EuroSciCon

6th Edition of International Conference on

Antibiotics, Antimicrobials and Resistance

October 11-12, 2018
Edinburgh, Scotland

Libera Latino et al., J Infec Dis Treat 2018, Volume 4
DOI: 10.21767/2472-1093-C2-005

Biochemical and structural study of colicin M and its orthologues targeting peptidoglycan biosynthesis: Potential use as novel antibiotics

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Colicins are plasmid-encoded bacteriocins produced by some *Escherichia coli* strains in order to kill competitors belonging to the same or related species. All known colicins share a same structural organization in three domains, each of them being devoted to a specific function: translocation through the outer membrane, binding to a specific outer membrane receptor and toxicity, from N to C termini, respectively (Cascalès *et al.,* 2007). Among colicins, colicin M (ColM) is the smallest colicin known to date and the only one known to interfere with peptidoglycan biosynthesis. It targets and cleaves the peptidoglycan lipid II intermediate at the periplasmic face of the inner membrane by exhibiting a phosphodiesterase activity leading to the formation of undecaprenol and 1-pyrophospho-MurNAc-(pentapeptide)-GlcNAc (El Ghachi *et al.,* 2006). These two products cannot be used or recycled for peptidoglycan biosynthesis, leading to cell lysis. During last years, several homologues of ColM produced by various bacteria such as *Pseudomonas* (Barreteau *et al.,* 2009), *Burkholderia* (Ghequire and De Mot, 2015) and *Pectobacterium* (Grinter *et al.,* 2012, 2014) were identified and characterized. These ColM-like proteins exhibit the same mode of action as ColM and displayed cytotoxic activity towards a limited number of bacterial species. Accordingly, no crossed cytotoxic activity has been demonstrated (Barreteau *et al.,* 2009; Chérier *et al.,* 2016), presumably due to the high specificity of reception and translocation machineries. Thus, reaching the lipid II target is clearly the crucial and limiting step to be considered in a perspective of exploitation of these colicin family members as tomorrow's antibiotics. We recently showed that the pectocin M1 (PcaM1, produced by *P. carotovorum*) and some of its variants were able to kill *E. coli* cells once addressed to the periplasm of this species using appropriate pASK vectors (Chérier *et al.,* 2016). In these conditions, PcaM1 and its isolated catalytic domain were effectively able to catalyze the degradation of lipid II, leading to the arrest of peptidoglycan biosynthesis and cell lysis. To the best of our knowledge, this was the first example of a ColM-like protein capable of killing another bacterial species, without any treatment affecting cell wall integrity. This result and the fact that lipid II is an essential and specific component through the whole bacterial world make of ColM and its orthologues very interesting agents to be exploited as new antibacterial agents. We thus propose the creation of a range of chimera colicins by an engineering approach, in order to get potent antibacterial molecules able to fight, either specifically or not, against various pathogenic bacterial species. Our first goal consists in getting chimera proteins with a narrow-spectrum antimicrobial activity. Our presentation will deal with our preliminary and encouraging results.

Biography

Libera Latino has completed her Ph.D. in Microbiology at the Université Paris-Saclay (Orsay, France). She is presently working as postdoc at I2BC (Orsay, France) and has published 8 papers in reputed journals.

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