Iron metabolism in pathogenic *Sporothrix* spp.

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INI/Fiocruz

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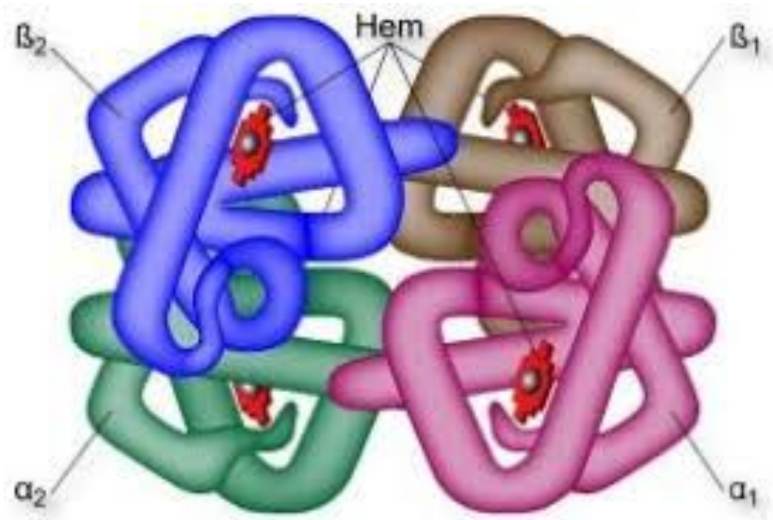
Iron importance in living organisms

- Cofactor of several enzymes
- Oxygen carriers
- Electron-transfer systems



Iron in infectious diseases

- Iron withholding as a defense mechanism

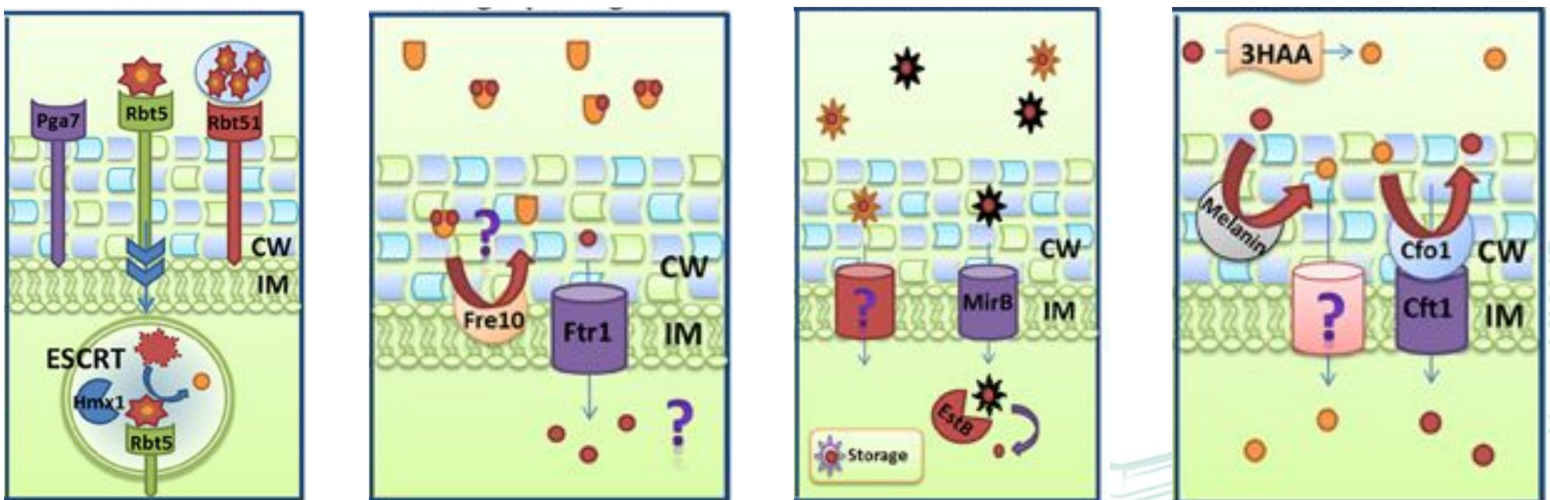
Iron withholding defense system.

Constitutive components
Siderophilins
Transferrin in plasma, lymph, cerebrospinal fluid
Lactoferrin in secretions of lachrymal & mammary glands and of respiratory, gastrointestinal and genital tracts
Ferritin within host cells
Processes induced at times of invasion
Prompt reduction in plasma iron & in absorption of iron from diet
Increased hepatic synthesis of hepcidin (ferroportin inactivator) to suppress release of iron by macrophages and by duodenal enterocytes. Increased synthesis of macrophage ferritin & decreased synthesis of ferroportin.
Removal of iron from sites of invasion
Release of neutrophils from bone marrow into circulation and then into invasion sites. Release of apolactoferrin from neutrophil granules followed by binding of iron in septic sites. Macrophage scavenging of hololactoferrin. Hepatic release of haptoglobin & hemopexin (to bind extracellular hemoglobin & hemin).
Macrophage suppression of microbial iron metabolism by synthesis of lipocalins (to bind siderophores), of nitric oxide (to disrupt invader iron metabolism) and of Nramp1 (to withhold growth-essential iron from invaders).
Induction in B lymphocytes of immunoglobulins to microbial cell surface receptors that bind either ferrated siderophores, ferrated siderophilins, hemoglobin, or heme.

Weinberg, Biochim Biophys Acta. 2009 Jul;1790(7):600-5.

