4 Obg and Membrane Depolarization Are Part of a Microbial Bet-Hedging Strategy that Leads to Antibiotic Tolerance.

Verstraeten N, Knapen WJ, Kint CI, Liebens V, Van den Bergh B, Dewachter L, Michiels JE, Fu Q, David CC, Fierro AC, Marchal K, Beirlant J, Versées W, Hofkens J, Jansen M, Fauvart M, Michiels J
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Recommendations:

Very Good 07 Aug 2015

Martin Marinus
F1000 Microbiology
University of Massachusetts Medical School, Worcester, MA, USA.

INTERESTING HYPOTHESIS | NEW FINDING | NOVEL DRUG TARGET

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In this paper, the hypothesis that a conserved GTPase, Obg, is involved in persistence leading to antibiotic resistance is proposed. The evidence tying Obg to expression of a toxin-antitoxin module and the subsequent membrane depolarization, is strong. The central action of Obg on cell metabolism ensures shutdown of cell division, a hallmark of persistence.

Disclosures
None declared

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Very Good 22 Dec 2015

Wolfgang Peti
F1000 Structural Biology
Brown University, Providence, RI, USA.

Rebecca Page
F1000 Structural Biology
Brown University, Providence, RI, USA.

NEW FINDING | NOVEL DRUG TARGET

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In this paper, the authors show that a conserved GTPase, Obg, plays a critical role in the development of antibiotic tolerance in both Escherichia coli and Pseudomonas aeruginosa. The authors show that this function of Obg is not related to its role in GTP metabolism or ribosome association. Rather, its role in persistence is dependent on the bacterial alarmone (p)ppGpp, to which it binds directly, and a single Type 1 toxin/antitoxin system hokB/sokB.

The authors show that the ability of Obg to induce persistence is due to the production of the HokB membrane-associated peptide, which binds the membrane and causes a loss of membrane potential. However, what is interesting about this system is that rather than killing the cell (which occurs with strong, robust HokB overexpression) the HokB expression level induced by Obg results only in the induction of persistence. The authors then show that this effect of Obg overexpression can be restored by expressing proteorhodopsin, which generates its own membrane potential and counteracts the effect of HokB.

This work is an advance in the field because it provides a clear role for Type 1 toxins in persistence, a phenomenon that has largely been correlated with the activities of Type II toxins, and because it reveals that the pathways used by both types of toxins to mediate persistence converge, through their requirement of ppGpp.

Disclosures
None declared

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Abstract:

ABSTRACT

Within bacterial populations, a small fraction of persister cells is transiently capable of surviving exposure to lethal doses of antibiotics. As a bet-hedging strategy, persistence levels are determined both by stochastic induction and by environmental stimuli called responsive diversification. Little is known about the mechanisms that link the low frequency of persisters to environmental signals. Our results support a central role for the conserved GTPase Obg in determining persistence in Escherichia coli in response to nutrient
starvation. Obg-mediated persistence requires the stringent response alarmone (p)ppGpp and proceeds through transcriptional control of the hokB-sokB type I toxin-antitoxin module. In individual cells, increased Obg levels induce HokB expression, which in turn results in a collapse of the membrane potential, leading to dormancy. Obg also controls persistence in Pseudomonas aeruginosa and thus constitutes a conserved regulator of antibiotic tolerance. Combined, our findings signify an important step toward unraveling shared genetic mechanisms underlying persistence.

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Comments: