Med. Mycol. J.
Vol. 60, 61-63, 2019
ISSN 2185-6486

Review

Resistance in the Environmental Pathogenic Fungus *Aspergillus fumigatus*

Takahito Toyotome[1, 2, 3]

[1] *Department of Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine*
[2] *Diagnostic Center for Animal Health and Food Safety, Obihiro University of Agriculture and Veterinary Medicine*
[3] *Medical Mycology Research Center, Chiba University*

ABSTRACT

Aspergillus fumigatus, an opportunistic pathogenic fungus, is common in the environment. Azole-resistant strains of *A. fumigatus* have recently been discovered in the environment. Acquisition of azole resistance has been considered to occur through unexpected selection due to fungicide use in agriculture. This review discusses the relationships of humans with *A. fumigatus* in the environment and the importance of anthropogenic activities in the spread of *A. fumigatus* worldwide.
Key words : One Health, *Aspergillus fumigatus*, azole, resistance

Introduction

Fungi serve major roles as decomposers and consumers in ecosystem processes[1)]. Both pathogenic and non-pathogenic fungi are important for ecosystem functions. The health of ecosystems— “One Health” —is strongly associated with human and animal health (http://www.oie.int/en/for-the-media/onehealth/), indicating that ecosystem imbalance is harmful for animal and human health. The appearance and spread of resistant microbes in the environment lead to ecosystem imbalance; this occurs through the use of antimicrobial agents that enhance resistance selection. This review discusses the association of the environmental pathogenic fungus *Aspergillus fumigatus* with human and animal health.

Emergence of azole-resistant *A. fumigatus* in the environment

A. fumigatus is commonly found in soil, air, and water. Antifungal agents used in agriculture affect the targeted plant pathogen as well as the environmental fungi. The acquisition of azole resistance in some targeted plant pathogens has been reported[2)]. Moreover, selective pressure has been considered to lead to the emergence of azole-resistant *A. fumigatus* strains in the environment[3-5)]. Such azole-resistant strains harbor unique tandem-repeats in the promoter region of the *cyp51A* gene together with non-synonymous change(s) in the coding region. The repeat is 34-, 46-, or 53-bp long and located approximately 300 bp upstream of the *cyp51A* start codon. The region contains AtrR- and SrbA-binding elements[6-8)], which regulate *cyp51A* expression. In addition to the duplication of the region upregulating *cyp51A* expression, amino acid substitutions contribute to azole resistance, except in the TR_{53}-type strain, which contains no substitution in *cyp51A*.

The most prevalent strain containing the TR_{34}/L98H mutation was traced back to 1998 in Italy[9)]. The second most prevalent strain (TR_{46}/Y121F/T289A) was first isolated in 2008[10)]. Buil et al. reported an increasing prevalence of azole-resistant strains in the Netherlands, although unsteadily after 2011[11)]. Environmental resistant strains have been spreading in the last two decades and have been found in six continents[12)]. There have also been several reports of these strains in Japan[13-16)].

Humans in the environment

There are numerous fungi, including the pathogenic ones, in the environment. *A. fumigatus* is present in the environment, suggesting that the pathogen affects humans and animals living in the ecosystems. Majority of the *A. fumigatus* strains

Address for correspondence: Takahito Toyotome, PhD
Department of Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Nishi 2-11, Inada-cho, Obihiro, Hokkaido 080-8555, Japan
Received: 17, April 2019, Accepted: 8, May 2019
E-mail: tome@obihiro.ac.jp

isolated from patients are susceptible to azoles, reflecting the frequency of susceptible strains in the environment. Following infection with susceptible *A. fumigatus* strains, mutations inducing resistance occasionally occur in a patient during long-term azole treatment[17]; however, the resistant strains rarely spread to the environment from the patients. Azole-resistant strains in the environment emerge naturally and are acquired by azole-naïve humans and animals. In 2016, a TR_{34}/L98H-type *A. fumigatus* strain was detected from the air in Japan[16]. However, in 2017, no azole-resistant *A. fumigatus* strains were isolated from the air collected from the same sites (unpublished data). The environmental frequency and clinical occurrence of azole-resistant *A. fumigatus* are presumed to be low in Japan. Nonetheless, continuous nationwide surveillance of such resistant strains is warranted.

Human activity in the environment

Owing to its ubiquitous presence in the environment, *A. fumigatus* may be transmitted by and spread through humans, animals, and other objects. Short tandem repeat analysis revealed that the TR_{34}/L98H-type *A. fumigatus* strain isolated from Japan was more closely related to overseas isolates than to domestic isolates[14]. Moreover, a TR_{46}/Y121F/T289A-type *A. fumigatus* strain isolated from Tokyo was clustered with Dutch isolates[13]. These results suggest that these strains were introduced from overseas. Dunne et al. have reported that plant bulbs imported from the Netherlands to Ireland were positive for azole-resistant TR_{34}/L98H-type and TR_{46}/Y121F/T289A-type strains, suggesting that those strains were transmitted across the border[18]. Human activity in imbalanced environments containing azole-resistant *A. fumigatus* may promote the spread of azole-resistant strains. In addition, environments imbalanced by the improper use of agricultural fungicides may induce new azole-resistant mutations in *A. fumigatus*. Continuous surveillance is imperative to detect emerging azole-resistant strains.

Fungi serve important functions, such as decomposition, in the ecosystem. It remains unclear, however, how azole-resistant *A. fumigatus* strains emerge. Moreover, ecosystem imbalance may be induced by unexpected selection due to antifungal agents, leading to emergence of resistant strains of *A. fumigatus* as well as other pathogenic fungi. Humans and animals are closely associated with both their local and overseas environments, suggesting that they are affected by the fungi in their environments. Therefore, continuous surveillance is warranted to detect emerging resistant strains.