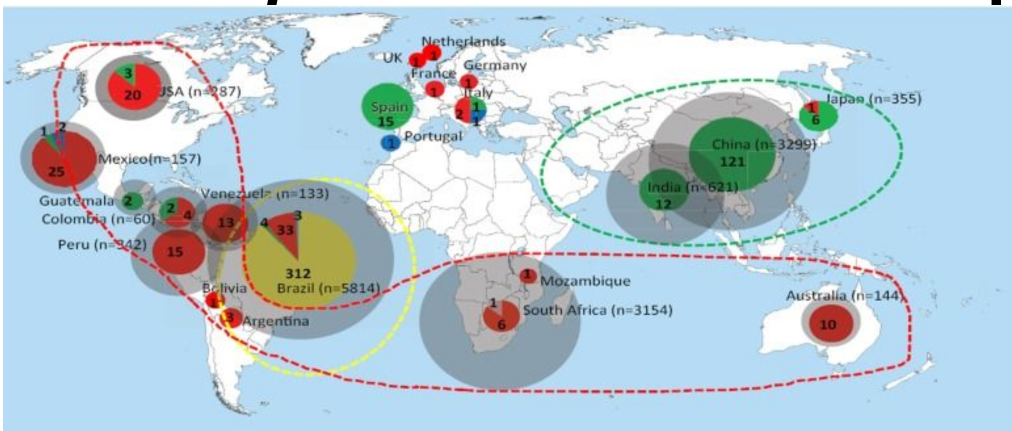
Fungal strategies for iron acquisition

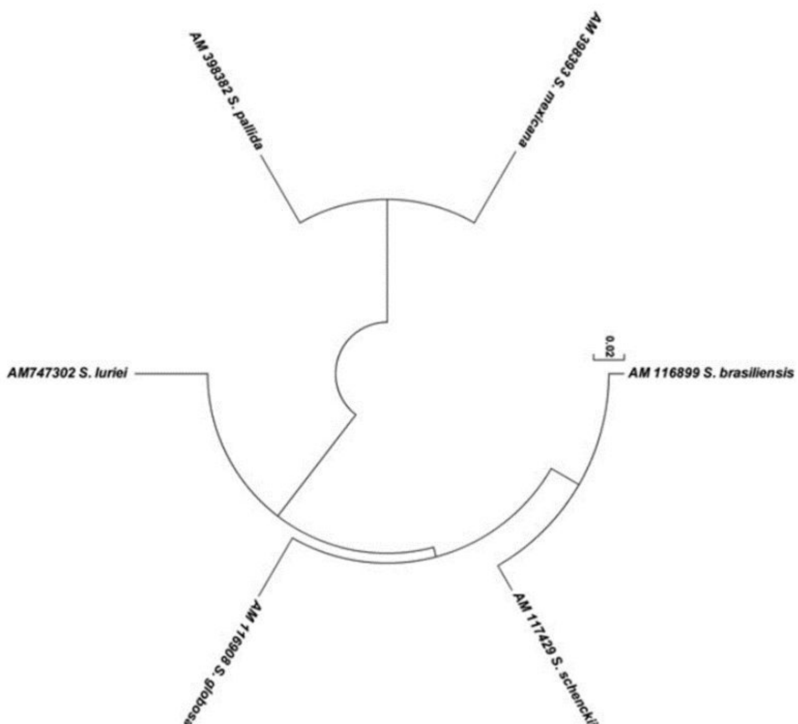
Hemoglobin and heme uptake | Acquisition form transferin | siderophores | Fe^{2+} uptake



Caza & Kronstad. Front Cell Infect Microbiol. 2013 Nov 19;3:80.

Sporothrix and sporotrichosis





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Sporothrix schenckii and *Sporothrix brasiliensis* genomes

Teixeira *et al. BMC Genomics* 2014, **15**:943
http://www.biomedcentral.com/1471-2164/15/943

BMC Genomics

RESEARCH ARTICLE **Open Access**

Comparative genomics of the major fungal agents of human and animal Sporotrichosis: *Sporothrix schenckii* and *Sporothrix brasiliensis*

Marcus M Teixeira[1], Luiz GP de Almeida[2], Paula Kubitschek-Barreira[3], Fernanda L Alves[4,5], Érika S Kioshima[1,6], Ana KR Abadio[1], Larissa Fernandes[7], Lorena S Derengowski[1], Karen S Ferreira[8], Rangel C Souza[2], Jeronimo C Ruiz[5], Nathalia C de Andrade[3], Hugo C Paes[1], André M Nicola[9,10], Patrícia Albuquerque[1,10], Alexandra L Gerber[2], Vicente P Martins[1], Luisa DF Peconick[1], Alan Viggiano Neto[1], Claudia B Chaucanez[1], Patrícia A Silva[1], Oberdan L Cunha[2], Fabiana FM de Oliveira[1], Tayná C dos Santos[1], Amanda LN Barros[1], Marco A Soares[4], Luciana M de Oliveira[4,11], Marjorie M Marini[12], Héctor Villalobos-Duno[13], Marcel ML Cunha[3], Sybren de Hoog[14], José F da Silveira[12], Bernard Henrissat[15], Gustavo A Niño-Vega[13], Patrícia S Cisalpino[5], Héctor M Mora-Montes[16], Sandro R Almeida[17], Jason E Stajich[18], Leila M Lopes-Bezerra[3], Ana TR Vasconcelos[2] and Maria SS Felipe[1,9*]

