FUNGAL BIOLOGY REVIEWS XXX (2018) 1–10

British Mycological Society promoting fungal science

journal homepage: www.elsevier.com/locate/fbr

Review

Biological, biochemical and molecular aspects of *Scedosporium aurantiacum*, a primary and opportunistic fungal pathogen

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ARTICLE INFO

Article history:
Received 6 December 2017
Received in revised form
13 March 2018
Accepted 18 March 2018

Keywords:
Biology
Interactions
Molecular aspects
Pathogenic fungi
Pathophysiology
Scedosporium aurantiacum

ABSTRACT

The present review summarises the current knowledge of the biology, biochemistry and molecular aspects of *S. aurantiacum* in context with the broader knowledge on *Scedosporium* spp, generated over the past decade. Recently, the genus has undergone two taxonomical reviews. *S. aurantiacum* is widely distributed in all ecological niches and geographical locations. It is a highly pathogenic opportunist capable of causing a broad range of diseases via infections occurring in the lungs, sinuses, eyes, bones, central nervous system and internal organs. While *S. aurantiacum* has a minor role in the colonisation of lungs in Germany and France, in Australia, it comprises approximately one-third of *Scedosporium* spp. recovered from cystic fibrosis lungs where it may co-exist with other prokaryotic lung inhabitants such as *Pseudomonas aeruginosa*. However, very little is known about mixed bacterial–fungal interactions or host–fungal interactions in the lungs, all of which may have an impact on disease outcome. Also, the nature of potential virulence factors such as production of particular proteases would require more research. A wide range of molecular diagnostic techniques now available can facilitate rapid and accurate identification of *Scedosporium* spp. in clinical specimens and environmental samples. However, molecular tools allowing gene overexpression and knockout studies are yet to be fully developed. A draft genome is currently available for *S. aurantiacum* strain WM 09.24 (CBS136047), an Australian environmental isolate. The emerging genomic tools and metabolic and transcriptomic studies discussed will further advance understanding of the pathogenic mechanisms of members of the genus *Scedosporium*, including *S. aurantiacum*.

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https://doi.org/10.1016/j.fbr.2018.03.001
1749-4613/

1. Introduction

Scedosporium species as global fungal pathogens

Scedosporium spp. are ubiquitous opportunistic pathogenic fungi that are significant emergent agents of disease increasingly identified partially due to application of new molecular identification technologies to identify and to distinguish between these fungi. The range of infections caused by *Scedosporium* spp. is broad including the lungs, central nervous system (CNS), bone, joint, skin and subcutaneous tissue (reviewed in Cooley *et al.*, 2007; Cortez *et al.*, 2008; Slavin *et al.*, 2015). Other than causing invasive disease, *Scedosporium* spp. also colonise the respiratory tract of cystic fibrosis (CF) patients and patients with prior lung damage (Pihet *et al.*, 2009; Blyth *et al.*, 2010a,b).

Scedosporium spp. are cosmopolitan fungi. Recent large scale studies in CF patients carried out in Germany (Sedlacek *et al.* 2015) have reported *S. apiospermum* and *S. boydii* as the most predominant *Scedosporium* species in patient samples with an overall prevalence of 3.1 %. In France, the overall prevalence of *Scedosporium* species in CF patient samples was 4 % but the distribution of the different *Scedosporium* species was not investigated (Parize *et al.*, 2014). There are also reports on colonisation and infection due to *Scedosporium* spp. in the setting of CF and in immunocompromised patients in Northern Spain (Lackner *et al.*, 2011). In Australia and in some European countries including France and Austria, these fungi are the second most common filamentous fungi colonising the airways of CF patients (Cimon *et al.*, 2000; Blyth *et al.*, 2010a: Masoud-Landgraf *et al.*, 2014) and overall, account for 33.3 % of invasive fungal disease due to filamentous fungi by other than *Aspergillus* species (Slavin *et al.*, 2015). *Scedosporium* infections cause 25–29 % of non-*Aspergillus* infections in organ transplant recipients in the USA and may occur post-surgery (Husain *et al.*, 2003; Cortez *et al.*, 2008; Pihet *et al.*, 2009). Recently, *Scedosporium* spp. have also been identified as a causative agent of mycetomas in Brazil (Sampaio *et al.*, 2017), yet *Scedosporium* infections remain rare in China (Wang *et al.*, 2015). In Australia, *Scedosporium* spp. are found in urban environment (see also below) and their presence in relatively high frequency is associated with environments of high human activity in Austria and other parts of Europe (Kaltseis *et al.*, 2009; Rougeron *et al.*, 2018).

