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Tryptophan Fluorescence Quenching in β-Lactam-Interacting Proteins Is Modulated by the Structure of Intermediates and Final Products of the Acylation Reaction

Submitted by Stéphanie Pinot on Thu, 06/06/2019 - 09:50

Titre	Tryptophan Fluorescence Quenching in β-Lactam-Interacting Proteins Is Modulated by the Structure of Intermediates and Final Products of the Acylation Reaction
Type de publication	Article de revue
Auteur	Triboulet, Sébastien [1], Edoo, Zainab [2], Compain, Fabrice [3], Ourghanlian, Clément [4], Dupuis, Adrian [5], Dubée, Vincent [6], Sutterlin, Laetitia [7], Atze, Heiner [8], Ethève-Quelquejeu, Mélanie [9], Hugonnet, Jean-Emmanuel [10], Arthur, Michel [11]
Editeur	American Chemical Society
Type	Article scientifique dans une revue à comité de lecture
Année	2019
Langue	Anglais
Date	6 Mai 2019
Titre de la revue	ACS Infectious Diseases
ISSN	2373-8227
Mots-clés	acylenzyme [12], d-transpeptidase [13], fluorescence quenching [14], l [15], tryptophan fluorescence [16], β-lactamase [17]
Résumé en anglais	In most bacteria, β-lactam antibiotics inhibit the last cross-linking step of peptidoglycan synthesis by acylation of the active-site Ser of d,d-transpeptidases belonging to the penicillin-binding protein (PBP) family. In mycobacteria, cross-linking is mainly ensured by l,d-transpeptidases (LDTs), which are promising targets for the development of β-lactam-based therapies for multidrug-resistant tuberculosis. For this purpose, fluorescence spectroscopy is used to investigate the efficacy of LDT inactivation by β-lactams but the basis for fluorescence quenching during enzyme acylation remains unknown. In contrast to what has been reported for PBPs, we show here using a model l,d-transpeptidase (Ldt) that fluorescence quenching of Trp residues does not depend upon direct hydrophobic interaction between Trp residues and β-lactams. Rather, Trp fluorescence was quenched by the drug covalently bound to the active-site Cys residue of Ldt. Fluorescence quenching was not quantitatively determined by the size of the drug and was not specific of the thioester link connecting the β-lactam carbonyl to the catalytic Cys as quenching was also observed for acylation of the active-site Ser of β-lactamase BlaC from M. tuberculosis. Fluorescence quenching was extensive for reaction intermediates containing an amine anion and for acylenzymes containing an imine stabilized by mesomeric effect, but not for acylenzymes containing a protonated β-lactam nitrogen. Together, these results indicate that the extent of fluorescence quenching is determined by the status of the β-lactam nitrogen. Thus, fluorescence kinetics can provide information not only on the efficacy of enzyme inactivation but also on the structure of the covalent adducts responsible for enzyme inactivation.

URL de la notice	http://okina.univ-angers.fr/publications/ua19731 [18]
DOI	10.1021/acsinfecdis.9b00023 [19]
Lien vers le document	https://pubs.acs.org/doi/10.1021/acsinfecdis.9b00023 [20]
Titre abrégé	ACS Infect Dis
Identifiant (ID) PubMed	31056908 [21]

Liens

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[21] http://www.ncbi.nlm.nih.gov/pubmed/31056908?dopt=Abstract

Publié sur *Okina* (http://okina.univ-angers.fr)