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Nadejda Berkova

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## **Inflammation, DNA damage and *Staphylococcus aureus* infection**

Berkova Nadia Nadejda, INRA, Agrocampus Ouest, Rennes, France,

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*Staphylococcus aureus* causes serious medical problems in human and animals. This oral presentation will demonstrate a newly identified mechanism used by *S. aureus* for fostering an infection.

We demonstrated that *S. aureus* can compromise host genomic integrity as indicated by bacteria-induced histone H2AX phosphorylation, a marker of DNA double strand breaks (DSBs) in the absence of apoptosis, in human cervix cancer HeLa and osteoblast-like MG-63 cells. This DNA damage is mediated by alpha phenol-soluble modulins (PSM $\alpha_{1-4}$ ), while a specific class of lipoproteins (Lpls), encoded on a pathogenicity island in *S. aureus*, dampens the H2AX phosphorylation thus counteracting the DNA damage. This DNA damage is mediated by reactive oxygen species (ROS), which promotes oxidation of guanine forming 7,8-dihydro-8-oxoguanine (8-oxoG). DNA damage is followed by the induction of DNA repair that involves a canonical DNA damage response (DDR) comprising the triggering of the ATM kinase-signaling pathway.

An examination of *S. aureus* strains, isolated from the same patient during acute initial and recurrent bone and joint infections (BJI), shows that recurrent strains produce lower amounts of Lpls and induce stronger DNA-damage.

DNA damage triggers cellular responses such as transient cell cycle arrest to allow time for DNA repair. Consequently, we investigated the ability of *S. aureus* strains from human and animal origins to affect the host cell cycle in human and animal cells. Flow cytometry analysis revealed a *S. aureus*-induced delay in the G2/M phase transition. The results of Western blot experiments showed that the 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, which was correlated with a reduction of the mitotic cell number.

Using size exclusion chromatography of *S. aureus* (MW2, USA400) supernatant, followed by mass spectroscopy analysis of corresponding peaks, we identified phenol-soluble modulin alpha (PSM $\alpha$ ) peptides as the likely candidates for this effect. Indeed, synthetic PSM $\alpha_1$  and PSM $\alpha_3$  caused a G2/M phase transition delay. The implication of PSM $\alpha$  in cell cycle alteration was confirmed by comparison of *S. aureus* USA300 (LAC wt) with the isogenic mutant LAC $\Delta$ psma, which lacks the *psma* operon encoding PSM $\alpha_1$  to 4; only the supernatant of LAC wt and not that of the mutant alters cell cycle progression. By testing the supernatant of *S.*

*aureus* isolates from patients with enterocolitis, we found that the degree of G2/M phase transition delay correlated with PSM $\alpha$ 1 production.

Analysis of *S. aureus* proliferation in asynchronous, G1- and G2-phase-enriched HeLa cells showed that the G2 phase was preferential for bacterial infective efficiency, suggesting that the G2 phase delay may be used by *S. aureus* for propagation within the host. We show that PSMs secreted by *S. aureus* induce DNA damage and alter the host cell cycle that promotes *S. aureus*-associated infection. Our findings redefine our understanding of mechanisms of *S. aureus*-host interaction and suggest that the balance between the levels of PSM $\alpha$  and Lpl expression impacts the persistence of the infection.