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SUMMARY OF THESIS*

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GENETIC DIVERSITY IN STRAINS OF *Yersinia pestis*

Yersinia pestis, a Gram-negative bacterium of the family Enterobacteriaceae, is a very homogeneous species when studied by phenotypic methods: it shows only one serotype, one phagetype and one biotype, subdivided into three biovars or geographic varieties. The introduction of molecular techniques has contributed to extension of the classical subdivision with the identification of new biovars and more than 16 ribotypes, allowing the tracking of the origin of strains involved in epidemiological events. The objective of the present work was to analyze specific regions of the *Y. pestis* genome susceptible to different mechanisms of mutations. For this, two approaches were used: analysis of the *pgm locus* in three highly virulent human strains (two Brazilian, P. CE 882 and P. Exu 340 and one strain from another South American focus, P. Peru 375) and the study of six VNTRs (variable number of tandem repeat) as possible markers to recognize and to track *Y. pestis* clones circulating in the foci of the northeast of Brazil. Differences in the stability of the *pgm locus* in the strains studied were observed: serial subcultures in Congo red agar plates (CRA) produced alterations in the *pgm locus* of the cultures derived from P. Exu 340 and P. Peru 375, while P. CE 882 was found to be highly stable. All six VNTR *loci* analyzed were amplified by PCR in all the strains. However, diversity in the number of alleles for the *loci* was evident: one allele for VNTR5 and VNTR6 three for VNTR1 and VNTR3, four for VNTR2 and five for VNTR4. *Y. pestis* strains of different geographic regions displayed similar amplification profiles for VNTR1, VNTR5 and VNTR6. The profile for VNTR2, VNTR3 and VNTR4, however, was distinct for some strains. The analysis of the size and the number of repeats for each VNTR allowed the identification of 23 genotypes in the 105 strains analyzed. Some of these genotypes had a wide geographic distribution, while others were specific for one region. To investigate the stability of the VNTRs *in vitro*, three strains were submitted to serial subcultures and the derived cultures were then analyzed. Parental and derived cultures revealed identical profiles for the six loci studied. Samples of *Y. enterocolitica* and *Y. pseudotuberculosis* were included in this work for comparison. Different patterns were found amongst the three species by the analysis of the VNTRs or MLVA (multiple-locus variable-number tandem repeat analysis). The results obtained by the analysis of different regions or *loci* (*pgm* and VNTRs) of the *Y. pestis* genome demonstrated intra-specific genetic diversity in this species, breaking the myth of the homogeneity of the Brazilian *Y. pestis* strains, which will contribute to future in-depth epidemiological, taxonomic and evolutionary studies.

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