BRUCELLA BEARS AN ATYPICAL RIBOFLAVIN PATHWAY INVOLVED IN VIRULENCE

F. A.Goldbaum.
Leloir Institute Foundation, Buenos Aires, Argentina

The penultimate step in the biosynthesis of riboflavin (vitamin B2) involves the condensation of 3,4-dihydroxy-2-butanone 4-phosphate with 5-amino-6-ribitylamino-2,4(1H,3H)-pyrimidinedione which is catalyzed by 6,7-dimethyl-8-ribityllumazine synthase (lumazine synthase). Pathogenic *Brucella* species adapted to an intracellular lifestyle comprise two genes (designated ribH1 and ribH2) with similarity to lumazine synthase genes, which are located on different chromosomes. The ribH2 gene (an immunodominant *Brucella* antigen) has been shown earlier to specify a lumazine synthase with an unusual decamer structure. The ribH1 gene is located inside a small riboflavin operon. The RibH1 protein is a homopentamer and appears to be the functional LS, whereas the decameric RibH2 is a paralog gene horizontally trasmited and is a virulence factor presumably acting as oxidative stress response factor. The latter observation prompted us to investigate further on the structural and enzymologic properties of RibH2, in order to find evidences that could give clues about the biological function of this protein. Sequence comparison of lumazine synthases from bacteria, plants and fungi suggests a family of proteins comprising bona fide lumazine synthase, archaeal riboflavin synthase and the RibH2 proteins of *Brucellae* and *Rhizobium* which may have additional functions besides their documented lumazine synthase activity. This analysis shows that the lumazine synthase fold contains structural plasticity, conserving a pyrimidine binding site but adapting for several different functions. Regulation of RibH2 expression by a FMN riboswitch appears to occur during *Brucella* multiplication inside host macrophages. Besides, recent experiments with null mutants of B. abortus in RibH2 show that this protein is a virulence factor, which confers resistance to oxidative stress inside macrophages. We aim to characterize the role of this atypical riboflavin biosynthetic pathway on the pathogenicity of Brucella spp. using a multidisciplinary approach