



Mini-review

Fungal ribotoxins: Natural protein-based weapons against insects



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ABSTRACT

Ribotoxins are fungal extracellular ribonucleases highly toxic due to their ability to enter host cells and their effective ribonucleolytic activity against the ribosome. The natural role of these proteins in the producing fungi is still unsolved. Nevertheless, recent studies showing the insecticidal properties of two ribotoxins from different origin support their involvement in defense mechanisms. Thus, it seems that not just the entomopathogen *Hirsutella thompsonii* expresses the ribotoxin hirsutellin A as a virulence factor but also *Aspergillus*, the main ribotoxin producer, does so. In this review we focus on this little known aspect of this family of proteins, their toxicity against insects, from the point of view of its biological relevance and its potential biotechnological applications.

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Nature provides numerous examples of self defense against predators in all living organisms. In particular, plants, fungi and bacteria produce a high variety of toxins against insects, many of which are proteins. From a biotechnological point of view, some of them are being developed for pest control, since conventional agrochemical pesticides show adverse effects on the environment and human health as well as a rapid emergence of pest resistance. Moreover, the high cost of discovering, developing and registering new synthetic pesticides have also contributed to increased interest in biopesticides (Glare et al., 2012).

Insect pathogenic fungi are of special interest since they play an important natural role in controlling insect pests. The approximately 1000 known species of entomopathogenic fungi target most, if not all, insect species, from sucking insects to many coleopteran and orthopteran pests, although individually have narrow host ranges. In fact,

products based on the species *Beauveria*, *Metarhizium*, *Lecanicillium* and *Isaria* are being commercialized (Faria and Wraight, 2007; Kim et al., 2014). However, efficacy limitations like dose response and specificity still need to be overcome. Therefore, a better understanding of fungal pathogenesis in insects at a molecular level is a demanding field in order to improve their application in a natural environment.

1. *Hirsutella thompsonii*

H. thompsonii is a well known entomopathogen fungus registered in 1981 as Mycar for the control of the citrus rust mite (McCoy, 1981). This formulation was soon abandoned due to its poor efficacy in field trials. Nevertheless, this mold has been recently studied against several mites. Mycohit is a formulation registered and commercialized in India for coconut eriophyid mites with success in extensive field trials studies (Sreerama Kumar and Singh, 2008). In fact, *Hirsutella* shows a high specificity to subclass Acari and it is clearly more virulent than the extensively studied

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Metarhizium anisopliae (Shaw et al., 2002; Rossi-Zalaf and Alves, 2006). *H. thompsonii* has been also tried as a biocontrol agent against the Varroa mite, the worst pathogen of the honey bee (Kanga et al., 2002; Peng et al., 2002). However, additional field assays are still to be performed. In addition, not much is known about the toxic molecules involved in its virulence. It has been described how extracellular media of a *H. thompsonii* culture has a pathogenic effect, with a very slow but high lethality against target insects (Vey et al., 1993). However, only the fungal ribotoxin hirsutellin A has been isolated and further studied, so far (Mazet and Vey, 1995).

2. Fungal ribotoxins

Extracellular chitinases and proteases are the protein-based toxins most abundant in insect pathogenic fungi, and are involved in cuticle invasion of their hosts. Nevertheless, they act in concert with many other factors (Clarkson and Charnley, 1996). Here we focus on a small but well established family of proteins named as fungal ribotoxins, which have potential virulence, although their biological role is still under study (Brandhorst and Kenealy, 1992; Yang and Kenealy, 1992). Ribotoxins are mainly produced by filamentous fungi of the genus *Aspergillus*, several of its species characterized as plant pathogens and in general a saprophytic genus (Martínez-Ruiz et al., 1999; Lacadena et al., 2007). The discovery of *H. thompsonii* as the only entomopathogen fungus producer of a ribotoxin, hirsutellin A, has opened a new view of these proteins as potential participants of an insecticidal activity (Herrero-Galán et al., 2008; Olombrada et al., 2013) (Fig. 1).

