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Population structure, genotypes and pathogenic phenotype of *Mycobacterium bovis* in Argentina (and Latin America)

M. Zumárraga ^a, F. Araujo ^b, A. Cataldi ^{a,*}

^a Instituto de Biotecnología, INTA, Argentina

^b Embrapa Gado de Corte, Campo Grande, MS, Brazil

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ABSTRACT

Mycobacterium bovis (*M. bovis*) is the causative agent of bovine tuberculosis, a global disease that in Argentina affects approximately 5% of cattle, particularly dairy cattle. Several genotyping methods that distinguish between different isolates of *M. bovis* have been reported. Among them, the most convenient are spoligotyping (a reverse line probe assay) and genotyping by Variable Number of Tandem Repeat (VNTR). In Argentina, unlike what happens in other countries in the region, there is a highly predominant spoligotype (SB0140), but the reason for this dominance is still unknown. In five countries of Latin America, a total of 244 different spoligotypes were found: 8.4% of isolates had orphan spoligotypes, whereas 91.6% formed clusters. Only 1 spoligotype was common to Argentina, Brazil and Chile. However, there were 10 spoligotypes shared between Argentina and Brazil; 2 between Argentina and Chile; and 1 between Chile and Brazil. In conclusion, despite the diversity of spoligotypes found in the five countries, there are major patterns predominating in Argentina, Brazil and Chile. These clusters may reflect a long-lasting active transmission of bovine tuberculosis.

The other goal of this study was to investigate whether there are *M. bovis* genotypes with differential virulence properties. While this is a topic already elucidated for other pathogenic bacteria, the properties for *M. bovis* are still unknown. First, the virulence of *M. bovis* isolates were tested in a mice model of progressive disease. Balb/c mice infected with the *M. bovis* reference strain AN5 showed a 50% survival after four months of infection, with a moderate number of lung bacillary counts. Two weeks after inoculation, it induced a strong inflammatory response with numerous granulomas and progressive pneumonia. In turn, the strain *M. bovis* 04-303, isolated from a wild boar, was the most lethal, and its most striking feature was sudden pneumonia development with extensive necrosis. Strain 04-302 induced a similar pathology, although to a lesser extent. In contrast, strains 534, V2 (both from cattle) and 02-2B (from humans) were less virulent, permitting higher survival after four months of infection. Thus, as reported with *Mycobacterium tuberculosis* clinical isolates, *M. bovis* also showed virulence variability. This variability can be attributed to the induction of different immune response profiles. The virulence of the most virulent strain was also evaluated in guinea pigs and cattle showing the same results. On the other hand, the genome of this strain was sequenced showing that the genome encodes for 3988 protein and 49 RNA genes. Some particularities of the genome sequence and a deduced proteome will be shown.

* Corresponding author.

E-mail address: cataldi.angeladrian@inta.gob.ar (A. Cataldi).

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A methodology was designed to establish whether a relationship exists between the genotype of *M. bovis* and the degree of pathogenicity it causes in cattle. The essence of this methodology is to establish a correlation between the genotype of *M. bovis*, the degree of progression of tuberculosis and animal age. To this aim, three correlates were used: (1) The genotype was based on the spoligotype; (2) The degree of bovine tuberculosis lesions were quantified with a score based on clinical observations in slaughterhouses, such as the number and location of granulomas, and the histopathologic features; and (3) These data were stratified by the approximated age of the animal, determined by the category (calf, steer, heifer, etc). Thus, the virulence was studied in infected cattle, and not in laboratory animals, through a detailed analysis of the lesions found in the slaughterhouses. The lesions were processed for histopathology and culture. As a control for genetic uniformity, the alleles of BoLA DRB3 were sequenced. Lineages with the highest pathogenicity scores were of low abundance and were found in the south of Cordoba province.

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