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Inactivation of the *fim* operon in *Shigella flexneri*: a new pathoadaptative event?

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Shigella flexneri infections remain a significant threat to public health in developing countries. Invasion of the colonic epithelium by *Shigella* induces an acute inflammatory response. Upon analysis of the sequenced genomes of three *S. flexneri* strains (2457T, 301 and 8401), we identified a ~23-kb genomic island adjacent to the *leuX*-tRNA gene (GI-*leuX*) carrying a *fim* locus for type 1 fimbriae. We observed that either *fimD* or *fimI* are interrupted by an IS1 and that *fimB*, encoding the tyrosine recombinase required for the off/on inversion of the *fim* promoter, is inactivated by the same nonsense mutation at codon 161 in the three strains. Other structural *fim* genes encode full-length, potentially functional, proteins. Analysis of GI-*leuX* in 62 *S. flexneri* clinical isolates by tiling PCR and RFLP revealed that these strains have various assortments of IS insertions in *fim* genes and most of them carry the same nonsense mutation in *fimB*. To investigate consequences of fimbriae production on the interaction of bacteria with host cells, we transformed the *S. flexneri* strain M90T with the plasmid pSH2 carrying the entire *E. coli fim* operon. Hemo-agglutination tests and electron microscopy analysis indicated that M90T/pSH2 produced functional fimbriae. As compared to the wild-type strain, this strain displayed a large increase in its abilities to adhere to and invade epithelial cells and was not affected in its ability to disseminate from cell to cell *ex vivo*. However, M90T/pSH2 exhibited a reduced virulence in the rabbit ileal loop model of shigellosis, inducing less damages and a weaker inflammation than the wild-type strain**.** Thus, even though production of fimbriae increased cell invasion *ex vivo*, it reduced the virulence of bacteria *in vivo*. These results suggest that production of fimbriae might be counterselected in the host and that mutations abolishing fimbriae expression represent a pathoadaptative event in *Shigella*.

Keywords: Shigella flexneri, pathoadaptative mutations, type 1 fimbriae