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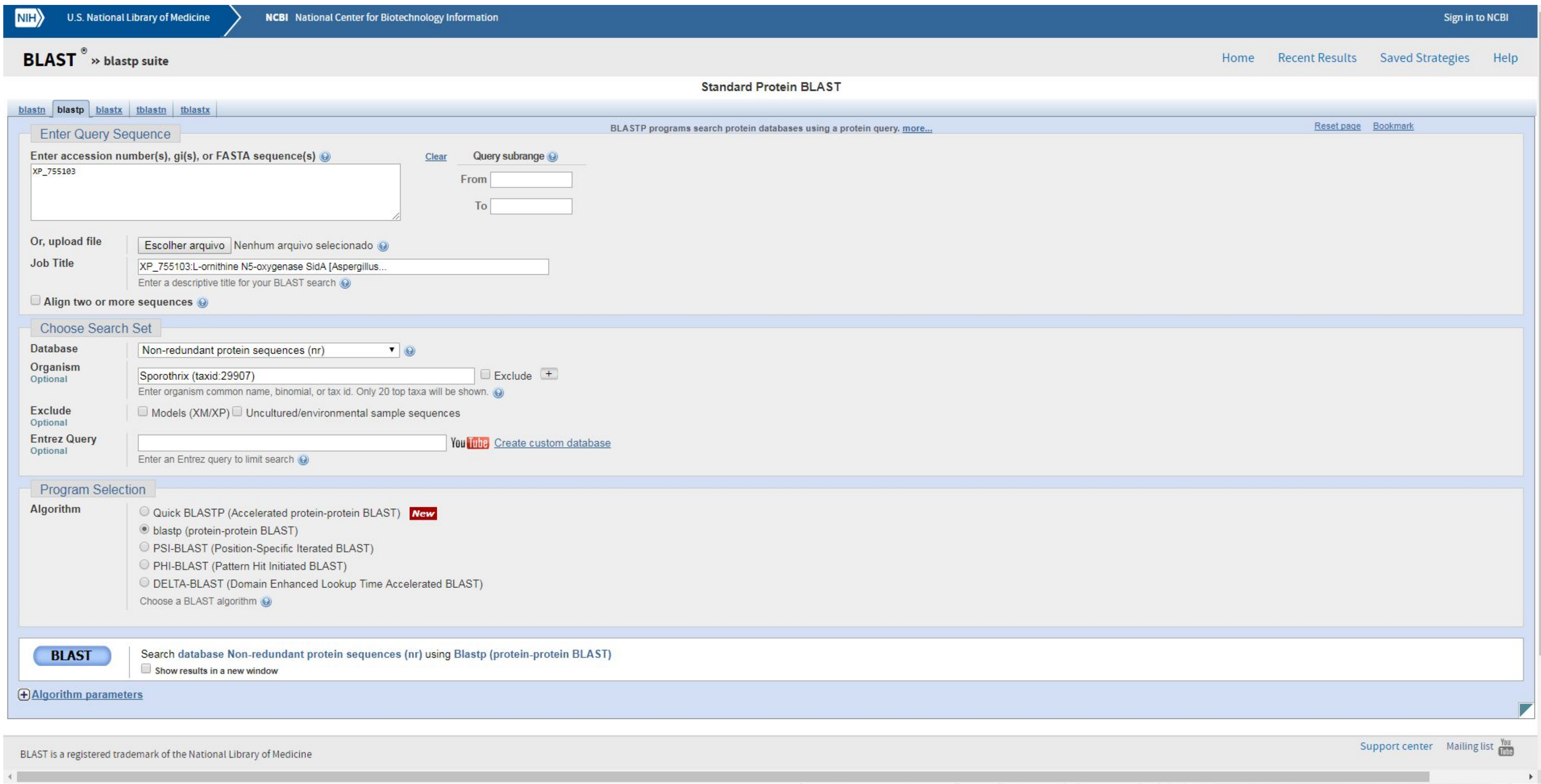
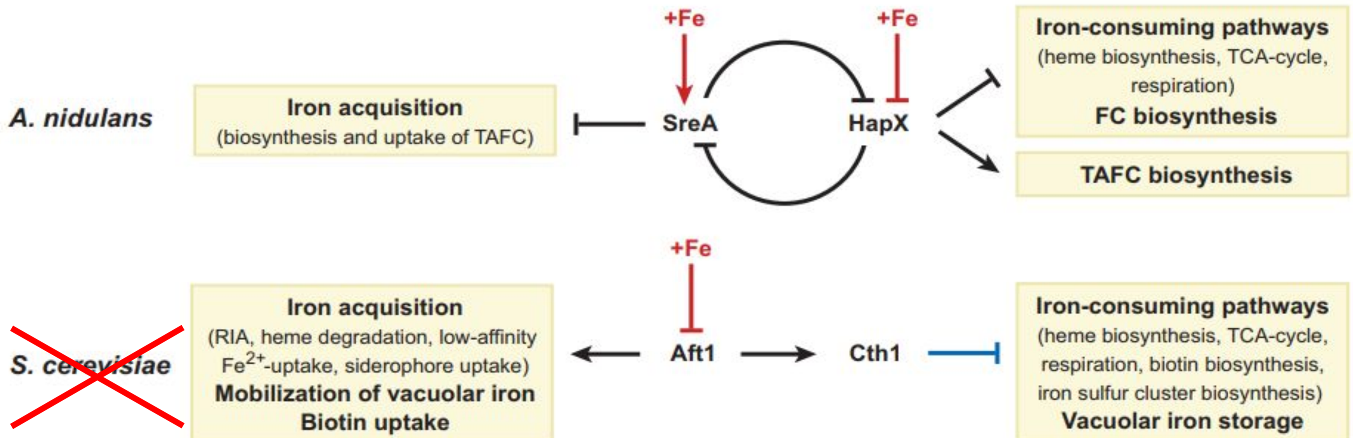
In silico analysis of *Sporothrix* spp. genomes

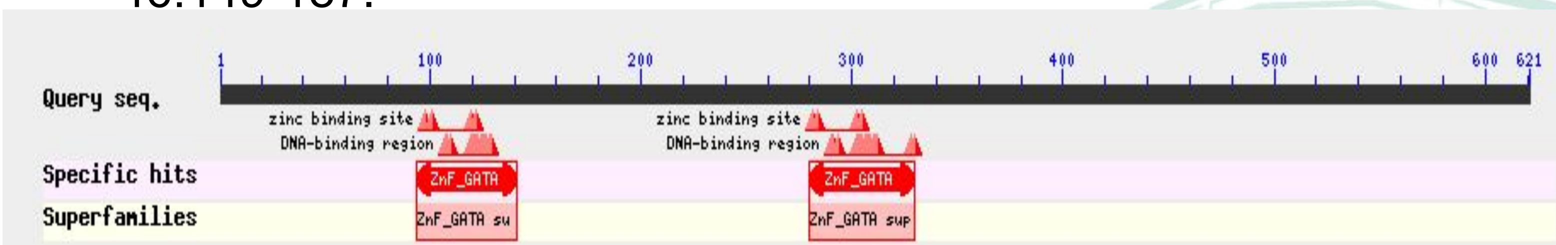


Regulation of iron metabolism

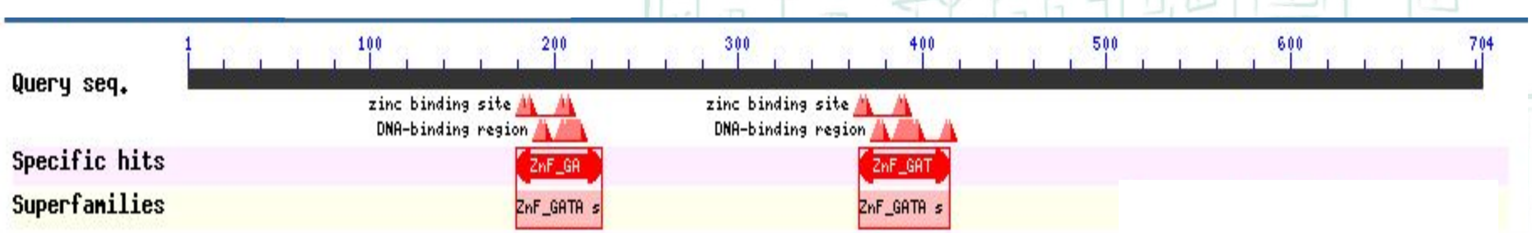


Hass et al. Annu Rev Phytopathol. 2008; 46:149-187.