While particular aspects of *Scedosporium* spp. have been discussed in previously published papers, this review focuses on bringing together the current knowledge of the biology, biochemistry and molecular characteristics of *S. aurantiacum*, an opportunistic pathogenic species colonising human lungs.

2. The genus *Scedosporium* and the taxonomic position of *S. aurantiacum*

The genus anamorph *Scedosporium* with its teleomorph *Pseudallescheria* has undergone numerous changes with the introduction of molecular phylogenetics, which has led to an increasing resolution at and below the species level. In addition, the fundamental change in fungal taxonomy allowing only a single name per fungal species, effectively abolishing the dual nomenclature based on the anamorph/teleomorph concept (Mcneill *et al.*, 2012) has resulted in the adoption of the name *Scedosporium* at the expense of *Pseudallescheria* (Lackner *et al.*, 2014).

The first comprehensive revision of the genus was conducted in 2005 by Gilgado *et al.* (2005) by analysing four genetic loci – β-tubulin (*BT2* = exon 2–4), *TUB* (=exon 5–6), calmodulin and the internal transcribed spacer region (ITS) of the rDNA gene cluster. This recognised *S. apiospermum* (incl. *P. boydii*) as a species complex, in addition to the separation of *S. aurantiacum* and *S. minutisporum* as distinct species. Within the *S. apiospermum/P. boydii* complex, three existing species were recognised: *P. angusta*, *P. ellipsoidea* and *P. fusoidea* (Gilgado *et al.*, 2005). A second revision further recognised a new species *S. dehoogii* and maintained *S. apiospermum* and *P. boydii* as distinct species (Gilgado *et al.*, 2008). Recently, another new species phylogenetically related to *S. aurantiacum* was described, based on ITS, *BT2* and calmodulin, named *S. cereisporum* (Crous *et al.*, 2016).

After the One Fungus = One Name movement (Hawksworth *et al.*, 2011) and sequencing studies, the genus *Scedosporium* now contains the following 10 species: *S. aurantiacum*, *S. minutisporum*, *S. desertorum*, *S. cereisporum*, and *S. dehoogii*, in addition to the *S. apiospermum* complex that comprises *S. angustum*, *S. apiospermum*, *S. boydii*, *S. ellipsoideum* and *S. fusoideum*. Importantly, *Lomentospora prolificans* (formerly *S. prolificans*) has been shown to be unrelated to *Scedosporium* and has therefore been reclassified as *L. prolificans* (Hennebert and Desai, 1974) the genus *Lomentospora* was reinstated for this species (Lackner *et al.*, 2012). The above information is relevant to the further study of *S. aurantiacum* as a pathogen and in its placement in the clinical context.

Identification of S. aurantiacum from environmental and clinical samples

In the laboratory, *S. aurantiacum* can be distinguished from other *Scedosporium* species based partly on its ability to tolerate temperatures up to 45 °C and the production of a yellow diffusible pigment usually observed at the reverse of the culture plate (Gilgado *et al.*, 2005; Ramsperger *et al.*, 2014). *S. aurantiacum* can also tolerate a high amount of $MgCl_2$ (5 %) compared to NaCl (Gilgado *et al.*, 2008). In *Scedosporium* species including *S. aurantiacum*, conidia can arise from solitary cylindrical conidiogenous cells or directly from undifferentiated hyphae, as well as from conidiogenous cells located at the end of conidiophores arranged in parallel (synnemata). The conidia produced from solitary conidiogenous cells are typically ovoid or subcylindrical, 5–14 μm long and 2–5 μm wide (Gilgado *et al.*, 2005). The size and shape of conidiogenous cells and conidia of *S. aurantiacum* are similar to those produced by *S. apiospermum* (Gilgado *et al.*, 2005). In some isolates, cylindrical conidia with a size similar to that of solitary conidia can also originate from synnemata (a group of erect conidiophores). Undifferentiated cells produce sessile, solitary, lateral, brown, smooth and thick walled ovoid conidia ranging from 6 to 10 μm in length and 3–5 μm in width (Gilgado *et al.*, 2005).

Please cite this article in press as: Nevalainen, H., et al., Biological, biochemical and molecular aspects of *Scedosporium aurantiacum*, a primary and opportunistic fungal pathogen, Fungal Biology Reviews (2018), https://doi.org/10.1016/j.fbr.2018.03.001