Listreia monocytogenes strains lacking multi-drug resistancetransporter (MDR) genes modulate type I interferon response andpromote better adaptive immunity (Ramot)

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Anat Afriat Herskovits, T.A.U Tel Aviv University, Life Sciences, School of Molecular Cell Biology & Biotechnology

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The intracellular bacterial pathogen Listeria monocytogenes activates a robust type I interferon response upon infection. This response is partially dependent on the multidrug resistance (MDR) transporter MdrM and relies on cyclic-di-AMP (c-di-AMP) secretion, yet the functions of MdrM and cyclic-di-AMP that lead to this response are unknown. Here we report that it is not MdrM alone but a cohort of MDR transporters that together contribute to type I interferon induction during infection. In a search for a physiological function of these transporters, we revealed that they play a role in cell wall stress responses.
A mutant with deletion of four transporter genes (mdrMTAC) was found to be sensitive to sublethal concentrations of vancomycin due to an inability to produce and shed peptidoglycan under this stress. Remarkably, c-di-AMP is involved in this phenotype, as overexpression of the c-di-AMP phosphodiesterase (PdeA) resulted in increased susceptibility of the mdrMTAC mutant to vancomycin, whereas overexpression of the c-di-AMP diadenylate cyclase (DacA) reduced susceptibility to this drug. These observations suggest a physiological association between c-di-AMP and the MDR transporters and support the model that MDR transporters mediate c-di-AMP secretion to regulate peptidoglycan synthesis in response to cell wall stress.

Contact for more information:

Ariela Markel ✉, VP Business Development, Healthcare , 02-6586608

Ramot at Tel Aviv University Ltd. P.O. Box 39296, Tel Aviv 61392 ISRAEL
Phone: +972-3-6406608
Fax: +972-3-6406675