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O0511 The type III secretion system uses the translocon as a pore-forming toxin to manipulate the host epigenome

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Background: Increasing evidence has linked modified histone-dependent chromatin remodelling with bacterial pathogenesis. This was mostly described with obligate or facultative intracellular pathogens and the most commonly reported modifications occurred on histones H3 and H4. *Pseudomonas aeruginosa* is an extracellular Gram-negative bacterium able to cause a large subset of infections including chronic infection in patients with cystic fibrosis. Like many other Gram-negative bacteria, *P. aeruginosa* manipulates eukaryotic host cells using secreted effectors delivered by the type III Secretion System (T3SS) or the type IV Secretion System (T6SS). The T3SS is a bacterial nanomachine that resembles a syringe on the bacterial surface. The T3SS needle inserts translocon proteins (popB-popD) into eukaryotic cell membranes allowing the injection of bacterial effectors (Exo toxins) which are responsible for the pathogenesis.Here we tested whether despite its extracellular lifestyle *P. aeruginosa* would be able to promote epigenetic modifications

Materials/methods: We acquired a large set of data which combines not only in vitro and biochemical data using purified translocon components, but also extensive genetic analysis using T3SS and T6SS mutants, and immunofluorescence microscopy which provided images of the PopB-PopD translocon during infection.

Results: We showed that *Pseudomonas aeruginosa* induces early T3SS-dependent dephosphorylation and deacetylation of histone 3 in eukaryotic cells. These epigenetic modifications are not conventionally triggered by injected effectors; notably, we exclude the role of T3SS-secreted exoenzymes (ExoS, ExoT, ExoY or ExoU) in this process. We demonstrated that the pore formed by the PopB-PopD translocon plugged into the host cell membrane leads to K^+ efflux, resulting in epigenetic modifications, as it has been previously observed with several pore forming toxins. In addition, like cholesterol-dependent pore forming toxins, we also demonstrated that PopB-PopD is responsible for the fragmentation of the mitochondrial network upon infection.

Conclusions: Our observations led us to reconsider the potential role of the T3SS translocon in the host/pathogen relationship and demonstrated that it is not a simple channel inserted into the target cell membrane in order to help funnel subversive T3SS effectors. Our results unveil a novel concept in which the translocon is a “pore forming toxin” and thus a genuine T3SS effector.