Role of the transcriptional regulator RegA in establishment of Brucella suis persistence in an original in vitro model

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Résumé

Oxygen deficiency is one of the environmental conditions encountered by Brucella during intramacrophagic replication and chronic infection of the host. At chronic stage of brucellosis, these bacteria can reside in immune structures where anoxic conditions predominate. Our previous studies demonstrated the high metabolic flexibility of Brucella suis with respect to oxygen deprivation. We evidenced the central role of the two-component system RegB/RegA in the coordinated control of oxidative respiration and denitrification respiratory systems, which are crucial for virulence and/or persistence in vivo. More importantly, RegA was found to be essential for B. suis persistence in mice. Recently, we developed an original in vitro model, characterized by progressive oxygen deprivation, which allowed to show that RegA is essential for optimal long-lasting in vitro persistence. To identify RegA-dependent genes and proteins in this model, global transcriptome analysis and whole proteome quantifications were performed by comparison of the wild-type B. suis to a regA mutant strain. These analyses were performed at the time point where anaerobic conditions become established, corresponding to the cessation of wild-type strain multiplication. Genetic validation by quantitative PCR (RT-qPCR) indicated that RegA potentially regulates 12% of the B. suis genes. The down-regulation of genes or proteins involved in cell envelope biogenesis and in cellular division suggests that RegA could be involved in establishment of a non-replicative state. In addition, RegA-dependent repression of an important number of genes involved in energy production may be indicative of a participation of RegA in the slowing-down of central metabolim as it enters into the persistence phase. This was substantiated by the finding that two-thirds of the differentially produced proteins belonging to this functional class were also found repressed, among which isocitrate lyase, the first enzyme of the glyoxylate shunt. Several genes of the virB operon were also found repressed by RegA as was its regulator VjbR. In conclusion, RegA was found to regulate genes that encode proteins of all functional groups. This makes the two-component system RegB/RegA a main regulatory system required for adaptation of B. suis to oxygen depletion, which can contribute to the constraint of bacterial growth, characteristic of chronic infection.

*Intervenant

Mots-Clés: Brucella, oxygen, persistence, two, component system, in vitro model