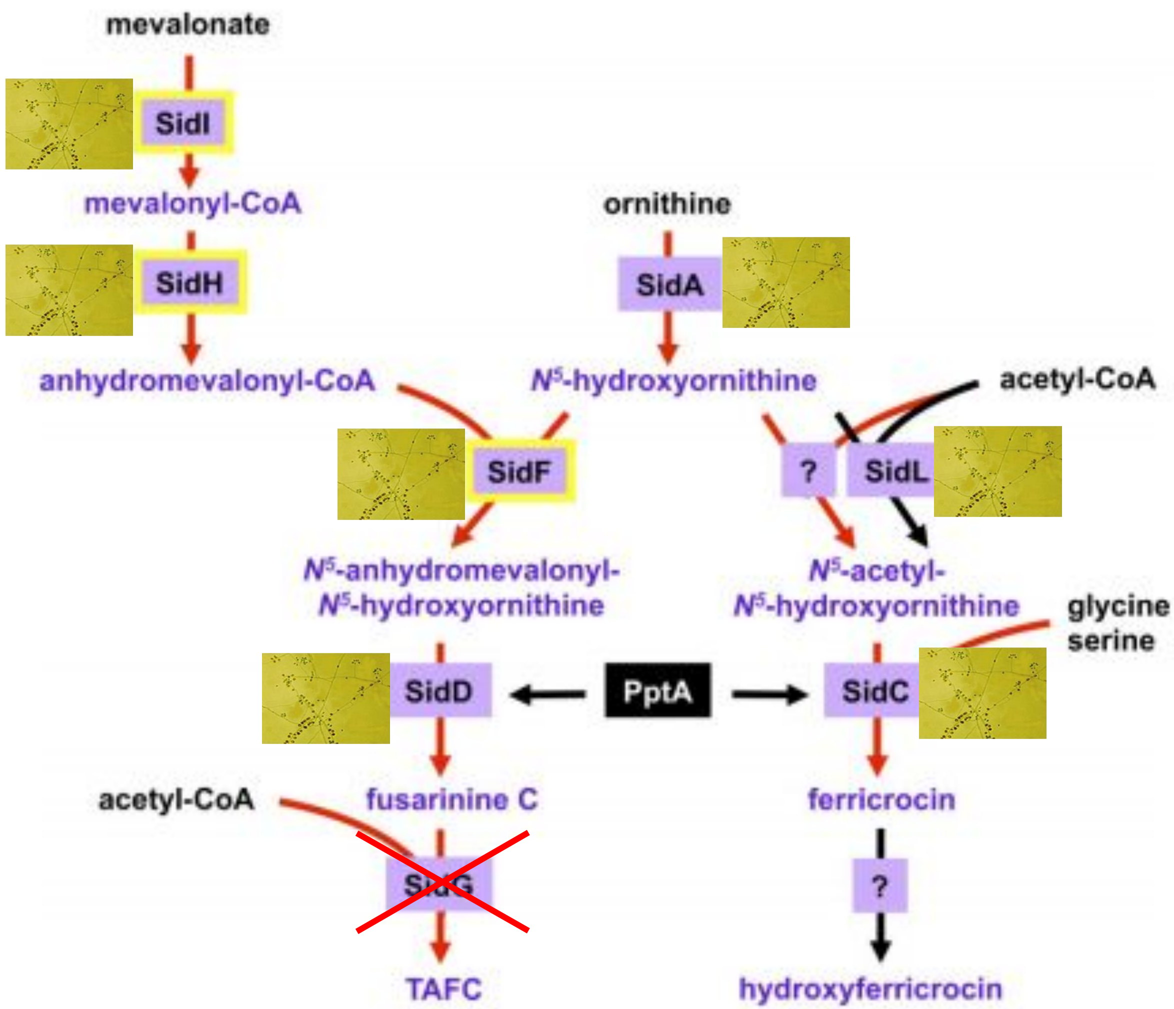
S. brasiliensis



S. schenckii

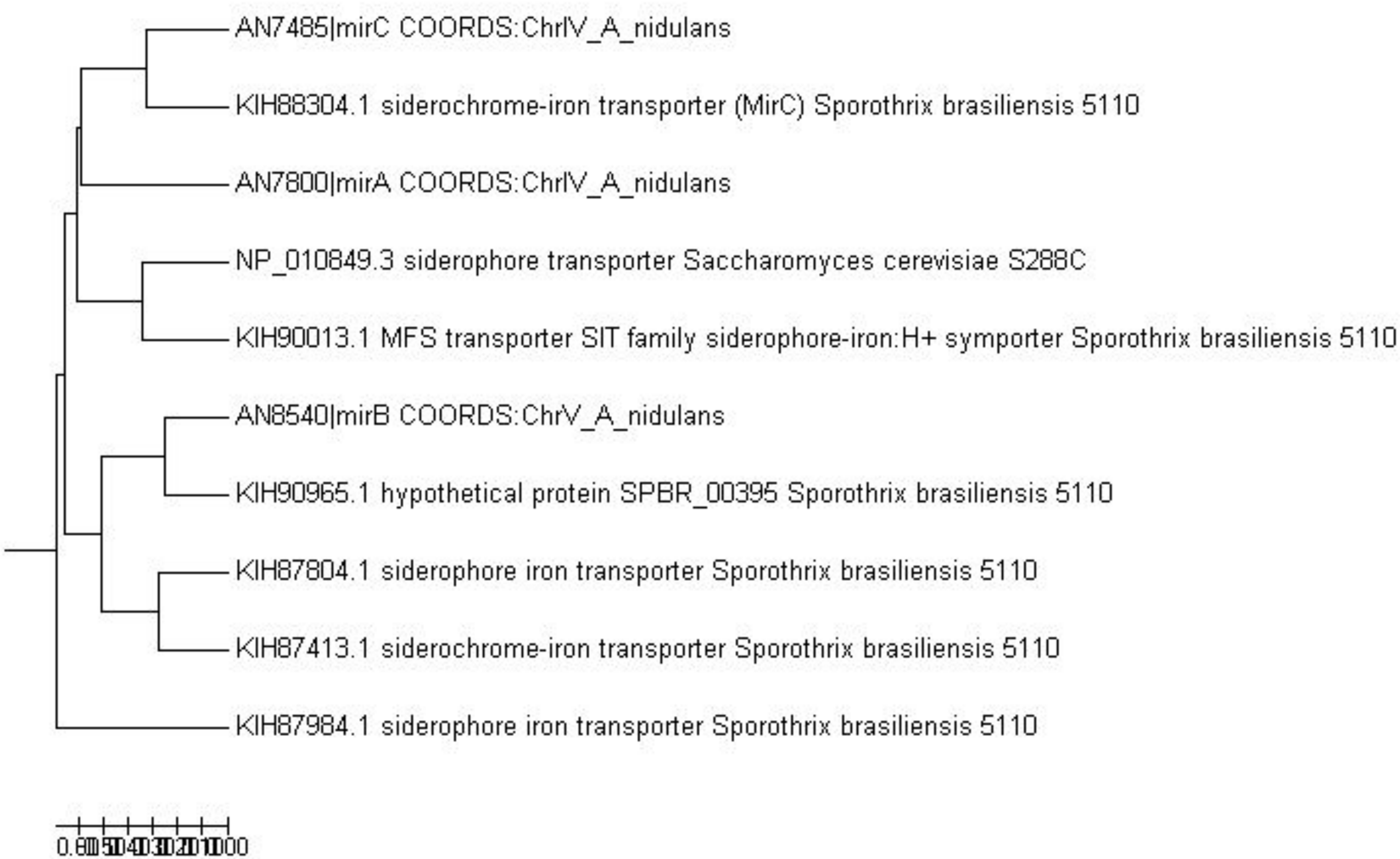


Sporothrix spp. siderophores

