GENOME WATCH

Pneu tricks

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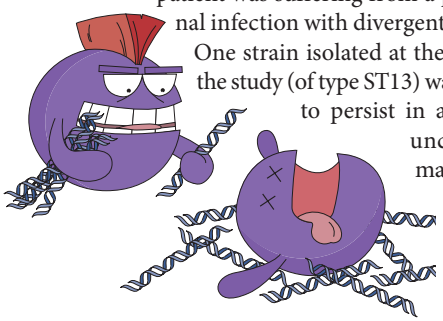
This month's Genome Watch looks at how recombination has provided *Streptococcus pneumoniae* with the adaptability to overcome challenges.

In their classic 1944 experiment, Avery, MacLeod and McCarty used *Streptococcus pneumoniae* (the pneumococcus) to establish DNA as the "transforming principle" (REF. 1). The instructions for capsule structure and virulence were shown to be transferred between strains, revealing the genetic flexibility of this species.

S. pneumoniae is a Gram-positive bacterium that can be found as a nasopharangeal commensal, a respiratory pathogen or a causative agent of invasive diseases such as meningitis. As such, *S. pneumoniae* causes a high disease burden worldwide. There are over 90 serotypes of *S. pneumoniae* as a result of variation in the structure of the polysaccharide capsule; this capsule is important for both immune recognition and virulence through resistance to phagocytosis. Two recent studies have used next-generation sequencing to begin to elucidate the part played by transformation in the interactions between *S. pneumoniae* and its host.

The first study followed one patient with chronic respiratory and middle-ear infections over a period of 7 months[2]. Eight strains of *S. pneumoniae* were isolated during symptomatic episodes, of which six were sequenced. Multilocus sequence typing revealed that these strains belonged to two different sequence types, ST13 and ST2011, indicating that the patient was suffering from a polyclonal infection with divergent strains. One strain isolated at the start of the study (of type ST13) was found to persist in a largely unchanged manner for 6 months, as a subsequent isolate showed no genic differences. However, other sequenced strains, which were isolated concurrently, revealed that large blocks of recombination had occurred between an ST2011 strain as a donor and an ST13 strain as a recipient. Isolates studied at months 3 and 7 showed a progressive accumulation of recombinations, indicative of sequential transfer of DNA. The final recombinant strain displayed at least 14 recombination events, each consisting of 737–56,521 bp and totalling over 156 kb, which represents 7.8% of the genome. Many of these recombination events were clearly identified as originating from one of the sequenced ST2011 strains, whereas an unsampled strain is thought to have donated DNA for several recombination events, indicating that there were further strains involved in the infection that were not isolated. Within the recombinant strains that were sequenced, the capsule biosynthesis locus was one of the loci that had recombined, changing from serotype 14 in the original strain to a serotype that could not be typed owing to the loss of genes involved in capsule biosynthesis. Another locus involved in recombination events included the gene encoding pneumococcal surface protein (*pspA*).



On a larger scale, 240 globally distributed strains from a single lineage of *S. pneumoniae* were sequenced[3]. The PMEN1 lineage, which is typically serotype 23F, was first identified in Barcelona in 1984 and has since been isolated in Africa, Asia and America. Within the PMEN1 lineage, large-scale recombinations are again apparent. The lineage is estimated to have originated in approximately 1970, and since then each strain has acquired recombinant segments totalling, on average, 74,097 bp, with individual recombination events in the various strains varying in size between 3 bp and 72,038 bp. Analysis of the 240 strains revealed that the PMEN1 lineage is likely to have originated in Europe, followed by unrestricted intercontinental transmission. Region-specific clusters of strains were found in South Africa, Vietnam and the United States. Specific loci were identified as having undergone high rates of recombination, including the capsule biosynthesis locus and *pspA*.

Since the introduction in 2000 of a vaccine covering seven serotypes, including serotype 23F, the incidence of serotype 23F strains has decreased, but strains of other serotypes have replaced them. Consistent with this, analysis of the 240 PMEN1 strains revealed the presence of vaccine escape recombinants, with three independent capsule-switching events from serotype 23F to serotype 19A having occurred since vaccine introduction. In addition, seven other independent capsule-switching events can be identified within the lineage. The gain of antibiotic resistance can also be traced, with resistance to fluoroquinolones and rifampicin developing many times through mutations in the antibiotic-target genes. Three elements carrying macrolide resistance cassettes were also found within the PMEN1 lineage, all integrated into Tn*916*, a transposon that was present in the progenitor of PMEN1 and which itself carries *tetM*, conferring tetracycline resistance.

Taken together, these studies reveal how, during both the course of a single infection and the evolution of a lineage, the massive adaptability provided through recombination enables *S. pneumoniae* to address challenges from the immune system, vaccines and antibiotics.

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Competing interests statement
The author declares no competing financial interests.