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Review

Insights to fungal biology through LaeA sleuthing

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ABSTRACT

LaeA was first identified as a novel *Aspergillus* nuclear protein which functions as a global regulator of secondary metabolism, morphogenetic development, and antibiotic production in various filamentous fungi. Since then, it has been studied extensively by research groups around the world in order to identify virulence factors, transcription factors and/or cryptic secondary metabolite gene clusters regulated by LaeA. The coupling of LaeA with VeA and VelB as a nuclear complex, the "Velvet Complex", has greatly impacted our understanding of transcriptional complexes in filamentous fungi and their association with epigenetic processes. This review will highlight insights into fungal biology by LaeA-led studies and areas of research that need further investigation.

1. Introduction

As a taxon, the Kingdom Fungi is renown for production of diverse secondary metabolites also referred to as natural products. These secondary metabolites are of intense interest to humankind as their activities range from extremely harmful (e.g. aflatoxin) to medically beneficial (e.g. penicillin). It has become increasingly clear that the particular set of secondary metabolites produced by any one species is likely contributing to niche specialization. For many decades it has been known that certain host specific toxins are equated with virulence in certain plant pathogenic fungi (e.g. T-toxin production by *Cochliobolus heterostrophus*). Also, beyond these clearcut cases, secondary metabolites have been shown to contribute to virulence of human pathogens (Ben-Ami *et al.*, 2009; Yin *et al.*, 2013a; Liu and Nizet, 2009), production against fungivores (Rohlfs *et al.*, 2007; Rohlfs and Churchill, 2011) and abiotic stress like UV, etc. (Kawamura *et al.*, 1999). The development of medicinal and biotechnologically important compounds from fungal secondary metabolites has further increased interest in their production (Emri *et al.*, 2013).

Early observations in secondary metabolite production in fungi showed that these metabolites are associated with morphological development of fungi, particularly sexual and asexual sporulation (Calvo *et al.*, 2002). Whereas several genetic studies indicated a linkage between both processes through signal transduction pathways (Hicks *et al.*, 1997; Shim and Woloshuk, 2001), it wasn't until the discovery of LaeA in 2004 (Bok and Keller, 2004) and the subsequent finding that it operates in a nuclear complex with VeA and VelB (Bayram *et al.*, 2008a), that a global regulatory process orchestrating secondary metabolism with fungal development was

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uncovered. LaeA, named for loss of *aflR* expression (AflR being the specific transcription factor regulation expression of genes in the aflatoxin and sterigmatocystin clusters, Woloshuk *et al.*, 1994; Fernandes *et al.*, 1998), is a novel methyltransferase whose S-adenosyl methionine (SAM) binding site is required for function (Bok *et al.*, 2006b; Patananan *et al.*, 2013). VeA and VelB are hypothesized to be DNA binding proteins although their exact function is not known (Bayram and Braus, 2012).

laeA deletants, first described in *Aspergillus* species, are reduced in the production of a multitude of secondary metabolites including sterigmatocystin, aflatoxin, penicillin, lovastatin, gliotoxin, endocrocin, and pseurotin (Amaike and Keller, 2009; Bok and Keller, 2004; Bok *et al.*, 2005; Brakhage, 2013; Vödisch *et al.*, 2011; Lim *et al.*, 2012). The impact of LaeA on fungal development and virulence was further deciphered through its partnering with VeA (Sarikaya Bayram *et al.*, 2010). VeA deletants display some but not all *ΔlaeA* phenotypes as well as exhibit distinct characteristics not seen in *ΔlaeA* strains (Bayram and Braus, 2012). The Velvet Complex trimer and its global impact on secondary metabolism and development is conserved in filamentous ascomycetes. Table 1 lists LaeA and VeA orthologs found in various fungal species. Our goal for this review is to briefly describe the known functions of LaeA followed by insights into fungal biology revealed by genetic and bioinformatic experimentation conducted on the protein itself and/or *laeA* mutants. Whereas much of the advances described below are "*Aspergillus*-centric", this is in large part due to the early discoveries in this genus and it is likely that many of the LaeA-led discoveries in *Aspergillus* will be applicable to other genera.

