# Gliotoxin from *Aspergillus fumigatus* abrogates leukotriene B4 formation through inhibition of leukotriene A4 hydrolase.

König S, Pace S, Pein H, Heinekamp T, Kramer J, Romp E, Straßburger M, Troisi F, Proschak A, Dworschak J, Scherlach K, Rossi A, Sautebin L, Haeggström JZ, Hertweck C, Brakhage AA, Gerstmeier J, Proschak E, Werz O (2019) Gliotoxin from *Aspergillus fumigatus* abrogates leukotriene B4 formation through inhibition of leukotriene A4 hydrolase. *Cell Chem Biol* 26(4), 524-534.



## Abstract

The epidithiodioxopiperazine gliotoxin is a virulence factor of *Aspergillus fumigatus*, the most important airborne fungal pathogen of humans. Gliotoxin suppresses innate immunity in invasive aspergillosis, particularly by compromising neutrophils, but the underlying molecular mechanisms remain elusive. Neutrophils are the first responders among innate immune cells recruited to sites of infection by the chemoattractant leukotriene (LT)B4 that is biosynthesized by 5-lipoxygenase and LTA4 hydrolase (LTA4H). Here, we identified gliotoxin as inhibitor of LTA4H that selectively abrogates LTB4 formation in human leukocytes and in distinct animal models. Gliotoxin failed to

inhibit the formation of other eicosanoids and the aminopeptidase activity of the bifunctional LTA4H. Suppression of LTB4 formation by gliotoxin required the cellular environment and/or reducing conditions, and only the reduced form of gliotoxin inhibited LTA4H activity. Conclusively, gliotoxin suppresses the biosynthesis of the potent neutrophil chemoattractant LTB4 by direct interference with LTA4H thereby impairing neutrophil functions in invasive aspergillosis.

**Involved units**

Biomolecular Chemistry Christian Hertweck Read more

Molecular and Applied Microbiology Axel Brakhage Read more

Transfer Group Anti-infectives Axel Brakhage Read more

**Leibniz-HKI-Authors**

**Axel A. Brakhage**

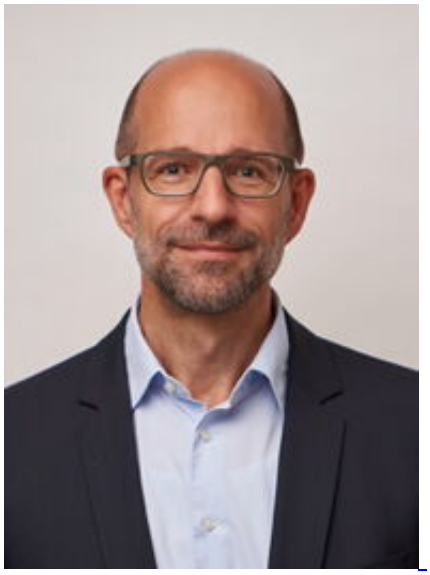
Details

**Jan Dworschak**

Details

**Thorsten Heinekamp**

Details



**Christian Hertweck**

Details

**Kirstin Scherlach**

Details

**Maria Straßburger**

Details

## Identifier

**doi:** 10.1016/j.chembiol.2019.01.001

**PMID:** 30745237