SCF Ubiquitin Ligase F-box Protein Fbx15 Controls Nuclear Co-repressor Localization, Stress Response and Virulence of the Human Pathogen *Aspergillus fumigatus*

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Abstract

F-box proteins share the F-box domain to connect substrates of E3 SCF ubiquitin RING ligases through the adaptor Skp1/A to Cul1/A scaffolds. F-box protein Fbx15 is part of the general stress response of the human pathogenic mold *Aspergillus fumigatus*. Oxidative stress induces a transient peak of fbx15 expression, resulting in 3x elevated Fbx15 protein levels. During non-stress conditions Fbx15 is phosphorylated and F-box mediated interaction with SkpA preferentially happens in smaller subpopulations in the cytoplasm. The F-box of Fbx15 is required for an appropriate oxidative stress response, which results in rapid dephosphorylation of Fbx15 and a shift of the cellular interaction with SkpA to the nucleus. Fbx15 binds SsnF/Ssn6 as part of the

RcoA/Tup1-SsnF/Ssn6 co-repressor and is required for its correct nuclear localization. Dephosphorylated Fbx15 prevents SsnF/Ssn6 nuclear localization and results in the derepression of gliotoxin gene expression. fbx15 deletion mutants are unable to infect immunocompromised mice in a model for invasive aspergillosis. Fbx15 has a novel dual molecular function by controlling transcriptional repression and being part of SCF E3 ubiquitin ligases, which is essential for stress response, gliotoxin production and virulence in the opportunistic human pathogen *A. fumigatus*.

Beteiligte Forschungseinheiten

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