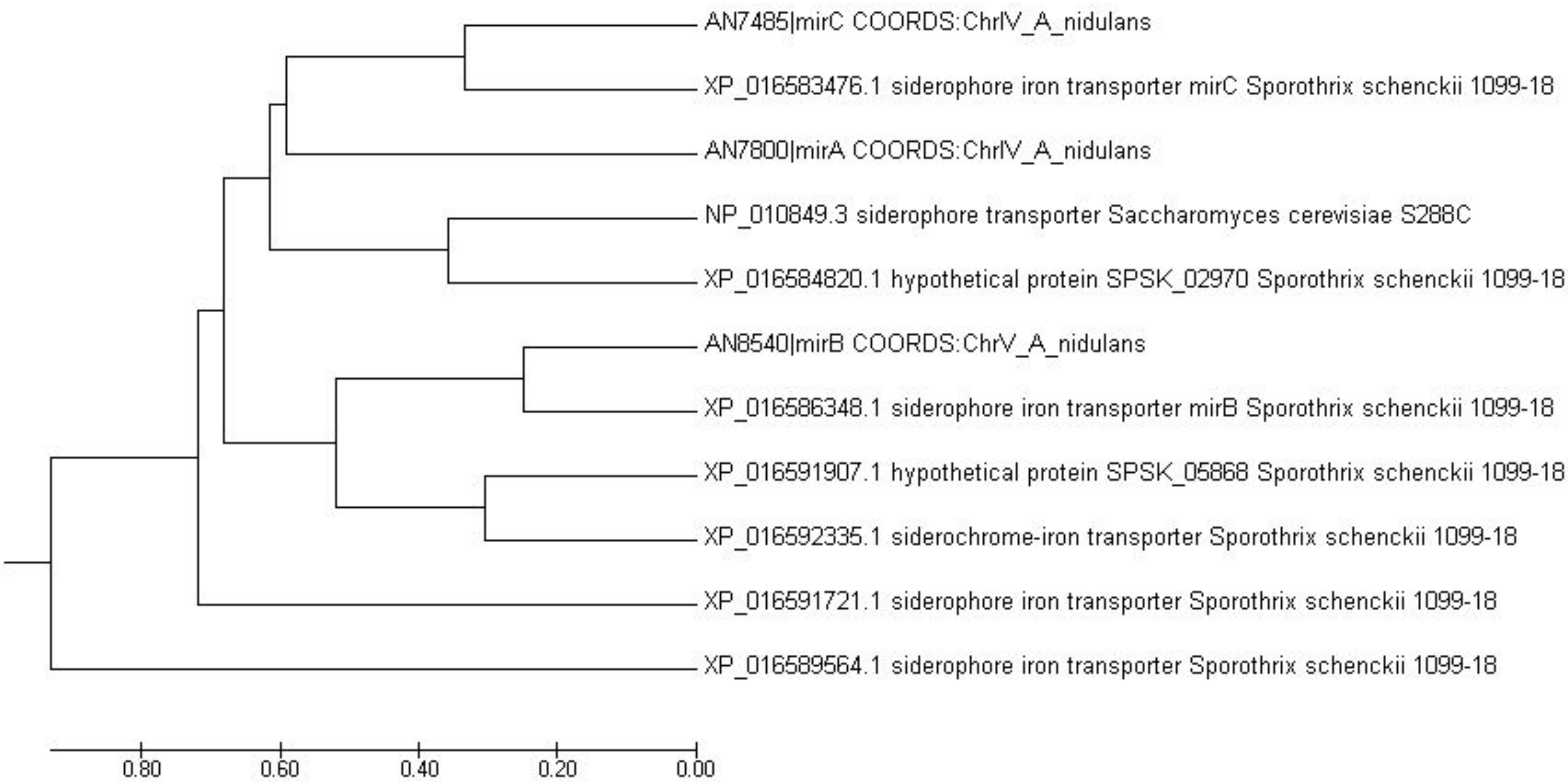


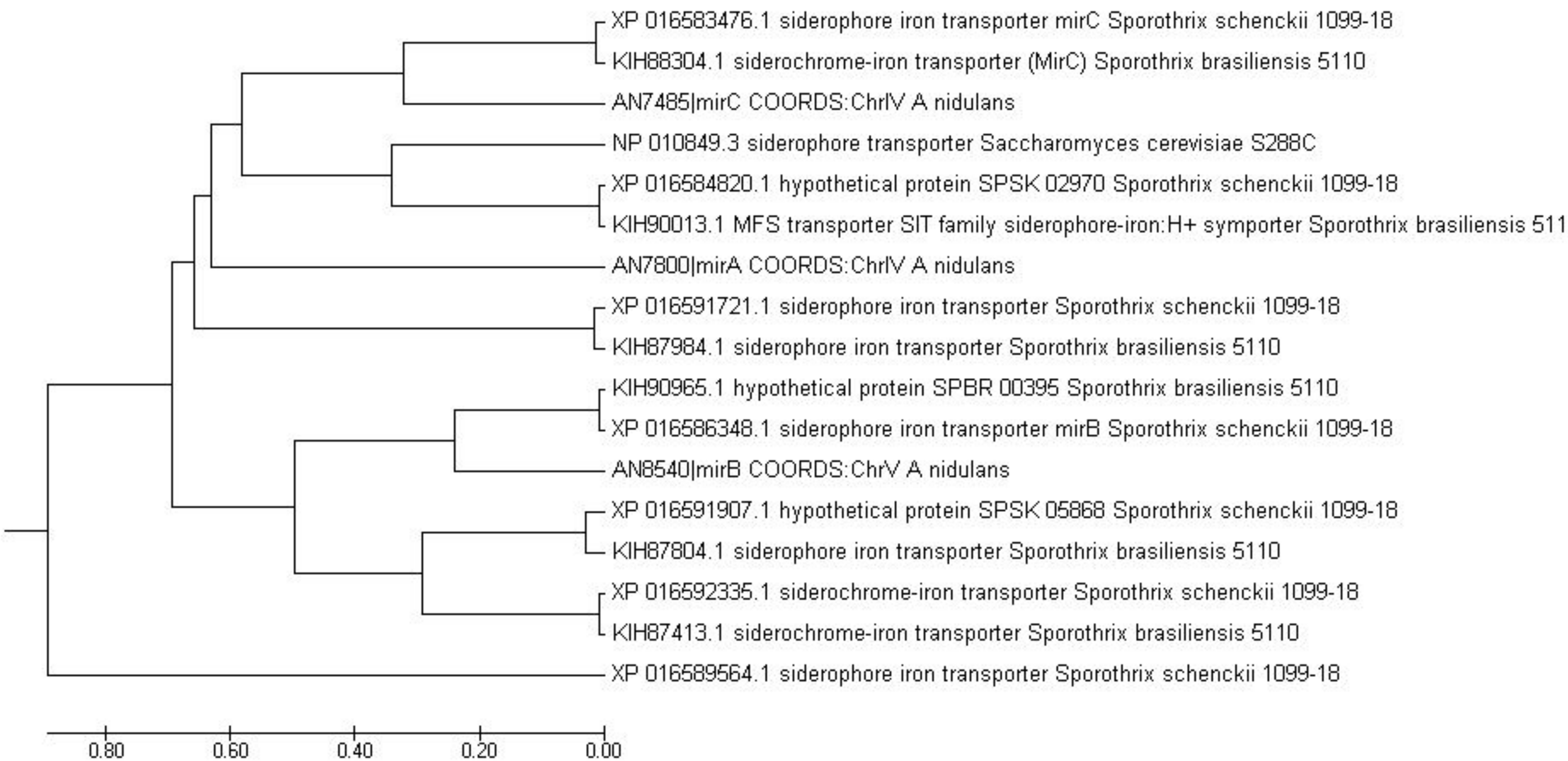
Adapted from Grundlinger et al. Mol Microbiol. 2013; 88(5):

