Journal of
Biomolecular Research & Therapeutics

Zhang, J Biomol Res Ther 2014, 3:3
DOI: 10.4172/2167-7956.1000e133

Editorial open access

Bacterial Persister, a Formidable Challenge in Therapeutics

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Received date: Apr 16, 2014; **Accepted date:** Apr 18, 2014; **Published date:** Apr 21, 2014

Editorial

Antibiotics are effective compounds in combating bacterial infections. However, with the widespread usage of antibiotics, two severe challenges were emerged to public health: bacterial drug resistance and tolerance. The formation of persisters often results in chronic and recurrent infections leading to more suffering and burden for patients. In comparison with studies of bacterial drug resistance, the nature of persisters and the mechanisms of their drug tolerance have remained more elusive.

In 1944, bacterial persistence was described for the first time that penicillin failed to cure *Staphylococcus* infections completely, which was just 4 years later than the first report of drug resistant bacteria [1]. Persisters, a distinct subpopulation of bacteria from genetically resistant mutants, can survive at the lethal concentration of a drug, but their genome and the susceptibility of antibiotic are identical to the rest of bacterial population [2]. Persistence is a universal phenomenon, which not only occurs in bacteria such as *Mycobacterium tuberculosis, Escherichia coli and Pseudomonas aeruginosa*, but also in parasites [3], fungi [4], and even tumor cells [5]. It was suggested that bacterial persistence is a phenotype variant to be slowly dividing or non-dividing state with the ability to tolerate lethal effects of antibiotics. Thus dormancy with less metabolic activity was supposed to be very important to persisters [6]. However, persisters in fact are more complicated and diverse than we previously assumed because dormancy is not sufficient for bacterial persistence. Orman and Brynildsen indicated that *E.coli* MG1655 persisters have heterogeneous metabolic activity and the bacterial persistence depends more on replication status rather than on metabolic activity by using fluorescence-activiated cell sorting [7]. Furthermore, *Mycobacterium smegmatis* persisters are able to keep a balance of cell division and death with isoniazid, and the growth rates of persister and non-presister cells are almost identical prior to isoniazid addition [8].

Considering the crisis of complexity of bacterial persistence, characterization of the mechanisms in the formation of bacterial persistence is becoming ever more and more urgent. In general, bacterial persistence is a stringent response induced spontaneously or environmentally which is controlled by (p)ppGpp to promote bacterial survival [9,10]. Toxin-antitoxin systems which encode cellular poison and antidote are prominent in the persister formation [9]. In *E. coli*, overexpression of HipA toxin can inhibit protein synthesis, which leads to arrest cell division and synergistically tolerate β-lactam and fluoroquinolone antibiotics [11]. When *hip*A7 was mutated, the number of persisters increased 10-10,000 folds compared with wild type E. coli under ampicillin treatment, while deletion of the hipBA module caused a sharp decrease in the formation of persisters in both stationary and biofilm populations [12,13]. Deletion of *rel*E and *spo*T in *Pseudomonas aeruginosa*, wild type *E. coli* and even *hip*A mutant caused a drastically reduction of persisters [13,14]. There are several environmental stresses contributing to the formation of bacterial persisters including nutrient starvation, oxidative stress, DNA damage, intracellular stress and quorum sensing [2]. Moreover, studies so far showed that several signaling systems were also involved in this persister formation. For instance, indole signaling induces persister formation in *E. coli* by activating oxidative stress and phage shock pathways to protect a sub-population against antibiotic treatment [15].

In conclusion, more and more effort and money have been paid for this formidable challenge, but the relative mechanisms are still not fully understood and needs to be explored in depth. Consequently, improved strategies should be developed such as new tools, innovative methods and in vivo models to eradicate persisters. And a more important thing, new antibiotics shall not be designed only for actively growing bacteria, but also persisters.

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