

The emerging pathogen *Mycobacterium ulcerans*: reductive evolution and clonal complexes

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Abstract

Mycobacterium ulcerans is the causative agent of Buruli ulcer, a necrotizing skin disease found predominantly in sub-Saharan Africa. Comparative genome analyses have shown that *M. ulcerans* has developed from a progenitor of the aquatic environmental mycobacterium *M. marinum*. In contrast to *M. ulcerans*, *M. marinum* only causes self-limiting granulomatous infections in humans.

Acquisition of the virulence plasmid pMUM001, encoding polyketide synthases that produce the macrolide cytotoxin mycolactone, massive gene decay (loss of 1.1 Mb of genomic DNA) and pseudogene formation are hallmarks of the development of *M. ulcerans* into a pathogen that causes chronic infections. Reductive evolution indicates that *M. ulcerans* is adapting to a new niche environment. Gain of the immunosuppressive toxin mycolactone is accompanied by loss of highly immunogenic proteins, suggesting an adaptation to survival in host environments that are screened by immunological defense mechanisms. Comparative genomic analyses indicate that *M. ulcerans* has developed two distinct lineages: (i) the “classical” lineage representing the most pathogenic genotypes – those that are found in Africa and Australia; and (ii) a less virulent “ancestral” lineage comprising strains from China/Japan, South America and Mexico.

While proximity to stagnant or slow flowing water bodies is a risk factor for acquiring Buruli ulcer, the mode of *M. ulcerans* transmission is poorly understood. Due to a striking genetic monomorphism of African *M. ulcerans* populations, conventional genetic typing methods have failed to differentiate isolates coming from the same endemic area. Comparison of the genomes of seven Ghanaian *M. ulcerans* isolates that appeared monomorphic by existing typing methods allowed us to identify a limited number of single nucleotide polymorphisms (SNPs) and to develop a real-time PCR SNP typing method. Genetic fingerprinting of disease isolates demonstrated a focal transmission pattern of the emerging pathogen in a highly endemic river valley of Ghana.

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