2. LaeA regulation of fungal development

Member of the Velvet Complex

As mentioned above, LaeA is a member of the Velvet Complex consisting of LaeA, VeA and VelB proteins. This complex was first described in *Aspergillus nidulans* but has since been characterized in several fungi (Hoff *et al.*, 2010; Wiemann *et al.*, 2010; Wu *et al.*, 2012 and Table 1). Both VeA and VelB, along with VosA and VelC, belong to the velvet family of fungal regulatory proteins (Bayram and Braus, 2012). This family of proteins is specific to fungi. Similarly to LaeA, VeA and VelB are known to be involved in various aspects of development and secondary metabolism in all ascomycetes where they have been studied, however fewer studies have addressed the role

Table 1 – LaeA and VeA orthologs in filamentous fungi

Gene name	Species	Function[a]	Reference
LaeA			
LaeA	*Aspergillus fumigatus*	SM, D, V	Bok *et al.*, 2005; Bok and Keller, 2004; Dagenais *et al.*, 2010; Sugui *et al.*, 2007; Ben-Ami *et al.*, 2009
LaeA	*Aspergillus nidulans*	SM, D	Bok and Keller, 2004
Lae1	*Trichoderma reesei*	SM, D, O	Seiboth *et al.*, 2012
LaeA	*Fusarium oxysporum*	SM, D, V	Lopez-Berges *et al.*, 2013
Lae1	*Fusarium verticillioides*	SM	Butchko *et al.*, 2012
ChLae1	*Cochliobolus heterostrophus*	SM, D, V	Wu *et al.*, 2012
LaeA	*Penicillium citrinum*	SM	Baba *et al.*, 2012
LaeA	*Aspergillus flavus*	SM, D, V	Amaike and Keller, 2011
PcLaeA	*Penicillium chrysogenum*	SM, D	Kamerewerd *et al.*, 2011; Kosalková *et al.*, 2009
LaeA	*Aspergillus oryzae*	SM	Oda *et al.*, 2011
FfLae1	*Fusarium fujikuroi*	SM, D, V	Wiemann *et al.*, 2010
LaeA	*Monascus pilosus*	SM, D	Lee *et al.*, 2013; Zhang and Miyake, 2009
LaeA-like	*Neotyphodium uncinatum*	not assessed	Zhang *et al.*, 2009
VeA			
VeA	*Aspergillus nidulans*	SM, D	Bayram *et al.*, 2008a
VeA	*Fusarium oxysporum*	SM, D, V	Lopez-Berges *et al.*, 2013
ChVel1	*Cochliobolus heterostrophus*	SM, D, V	Wu *et al.*, 2012
BcVeA	*Botrytis cinerea*	SM, D, V	Yang *et al.*, 2013
VeA	*Penicillium citrinum*	SM	Baba *et al.*, 2012
VeA	*Aspergillus flavus*	SM, D, V	Amaike and Keller, 2011
PcVelA	*Penicillium chrysogenum*	SM, D	Kamerewerd *et al.*, 2011
FfVel1	*Fusarium fujikuroi*	SM, D, V	Wiemann *et al.*, 2010
VeA	*Dothistroma septosporum*	SM, D	Chettri *et al.*, 2012
FgVeA	*Fusarium graminearum*	SM, D, V	Jiang *et al.*, 2011; Merhej *et al.*, 2012
VeA1	*Histoplasma capsulatum*	SM, D, V	Laskowski-Peak *et al.*, 2012
VeA	*Aspergillus fumigatus*	SM, D, V	Dhingra *et al.*, 2012
FvVE1	*Fusarium verticillioides*	SM, D	Li *et al.*, 2006
VeA	*Fusarium verticillioides*	SM, D, V	Myung *et al.*, 2012
MVE1	*Mycosphaerella graminicola*	SM, D	Choi and Goodwin, 2011
Ve1	*Neurospora crassa*	SM, D	Bayram *et al.*, 2008b

a SM = secondary metabolism, D = fungal development, V = virulence, O = other.