Acknowledgments

Intramural funding was provided by the Obihiro University of Agriculture and Veterinary Medicine, and a grant under Grant Number JP19fm0208024 was provided by Japan Agency for Medical Research and Development (AMED) to TT. The authors would like to thank Enago (www.enago.jp) for the English language review.

Conflict of interest

No conflict of interest.

This article was presented at the 62nd Annual Meeting of the Japanese Society for Medical Mycology, Tokyo, in 2018.

References

1) Treseder KK, Lennon JT: Fungal traits that drive ecosystem dynamics on land. Microbiol Mol Biol Rev **79**: 243-262, 2015.
2) Horita H: Resistant fungi causing sugar beet and potato diseases in Hokkaido and the countermeasures. Sugar starch Inf **71**: 47-51, 2018. [In Japanese]
3) Chowdhary A, Kathuria S, Xu J, Meis JF: Emergence of azole-resistant *aspergillus fumigatus* strains due to agricultural azole use creates an increasing threat to human health. PLoS Pathog **9**: e1003633, 2013.
4) Verweij PE, Ananda-Rajah M, Andes D, et al: International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. Drug Resist Updat **21**: 30-40, 2015.
5) Toyotome T, Hagiwara D, Takahashi H, Watanabe A, Kamei K: Emerging antifungal drug resistance in *Aspergillus fumigatus* and among other species of *Aspergillus*. Curr Fungal Infect Rep **12**: 105-111, 2018.
6) Hagiwara D, Miura D, Shimizu K, Paul S, Ohba A, Gonoi T, Watanabe A, Kamei K, Shintani T, Moye-Rowley WS, Kawamoto S, Gomi K: A novel Zn_2 -Cys_6 transcription factor AtrR plays a key role in an azole resistance mechanism of *Aspergillus fumigatus* by Co-regulating *cyp51A* and *cdr1B* expressions. PLoS Pathog **13**: 1-31, 2017.
7) Gsaller F, Furukawa T, Carr PD, Rash B, Jöchl C, Bertuzzi M, Bignell EM, Bromley MJ: The mechanistic basis of pH-dependent 5-flucytosine resistance in *Aspergillus fumigatus*. Antimicrob Agents Chemother **62**: doi: 10.1128/AAC.02593-17.
8) Paul S, Stamnes M, Thomas GH, Liu H, Hagiwara D, Gomi K, Filler SG, Moye-Rowley WS: AtrR is an essential determinant of azole resistance in *Aspergillus fumigatus*. MBio **10**: doi: 10.1128/mBio.02563-18.
9) Lazzarini C, Esposto MC, Prigitano A, Cogliati M, De Lorenzis G, Tortorano AM: Azole resistance in *Aspergillus fumigatus* clinical isolates from an italian culture collection. Antimicrob Agents Chemother **60**: 682-685, 2016.
10) Wiederhold NP, Gil VG, Gutierrez F, Lindner JR, Albataineh MT, McCarthy DI, Sanders C, Fan H, Fothergill AW, Sutton DA: First detection of TR34 L98H and TR46 Y121F T289A Cyp51 mutations in *Aspergillus fumigatus* isolates in the United States. J Clin Microbiol **54**: 168-171, 2016.
11) Buil JB, Snelders E, Denardi LB, Melchers WJG, Verweij PE: Trends in azole resistance in *Aspergillus fumigatus*, the Netherlands, 1994–2016. Emerg Infect Dis **25**: 176-178, 2019.

12) Resendiz Sharpe A, Lagrou K, Meis JF, Chowdhary A, Lockhart SR, Verweij PE; ISHAM/ECMM *Aspergillus* Resistance Surveillance working group: Triazole resistance surveillance in *Aspergillus fumigatus*. Med Mycol **56(Suppl 1)**: 83-92, 2018.
13) Hagiwara D, Takahashi H, Fujimoto M, Sugahara M, Misawa Y, Gonoi T, Itoyama S, Watanabe A, Kamei K: Multi-azole resistant *Aspergillus fumigatus* harboring Cyp51A TR_{46} / Y121F/T289A isolated in Japan. J Infect Chemother **22**: 577-579, 2016.
14) Toyotome T, Hagiwara D, Kida H, Ogi T, Watanabe A, Wada T, Komatsu R, Kamei K: First clinical isolation report of azole-resistant *Aspergillus fumigatus* with TR_{34}/L98H-type mutation in Japan. J Infect Chemother **23**: 579-581, 2017.
15) Tsuchido Y, Tanaka M, Nakano S, Yamamoto M, Matsumura Y, Nagao M: Prospective multicenter surveillance of clinically isolated *Aspergillus* species revealed azole-resistant *Aspergillus fumigatus* isolates with TR_{34}/L98H mutation in the Kyoto and Shiga regions of Japan. Med Mycol 2019, doi: 10. 1093/mmy/myz003. [Epub ahead of print]
16) Onishi K, Muhammad Sarumoh B, Hagiwara D, Watanabe A, Kamei K, Toyotome T: Azole-resistant *Aspergillus fumigatus* containing a 34-bp tandem repeat in *cyp51A* promoter is isolated from the environment in Japan. Med Mycol J **58**: E67-E70, 2017.
17) Verweij PE, Kema GH, Zwaan B, Melchers WJ: Triazole fungicides and the selection of resistance to medical triazoles in the opportunistic mould *Aspergillus fumigatus*. Pest Manag Sci **69**: 165-170, 2013.
18) Dunne K, Hagen F, Pomeroy N, Meis JF, Rogers TR: Inter-country transfer of triazole-resistant *Aspergillus fumigatus* on plant bulbs. Clin Infect Dis **65**: 147-149, 2017.