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Human and tuberculosis co-evolution: An integrative view

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S U M M A R Y

Tuberculosis (TB) ranks as the second cause of death from an infectious disease worldwide after HIV. Archaeogenetics and evolutionary scenario for the *Mycobacterium tuberculosis* complex (MTBC) are in favor of a long-term interaction between tuberculosis and humans, predating the Neolithic period, contrary to the traditional belief. If tuberculosis evolved as a human pathogen in Africa and has spread outside Africa about more than ten-thousand years ago, its life history traits have been shaped by the immune system. Numerous studies described a variety of human susceptibility factors to TB, suggesting that MTBC strains have evolved different ways to overcome this system. However, the results of these studies reveal some inconsistencies even within populations. The temporally varying history of epidemics and ever-varying genetic diversity of pathogens and strains could easily contribute to blur out signal of selection in our human genome. Palaeomicrobiology gives the opportunity to genotype ancient TB strains circulating in past populations. Accessing ancient human pathogens allows us to a better understanding of infectious agents over a longer time scale and confrontation with the dynamic of modern TB strains. Nevertheless, we have to consider tuberculosis as a multifactorial disorder in which environmental factors interact tightly with human and pathogen genetic.

1. Introduction

In 2011, the estimation of new cases of tuberculosis was 8.7 millions and this number is higher than at any other time in history, with a peak of incident cases in 2004. 1.4 million people died from TB, about two-thirds of whom were HIV-negative individuals [1].

TB remains clearly an infectious disease of poverty tightly associated with overcrowding, under-nutrition (diabetes) and addiction behaviors (alcohol consumption and smoking), together with HIV co-infection (twenty-fold increase). New genetic tools and knowledge about the genome (GWA and whole-genome-sequencing) are now available and offer a revolutionary increase in power to identify variants in genes or genome region involved in susceptibility to infectious agents. It is clear that we are facing a complex puzzle with a potentially large range of powerful factors such as the human genetic background, changes in environmental, socio-economic and cultural factors (urbanization, lifestyle, human health control, globalization of exchanges and migrations). We have to unravel a complex tangle in order to develop an integrative view.

2. Origin and history of tuberculosis

Until a few years ago, the traditional belief was that *Tuberculosis mycobacterium* originated in animals and was transferred to humans during the domestication process in the so-called “fertile crescent”. The first human settlements provided new ecological niches by concentrating humans and by increasing contacts with animals. Comparative genomic and molecular markers analyses suggested a very different scenario, making the human strain, *Mycobacterium tuberculosis*, the most ancient strain [2].

High death rates from TB were observed in Europe from the 17th to 19^{the} centuries (20–30% of all mortality) and in North America during the 18th and 19th centuries. Then it declines until 1993 when the World Health Organization declared tuberculosis to be a ‘global emergency’. Looking for characteristic bone TB lesions (mainly spinal ones) in human (or animal) remains and identifying the ancient strain by molecular analysis are the only ways to confirm this hypothesis. The earliest molecular identification of tuberculosis and *M. tuberculosis* lineage (characterized by the TbD1 deletion) dates back to approximately 7000 BC [3] from a Pre-Pottery Neolithic period site where both animal domestication and agriculture is attested. It supports the hypothesis of an evolution from an ancestral progenitor strain. Unfortunately, no analysis has been

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performed on cattle remains. A large collection of 160 Ancient Egyptian bone samples has been tested for the molecular presence of tuberculosis. They all came from Abydos (Upper Egypt) and Thebes-West, covering the period of 3000-500 BC [4,5]. They used spoligotyping to identify the mycobacterial strains. This typing reveals evidence for ancestral (no deletion of TbD1 but presence of RD9) *M. tuberculosis* strains in pre-and early Egyptian dynasty (3500-2650 BC). They also found possible *Mycobacterium africanum* signatures in the Middle-Kingdom tomb of Thebes-West (2050-1650 BC). Modern strains of tuberculosis were identified in samples from the New Kingdom to Late Period tombs (1500-500 BC) [6]. No *M. africanum* strain has been detected in Medieval or more recent human series [5]. Aymyrlyg in South Siberia (dating from the iron age period in South Siberia), is the only site where *Mycobacterium bovis* was found in archeological remains [7]. There is no doubt of pre-Colombian cases of tuberculosis in North America, Mexico and South America [8]. It seems obvious that going through our history, the successively occurrences of settlement, domestication and more recently urbanization/industrialization and global exchanges have considerably modified the infectious landscape.

3. Human genetic susceptibility to tuberculosis

Variation in TB susceptibility across humans is well established and genetic factors determine, in part, differences in host resistance to infection with *Mycobacterium*. Numerous studies including twin analysis, case-control studies, genome-wide linkage and genome-wide association analysis show that different specific variations seem to be involved in resistance to TB. First, for a better understanding, it is necessary to have an overview of the TB immune response. Both innate and adaptive responses are involved in the defence of the body against tuberculosis. The severity, localization and outcome depend largely on the balance of *M. tuberculosis* and host immune mechanisms.

