA is also seen to regulate secondary metabolism as reported in another fungus (Unpublished Data).

3. CONCLUSION

Secondary metabolites play a significant role in the development and pathogenesis of the fungus since its discovery more and more filamentous fungi have shown to have homologues of *LaeA* which are known to play the same role. This shows that it is conserved across the filamentous fungi. Since most of the secondary metabolite genes remain silent under normal conditions, the study of global regulators is important as these will activate these clusters and help in the study of metabolites and or new metabolites.

ACKNOWLEDGEMENT

The work was supported by the grants (No. BT/PR4100/AGR/2/844/2012) from Department of Biotechnology, Ministry of Science and Technology, Govt. of India.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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