*Sporothrix brasiliensis s*iderophore transporters

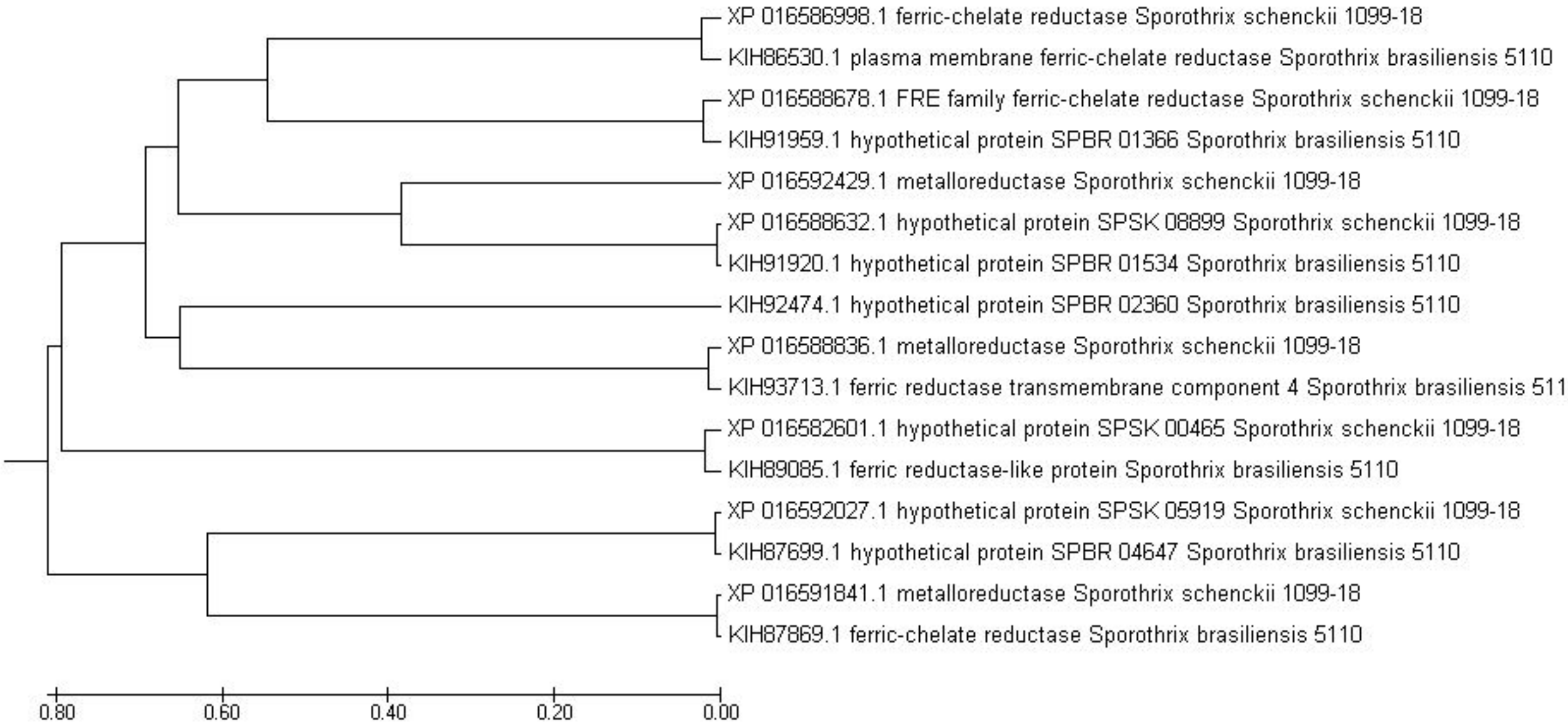


*Sporothrix schenckii s*iderophore transporters




XP 016583476.1 siderophore iron transporter mirC Sporothrix schenckii 1099-18
KIH88304.1 siderochrome-iron transporter (MirC) Sporothrix brasiliensis 5110
AN7485|mirC COORDS:ChrIV A nidulans
NP 010849.3 siderophore transporter Saccharomyces cerevisiae S288C
XP 016584820.1 hypothetical protein SPSK 02970 Sporothrix schenckii 1099-18
KIH90013.1 MFS transporter SIT family siderophore-iron:H+ symporter Sporothrix brasiliensis 5110
AN7800|mirA COORDS:ChrIV A nidulans
XP 016591721.1 siderophore iron transporter Sporothrix schenckii 1099-18
KIH87984.1 siderophore iron transporter Sporothrix brasiliensis 5110
KIH90965.1 hypothetical protein SPBR 00395 Sporothrix brasiliensis 5110
XP 016586348.1 siderophore iron transporter mirB Sporothrix schenckii 1099-18
