Molecular epidemiology of tuberculosis

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ABSTRACT

Tuberculosis is a global epidemic, with one third of the world’s population estimated to be infected, around 9 million new active cases per year and close to 2 million deaths per year. Without adequate chemotherapy tuberculosis may be a mortal disease.

A century ago, the estimated tuberculosis incidence in Sweden was higher than in most high incidence countries of today’s sub-Saharan Africa. Today however, the majority of patients with tuberculosis in Sweden are immigrants from countries with a high incidence of tuberculosis. The incidence among the Swedish-born population has continued to decrease while it has increased among the foreign-born. In the West African country Guinea-Bissau, tuberculosis is a common disease and the incidence is believed to be further increased by the epidemic of the human immunodeficiency virus. In countries like Sweden the mortality was dramatically reduced about half a century ago when living conditions improved, public health measures were taken and treatments were made available. These gains are however seriously jeopardized by the now emerging multidrug resistant and extensively drug-resistant tuberculosis.

Different genotypes of Mycobacterium tuberculosis complex predominate in different geographical regions of the world and strain-to-strain variations may have important consequences for instance when it comes to transmissibility. Future diagnostics, drugs and vaccines are affected by these strain variations and it is therefore of great importance to establish the whole spectrum of strains of the M. tuberculosis complex worldwide. Despite the high prevalence of tuberculosis in Africa, relatively little is known about the M. tuberculosis complex genetic diversity in this continent. The studies included in this thesis phylogenetically and epidemiologically characterized M. tuberculosis complex isolates obtained from tuberculosis patients in Sweden and Guinea-Bissau using molecular techniques such as Restriction Fragment Length Polymorphism, spacer oligonucleotide typing and 24-loci Mycobacterial Interspersed Repetitive Units-Variable Numbers of Tandem Repeats. The work was performed with the view to understand species and strain diversity as well as transmission patterns.

It was illustrated that the great majority of tuberculosis patients with drug resistant isolates in Sweden were foreign-born and that their strain lineages to a large extent reflected genotypes common in their country of origin. One large outbreak of isoniazid resistant tuberculosis was identified, up to date (October 2011) involving 117 patients, mainly from the Horn of Africa. This outbreak represents one of the largest outbreaks of tuberculosis ever reported in a low incidence country and was an important warning signal to the Swedish authorities. By whole genome sequencing this outbreak strain showed to be exceptionally stable genetically. It was obvious that molecular epidemiological typing is a powerful tool to monitor and identify chains of transmission which could indicate deficiencies in national tuberculosis control programs. It was also discovered that Beijing lineage strains, which elsewhere in the world have caused large outbreaks, have not been able to spread within Sweden in spite of the proximity to high prevalence countries such as Russia and the Baltic countries. When isolates from patients born in Sweden before 1945 were studied, a highly homogenous bacterial population with a domination of the T, Haarlem and Latin-American-Mediterranean lineages was found. It was concluded that evolutionary recent (PGG2/3) strains restricted to Sweden and its immediate neighbours appeared to have caused the epidemic during the first half of the 20th century, while ancestral (PGG1) strains were usually linked to immigrant populations in today’s Sweden. Guinea-Bissau was revisited and it was established that the country has the highest prevalence of M. africanum recorded in the African continent and that the Guinea-Bissau family of strains demonstrated high phylogeographical specificity for Western Africa.