초청강연-6

Bacterial Stringent Signal Directs Virulence and Survival in *Vibrio cholerae*.

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The stringent response (SR) is characterized as a bacterial defense mechanism in response to various growth-inhibiting stresses. It is activated by accumulation of a small nucleotide regulator, (p)ppGpp, and induces global changes in bacterial transcription and translation. Recent work from our group has shown that (p)ppGpp plays a critical role in virulence and survival in *Vibrio cholerae*. The genes, *relA* and *relV*, are involved in the production of (p)ppGpp, while the *spoT* gene encodes an enzyme that hydrolyzes it in *V. cholerae*. A mutant strain defective in (p)ppGpp production (i.e. *△relA△relV△spoT* mutant) lost the ability to produce cholera toxin (CT) and lost their viability due to uncontrolled production of organic acids, when grown with extra glucose. In contrast, the *△relA△spoT* mutant, a (p)ppGpp overproducer strain, produced enhanced level of CT and exhibited better growth in glucose supplemented media *via* glucose metabolic switch from organic fermentation to acetoin, a neutral fermentation end product, fermentation. These findings indicates that (p)ppGpp, in addition to its well-known role as a SR mediator, positively regulates CT production and maintenance of growth fitness in *V. cholerae*. This implicates SR as a promising drug target, inhibition of which may possibly downregulate *V. cholerae* virulence and survival fitness. Therefore, we screened a chemical library and identified a compound that induces medium acidification (termed iMAC) and thereby loss of wild type *V. cholerae* viability under glucose-rich conditions. Further, we present a potential mechanism by which the compound inhibits (p)ppGpp accumulation. Together, these results indicate that iMAC treatment causes *V. cholerae* cells to produce significantly less (p)ppGpp, an important regulator of the bacterial virulence and survival response, and further suggesting that it has a therapeutic potential to be developed as a novel antibacterial agent against cholera.