Cellular uptake of *M. tuberculosis* is performed by five major types of cell membrane-bound receptors: the macrophage mannose receptor (MR or CD206), the complement receptor 3 (CR3 or CD11b/CD18) the dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN or CD209), dectin-1 and Toll-like receptors (TLR, specially TLR1, TLR2, TLR6 and TLR9) on many cell types. An inflammatory response follows, regulated by production of pro-inflammatory cytokines (TNF, Il-1β, Il-6, Il-12, Il-10 and Il 18) and chemokines responsible for recruitment of inflammatory cells to the site of infection (Il-8 or CXCL8, MCP-1 or CCL2, RANTES or CCL5, CXCL10 or IP-10). Some other innate molecules play a key role NOS2 (iNOS) with a bactericidal activity and NRAMP1 (coded by SLC11A1), part of the phagosome.

First, susceptibility to TB in humans seems to involve many loci and types of genes. Second, a large variability in genetic and allelic association is observed when comparing studies between populations. It means that a geographic and/or genetic component occurs. What could be the cause of these discrepancies between the association of immune genes and TB?

We have to take into account the fact that a lot of analysis was performed on patients with clinical TB (pulmonary TB or extra-pulmonary TB). Patients with latent TB or during the primary infection (asymptomatic) are never considered. This is specifically critical because innate genes are at the frontline of the fight against TB pathogens. Different levels of defence are successively or specifically implicated in disease progression and in the clinical manifestations of TB (extra-pulmonary, pulmonary and *Tuberculosis meningitis*). All the data now collected clearly demonstrate that the host's genetic background plays a key role in TB infection.

The challenge is to have a more integrative view, conducting multiloci and multigene studies to define genetic pluri-loci profiles. Previous analyses are really promising [9] concerning the association of different human HLA types and *M. tuberculosis* strain genotype. It could easily explain why single variant associations have replicated inconsistently as the association is detectable only in the presence of specific variants within other genes. We have to consider the gene−gene interactions (epistasis). We cannot exclude some other regulating factors such as microRNA (22 nucleotide short non-coding RNAs) or other epigenetic elements (methylation patterns) which are able to regulate the transcriptional rate [10,11,12].

4. Human-pathogens co-evolution

The collection of 1605 patient isolates, pooling the data of Reed and colleagues [13] and Gagneux and collaborators [14] shows the highly geographical structure of the TB lineages (Figure 1). The association of the 5 main lineages with a particular geographical region is obvious. The East-Asian lineage including the Beijing strain, is largely preponderant in Eastern and Southeast Asia. On the contrary, the European-American/African lineage is clearly the most frequent lineage in Europe, Near- and Middle-East and different African subregions. The Indo-Oceanic lineage is dominant in either Southeast Asia or Indian subcontinent, specially the Philippines, Vietnam and India. Around sixty-eight percent of isolates within the East African/Indian lineage come from the Indian subcontinent (including India, Pakistan and Bangladesh) or, for a small proportion to the East Africa region. Finally, the atypical MTC strains are restricted to West-African populations, strains that have been usually named *M. africanum* because of the RD9 deletion. The trends observed in the global structure of genetic populations are strong arguments for mycobacterial lineages adapted to particular human populations.

Human populations on the earth live in different climatic zones and environments. Species richness in human pathogens is strongly correlated with latitude, tropical areas harboring the higher diversity comparing to more temperate areas [15]. The recurrent exposure to specific pathogen community and epidemics probably acted as selective pressures on human genetic pattern. One can imagine that a long-time period of exposure to TB probably results in a strong positive selection favoring resistance to TB. The first signs of urbanization in the world are described in the fertile crescent. We can make the assumption that this major event was the beginning of a strong selective force in Near-East and European populations according the scenario of Europe colonization. Two studies are very interesting from this point of view. The first one points on the correlation between the duration of urban settlement and the frequency of the SLC11A1 (Nramp1) 1729 + 55del4 (rs17235416) [16]. The second one concerns the regional pattern of three Toll-Like Receptor 2 polymorphisms. The 2029 C/T polymorphism is absent in European and non-European populations with the exception in the Vlax-Romani population. The 1892 C/G is exclusively found in European populations and the last one 2258 G/A is present in Europeans including Vlax-Roma even if it is at a very low frequency [17]. Both of these receptors are involved in the first line of defence against pathogenic microorganisms, the innate immune system: SCL11A1 is one of the major determining factor of natural resistance to intracellular infections and TLR 2 recognizes a large array of pathogen-associated molecular patterns. These findings argue for an occurrence of variants after the split of the populations in the Middle-East. In the presence of selection pressure, different variants in the same gene may have emerged independently. A large number of studies revealed different HLA associations in various ethnic population [18]. Tuberculosis was found to be the only phenotypic manifestation in several children with genetic defects of the IL-12/23-IFNgamma circuit, and