The secret weapon that allows Staphylococcus aureus to hijack your cell cycle

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Statement of the Problem: Bacterial cyclomodulins are a growing family of microbial virulence factors that not only alter host cell cycle progression, but that also interfere with host cell activity, thus favoring the hijacking of host cell protective functions for their own benefit. *Staphylococcus aureus* (*S. aureus*), a highly versatile Gram-positive pathogen can cause life-threatening infections. The implication of *S. aureus* in the alteration of the eukaryotic cell cycle and the biological significance of such an alteration has not been fully investigated.

Aim: The purpose of the study is to explore the mechanism and to identify staphylococcal compounds that caused host cell cycle arrest and to evaluate the benefit provided by cyclomodulins to bacteria.

Methodology & Theoretical Orientation: Flow Cytometry analysis, size exclusion chromatography, mass spectroscopy analysis, Western blotting and immunofluorescence methods were used to identify staphylococcal cyclomodulins and characterize the mechanism.

Findings: We demonstrated that *S. aureus*-induced G2/M transition delay was associated with the accumulation of inactive cyclin-dependent kinase Cdk1, a key inducer of mitosis entry, and with the accumulation of unphosphorylated histone H3. Phenol-soluble modulin a (PSMa) peptides were found responsible for this effect. The use of *S. aureus* mutants confirmed the findings. We showed that the G2 phase was preferential for bacterial proliferation and found that PSMa-induced G2/M transition delay correlated with a decrease in the defensins genes expression. We demonstrated that additionally to secreted staphylococcal cyclomodulins the membrane-anchored lipoprotein-like proteins exert cyclomodulin activity.

Conclusion & Significance: Our findings demonstrate that an alteration of the eukaryotic cell cycle enhances an infective efficiency of bacterial pathogens, suggesting that such an alteration may be used by *S. aureus* for propagation within the host. Moreover, the correlation of PSMa-induced G2/M transition delay with a decrease in the defensins genes expression suggests a reduction of antibacterial functions of infected cells.

Biography

Nadejda Berkova has her expertise in host-pathogen interaction. Her research interest focuses on the molecular understanding of immunological pathways and analysis of gene expression in the context of immune deregulation of the organism. She investigates the mechanistic strategies of pathogens to subvert the host defense for their own benefit. Her team identified several staphylococcal cyclomodulins, the family of bacterial effectors that induce eukaryotic cell cycle alterations, and demonstrated the involvement of these bacterial compounds in the alteration of the host immune response. These findings are important for the development of new anti-infective and anti-inflammatory strategies.

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