AN8540|mirB COORDS:ChrV A nidulans
XP 016591907.1 hypothetical protein SPSK 05868 Sporothrix schenckii 1099-18
KIH87804.1 siderophore iron transporter Sporothrix brasiliensis 5110
XP 016592335.1 siderochrome-iron transporter Sporothrix schenckii 1099-18
KIH87413.1 siderochrome-iron transporter Sporothrix brasiliensis 5110
XP 016589564.1 siderophore iron transporter Sporothrix schenckii 1099-18
0.80
0.60
0.40
0.20
0.00

Reductive iron uptake

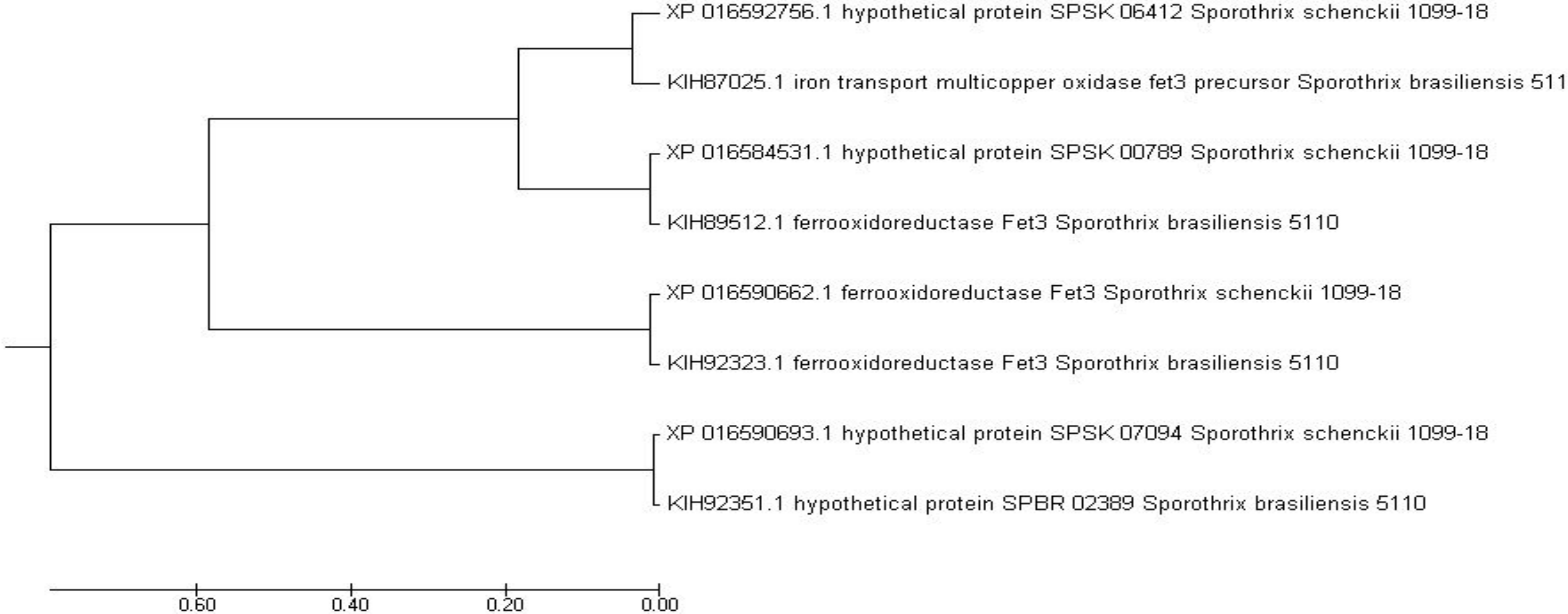


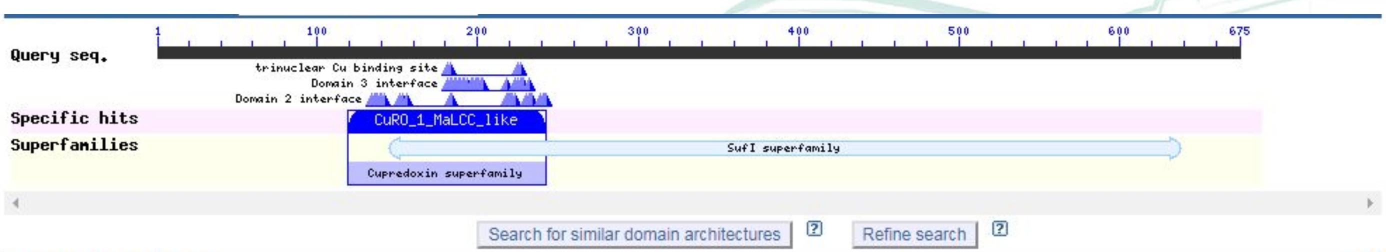
Search for similar domain architectures | Refine search

List of domain hits

Name	Accession	Description	Interval	E-value
[+] NOX_Duox_like_FAD_NADP	cd06186	NADPH oxidase (NOX) catalyzes the generation of reactive oxygen species (ROS) such as ...	346-611	8.16e-54
[+] Ferric_reduct	pfam01794	Ferric reductase like transmembrane component; This family includes a common region in the ...	181-298	1.55e-30

