**Chlamydia exploit the mammalian tryptophan-depletion defense strategy as a counter-defensive cue to trigger a survival state of persistence**

**TOPICAL OUTLINE**

**Abstract**

**Introduction**

 **Persistence**

 **Up-Trp and Down-Trp sets of proteins**

 **Rationale to explain feasibility of Up-Trp selection as a pathogen strategy**

 **Phylogenetic extension of the Trp-content analysis to the *Chlamydiales* Order**

**Different mechanisms yield a common outcome of Trp depletion in Man and Mouse**

 **The mouse IFN-γ/GTPase/cytotoxin/Trp-depletion mechanism**

 **The human IFN-γ/indoleamine dioxygenase/Trp-depletion mechanism**

 **Opposite adjustments of cytotoxin in *C. muridarum* and *C. trachomatis***

**Crucial features of the Trp-responsive network supporting rapid pathogen proliferation**

 **Permeases**

 **Virulence factors**

 **Key metabolic steps**

**Reductive evolution of Trp biosynthesis in *Chlamydiales***

 **Extreme phylogenetic variation of reductive evolution for *trp* genes**

 **Does *Simkania* retain the ancestral *trp* operon?**

 **Variant linkages of chorismate to menaquinone and aromatic amino acids**

 **The Trp/kynurenine/Trp cycle**

 **Indole utilization**

 ***Coxiella* *burnetii*: Lateral gene transfer (LGT) recipient of the *Simkania* *trp* operon?**

**Which events of Up-Trp and Down-Trp selection preceded divergence of *Chlamydiaceae*?**

 ***Chlamydiales* Up-Trp selection.**

 ***Chlamydiales* Down-Trp selection.**

 ***Chlamydiaceae* Up-Trp selection**.

 ***Chlamydiaceae* Down-Trp selection.**

**The highly expansive distribution of TyrP orthologs and paralogs in *Chlamydiales***

 ***Chlamydiaceae***

 **Distribution of *tyrP* genes in *Chlamydiales***

 **Lysosomal degradation as a source of Trp**

***Chlamydiaceae* are the sole taxon family within *Chlamydiales* to deploy the recently recognized DH6N pathway of menaquinone biosynthesis**

 **Comparison of the classic DH2N pathway with the DH6N pathway**

 **Features of DH6N pathway variation in *Chlamydiaceae***

 **Menaquinone genes located on the lagging strand of replication**

**Dramatic Down-Trp selection of the joined chorismate/menaquinone pathway in *Chlamydiaceae***

**Concluding perspective**

**Acknowledgments**

**References**

**Figure legends**

 **Fig. 1.** **Common and differential steps of the mammalian immune response: comparison of the mouse host (left side) with the human host (right side).**

 **Fig. 2. Key elements in the *C. trachomatis* pathogen of a response network which is tuned to adequate Trp availability from human host cytosol.**

 **Fig. 3. Biochemical pathway for Trp biosynthesis.**

 **Fig. 4. Events of Up-Trp and Down-Trp selection in phylogenetic context.**

 **Fig. 5**. **Multiplicity of the TyrP transporter for Trp in the *Chlamydiales* Order.**

 **Fig. 6.** **Variant menaquinone pathways in nature.**

 **Fig. 7.** **Comparison of the Trp content of the chorismate/menaquinone pathway in *Chlamydia* *trachomatis* (Ctra), its close relative *Protochlamydia* *amoebophila* (Pamo), the classic bacterium *Escherichia* *coli* (Ecol), and *Streptomyces* *coelicolor* (Scoe).**