Mycobacterial Diseases
ISSN: 2161-1068

Actor, J Mycobac Dis 2013, 2:2
DOI: 10.4172/2161-1068.1000e122

Editorial Open Access

Tuberculosis as a Persistent Malady

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Keywords: Tuberculosis; Cord factor; Immunopathology; Phthisis

For the past 15 years, our laboratory has been actively engaged in delineating the mechanisms of the mycobacterial glycolipid trehalose 6, 6'-dimycolate (TDM) that initiate development of immunopathology during infection. On occasions that seem all too rare, we take the opportunity to delve into historical perspectives of disease to understand previous views of pathology which form the basis for molecular mechanisms that drive disease development and host responses. *Mycobacterium tuberculosis*, the bacteria responsible for causing tuberculosis (TB), has been a societal scourge for much of recorded human history. Throughout recorded history, consumption has no bias to favor men of historical importance, although certainly men of power were not spared. English Kings (Henry VII, died 1509), French monarchs (Charles IX, 1574; Louis XIII, 1643; Louis XVII, 1795); and American Presidents (James Monroe, 1831; Andrew Jackson, 1845) were afflicted. Similarly, a life of creativity was no shelter from disease. Roman poets (Catullus; 54 BC), romantic composers (Frederic Chopin, 1949), and troubled painters (Edvard Munch, 1944) were just a few among the many creative individuals susceptible to disease. Philosophers (Immanuel Kant, 1804), mathematicians (Niels Abel, 1829), and authors (Henry David Thoreau, 1862; George Orwell, 1950) all succumbed to the acid fast pathogen. Even a life of stardom cannot shield the destructive actions of tuberculosis; Ringo Starr of Beatles fame needed a little help from his physician friends to overcome childhood TB.

Historical documents include descriptive tuberculosis as present in the human population prior to 2400 BCE, with confirming scientific evidence of spinal column pathology detected in Egyptian mummies. Indeed, the term "consumption", appears in Greek literature circa 460 BCE, where Hippocrates identified "phthisis" as the most widespread and fatal disease of the times. In 1650, Sylvius described the tubercle, while many great physicians carefully added observations to support the link between organism and consumption (Laënnec and Schönlein to name a few) prior to Robert Koch's discovery and isolation of the tubercle bacillus.

Certainly reports of Tuberculosis being present in 500,000 year old hominid fossils peak the interest, yet until recently osteoarchaeological DNA analysis has only been accurately able to confirm human bouts of infection from the Middle Ages (11th to the 13th century) [1,2]. This is now changing, as a recent investigation identified organisms present in adult skeletons of Europeans that are 7000 years old [3]! Indeed, this report by Masson, et al., may represent one of the oldest palaeopathological and palaeomicrobiological tuberculosis cases discovered to date. This now opens up the doorway to utilization of novel techniques and tools to prove epidemiological spread of organism between populations, and perhaps even confirm novel hypotheses relative to the concepts of genetic stability of proteins and epitopes within this organism which are necessary for survival and expansion from host to host. Specifically, the confirmation of evolutionary conserved enzymes for lipid generation will be invaluable to identify virulence factors required for organism's persistence and disease development.

With the advent of powerful molecular tools comes the need for new models to mesh with historical observations. It was Koch that first described the importance of lipids in morphology of organism growth in broth culture. Cord factor, as so termed because organisms grew in serpentine cords, was a virulence factor integrally involved in pathogenesis [4]. In fact, cord factor was certainly part of the magical cure put forth by Koch, as a physician's tool to curb consumption [5]; and while the curative effects of the tuberculin product may have been ill-received [6], it did lead to the eventual discovery of BCG as a potent vaccine candidate [7]. Many years later in the 1940's and 1950's, Middlebrook and Dubos, as well as Bloch and Noll, reported that mycobacterial lipids as defined cytochemical moieties were required for persistence and pathogenicity [8-12]. These concepts were advanced in the 1970's by Goren and colleagues [13], and have come to hold a place of morphological significance and importance in the pre-molecular scientific community.

With the advent of biochemical analysis and interpretation of genes and associate regulatory pathways, we have come to a greater appreciation of the contribution that mycobacterial lipids play in the role of immunopathology during disease [14,15]. These new procedures and analyses are invaluable for understanding the molecular events determining immune reactivity that culminates in human disease. And certainly, understanding these molecular concepts are critical for targeted development of vaccines and therapeutics. Unfortunately, there is still a gap in our complete understanding of molecular pathology of this organism, one in which model systems give hope but not cures for the human malady. As Koch wrote in 1890, "Here again is a fresh and conclusive proof of that most important rule for all experimentalists, than an experiment on an animal gives no certain indication of the result of the same experiment upon a human being" [5]. We can all appreciate that there remains much to accomplish in control and prevention of tuberculosis. We certainly continue to examine the role that unique mycobacterial lipids play in induction of pathology. However, every once in a while, it is sufficient to appreciate the older literature as a way to focus on the larger picture, and perhaps even gain insights into the morphological phenomena that we try to understand using novel molecular tools. In this way we can appreciate the past as we move to the future, and towards eventual control of an ancient and persistent malady.

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Received November 23, 2013; **Accepted** November 23, 2013; **Published** December 02, 2013

Citation: Actor JK (2013) Tuberculosis as a Persistent Malady. J Mycobac Dis 3: e122. doi:10.4172/2161-1068.1000e122

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