Fungal ribotoxins are extracellular ribonucleases with an extraordinary specificity against the ribosome. Their RNA target, the sarcin/ricin loop (SRL), is localized in the large ribosomal subunit and it is essential for ribosome function, participating in the activation step of several translation factors involved in all steps of protein synthesis (García-Ortega et al., 2010). Ribotoxins cleave just one phosphodiester bond of the SRL, enough to impair its essential function. This catalytic activity has been extensively studied as it has been their structure and relationship with other non-toxic extracellular ribonucleases also produced by fungi. In fact, there is an extended literature regarding these properties with the best known members of the family: α -sarcin, from *Aspergillus giganteus*, and restrictocin, from *Aspergillus restrictus* (Lacadena et al., 2007; Plantinga et al., 2008). These two fungal ribotoxins differ in just a 15% of their sequence showing practically identical structure and activity properties.

Due to their high efficacy to inactivate the ribosome of the target cell, fungal ribotoxins are considered one of the most potent toxins known. The universality of the SRL sequence and structure makes ribosomes from all kingdoms of life susceptible to ribotoxin action (Schindler and Davies, 1977; Endo and Wool, 1982; García-Ortega et al., 2010; Olombrada et al., 2013). Even the producer organism requires a high efficiency secretion pathway to prevent cytotoxicity (Lamy and Davies, 1991).

The toxicity of these proteins is also dependent on their ability to enter cells, with the limiting step based on lipid interaction (Oñaderra et al., 1993; Turnay et al., 1993; Olombrada et al., 2013). Preference for acidic phospholipids has been described, but a receptor interaction has not been

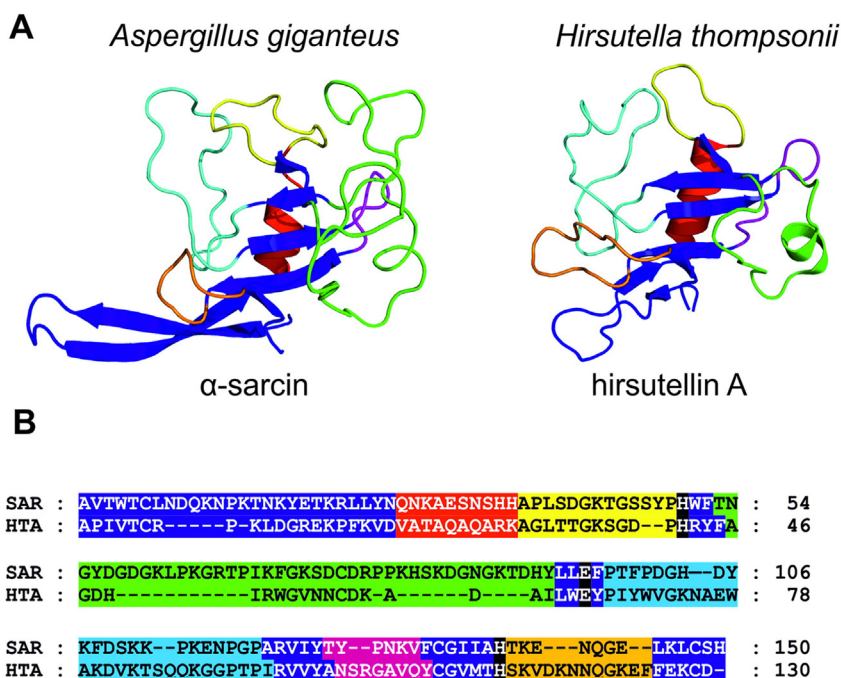


Fig. 1. Structure (A) and sequence alignment (B) of α -sarcin (PDB ID: 1DE3) and hirsutellin A (PDB ID: 2KAA). Color code of structural elements: β -sheet, dark blue; α -helix, red; loop 1, yellow; loop 2, green; loop 3, cyan; loop 4, magenta; loop 5, orange. Catalytic residues are black boxed in the sequences. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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