Ferroxidases



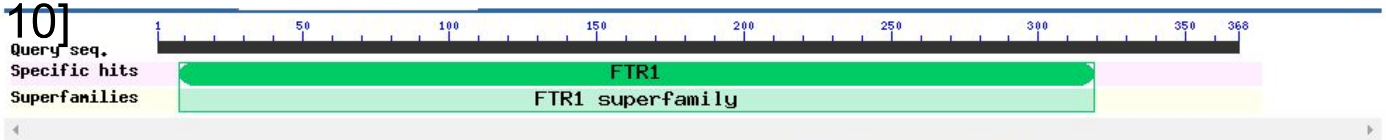


List of domain hits

Name	Accession	Description	Interval	E-value
[+] CuRO_1_MaLCC_like	cd13854	The first cupredoxin domain of the fungal laccases similar to Ma-LCC from Melanocarpus ...	119-243	2.89e-69
[+] SufI super family	cl28276	Multicopper oxidase with three cupredoxin domains (includes cell division protein FtsP and ...	145-638	8.00e-56

Iron transporters

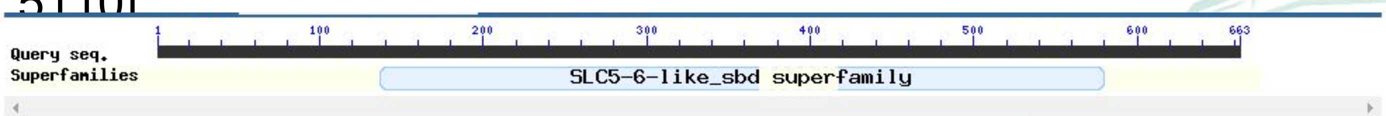
KIH92322.1 high-affinity iron transporter [Sporothrix brasiliensis 5110]



List of domain hits

Name	Accession	Description	Interval	E-value
[+] FTR1	pfam03239	Iron permease FTR1 family;	8-319	1.21e-56

KIH92556.1 metal iron transporter [Sporothrix brasiliensis 5110]



List of domain hits

Name	Accession	Description	Interval	E-value
[+] SLC5-6-like_sbd super family	cl00456	Solute carrier families 5 and 6-like; solute binding domain; This superfamily includes the ...	137-580	1.58e-146

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Heme uptake

Molecular Microbiology (2004) **53**(4), 1209–1220   doi:10.1111/j.1365-2958.2004.04199.x

A family of Candida cell surface haem-binding proteins involved in haemin and haemoglobin-iron utilization

Ziva Weissman and Daniel Kornitzer*
Department of Molecular Microbiology, Technion – B. Rappaport Faculty of Medicine, and the Rappaport Institute for Research in the Medical Sciences, Haifa 31096, Israel.

Summary

The ability to acquire iron from host tissues is a major virulence factor of pathogenic microorganisms. Candida albicans is an important fungal pathogen, responsible for an increasing proportion of systemic infections. C. albicans, like many pathogenic bacteria, is able to utilize haemin and haemoglobin as iron sources. However, the molecular basis of this pathway in pathogenic fungi is unknown. Here, we identify a conserved family of plasma membrane-anchored proteins as haem-binding proteins that are involved in haem-iron utilization. We isolated RBT51 as a gene that is sufficient by itself to confer to S. cerevisiae the ability to utilize haemoglobin iron. RBT51 is highly homologous to RBT5, which was previously identified as a gene negatively regulated by the transcriptional suppressor CaTup1. Rbt5 and Rbt51 are mannosylated proteins that carry the conserved CFEM domain.

ardson and Warnock, 1997). The ability to cause systemic infection depends on specific virulence factors that enable C. albicans to adhere to epithelial cells, penetrate tissues and cause damage (Hube et al., 1997; Lo et al., 1997; Sanglard et al., 1997; Gale et al., 1998). In addition, like all microbial pathogens, C. albicans needs to be able to extract nutrients from the host environment in order to proliferate. An important limiting nutrient in host tissues is iron: it has long been known that a number of host proteins play key defence roles against microorganisms by withholding free iron, a defence method that has been called 'nutritional immunity' (Kochan, 1973; Weinberg, 1975); conversely, successful pathogens have by necessity evolved mechanisms to acquire iron from the host tissues (Payne, 1993). Different mechanisms for extracting iron from host proteins have been characterized in bacterial pathogens, including utilization of haem and haemoglobin iron (Ratledge and Dover, 2000). The pathways of haemoglobin iron utilization were extensively characterized in Gram-negative bacteria (reviewed in Genco and Dixon, 2001), and a haem-iron acquisition apparatus was recently described in a Gram-positive pathogen (Dryla et al., 2003; Mazmanian et al., 2003).

Most of our information on fungal iron uptake mechanisms was derived from studied in the related, but non-

The Mannoprotein Cig1 Supports Iron Acquisition From Heme and Virulence in the Pathogenic Fungus *Cryptococcus neoformans*

Brigitte Cadieux,[1,2] Tianshun Lian,[1,a] Guanggan Hu,[1] Joyce Wang,[1,a] Carmelo Biondo,[3] Giuseppe Teti,[3] Victor Liu,[1] Michael E. P. Murphy,[2] A. Louise Creagh,[1] and James W. Kronstad[1,2]
[1]Michael Smith Laboratories and [2]Department of Microbiology and Immunology, The University of British Columbia, Vancouver, Canada; and [3]Department of Pathology and Experimental Microbiology, University of Messina, Italy

No *ctr5*, *ctr51* or *cig1* homologs were found

Conclusions

- Strategies for iron acquisition by *S. brasiliensis* and *S. schenckii* are similar;
- Both species produce siderophores, high and low affinity iron transporters, and reductases;
- Heme utilization by *Sporothrix* spp. remains to be explored.

Perspectives

- Studies on iron-related gene expression;
- Exploration of heme utilization by *Sporothrix*;
- Characterization of iron metabolism in other *Sporothrix* species.

Acknowledgements

- Fundação Oswaldo Cruz
  - Dr. Rosely Maria Zancopé-Oliveira
  - Dr. Manoel Marques Evangelista de Oliveira
  - Luã Cardoso de Oliveira, Msc
- Universidade Federal de Goiás
  - Dr. Célia Maria de Almeida Soares
  - Dr. Alexandre Melo Bailão
  - Dr. Mirelle Garcia Silva Bailão
  - Dr. Lilian Cristiane Baeza