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Update on the Microbiology and Immunology of Tuberculosis

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Abstract

Mycobacterium tuberculosis (Mtb) infects a quarter of humanity. Worldwide, over 5 million new cases of tuberculosis are estimated to occur annually by the World Health Organization resulting in approximately one million deaths. The resurgence of tuberculosis in the world and in the USA has prompted a renewed effort in control and study of Mtb. The resurgence of tuberculosis is due partly to the over reliance on chemoprophylaxis and decreases in public health resources and control programs. The requirement for prolonged therapy and poor patient compliance have led to the increased incidence of multiple drug resistant Mtb (MDRTB). The additional interaction with the AIDS epidemic has further aggravated the tuberculosis (Tb) epidemic. The resurgence of Tb has prompted renewed effort in the study of Mtb. The use of molecular biology techniques in studies of Mtb and cellular immunology over the last few years have resulted in many new developments.

Cloning of Mtb specific DNA sequences and its application have already facilitated the clinical therapeutics for Tb. The recent introduction of culture method based on detection of radiolabeled metabolites, such as CO2, and the gene probe method for speciation of Mycobacterium have decreased the time for the laboratory to define a person with Tb.

The discovery of insertional sequences for Mtb have resulted in the development of restriction fragment polymorphism (RFLP) for the studies of the epidemiology of Tb. Epidemiologic studies using the RFLP method has defined nosocomial transmission of Mtb and differentiated reactiviation Tb from newly acquired Tb. In recent studies conducted in New York, over 50% of cases of Tb was attributed to newly acquired Tb based on the finding of clonal pattern by RFLP. Furthermore, HIV infection was an important risk factor for newly acquired Tb. Both findings have influenced public health and hospital policies for the control of Tb.

The discovery of mycobacteriaphages and the sequencing of their genomes allowed the first genetic manipulation of Mtb. The genetically altered mycobacteriaphage can shuttle new gene into Mtb or disrupt Mtb genes to create auxotroph and to study virulence determinants. The shuttling of new gene is highlighted by the introduction of the fire-fly luciferase gene into Mtb. The development of the mycobacteriaphage containing the luciferase gene will permit rapid clinical determination of antimicrobial resistant Mtb.

Disruption of Mtb genes has resulted in the first identification of amino acid auxotroph. Understanding of the mechanism may allow targeted drug development. An alterative

approach of cloning Mtb genes into Escherichia coli has identified Mtb virulence determinant important for entry into mammalian cells and intramacrophage survival.

Isoniazid (INH) is the main treatment drug in the multidrug therapy of Tb since its introduction in the 1950s. The recent cloning of catalase gene (KatG) and the INH resistance determinant (InhA) have unveiled the mystery of INH. Cloning and expression of InhA gene revealed for the first time that INH interferes with mycolic synthesis.

Recent developments in immunology and particularly in Leishmaniasis has led to the understanding of T helper (h) types in the pathogenesis of intramacrophage infection. Two Th types have been described in murine system and data in human suggest a similar system. Th types are defined by the secreted cytokines because they are phenotypically indistinguishable. Th-1 cells produce interleukin (IL)-2, interferon (IFN)y. Th-2 cells produce IL-4, IL-5, IL-6, and IL-10. These cytokines feedback to inhibit macrophage activation. Predominance in Th-2 over Th-1 is thought to play an important role in the pathogenesis of several intracellular pathogens. Using mice, an animal which has innate resistance to Mtb infection, an orderly production of first IFN-y followed by IL-4 has been described. This is thought to be important in the self-cure observed for mice infected with virulent Mtb. The role of Th-1 and Th-2 in human tuberculosis is actively investigated in many laboratories. Recently, in vitro studies of host immune response against Mtb have defined that tumor necrosis factor mediates the early control of Mtb by alveolar macrophages. In vitro studies from our laboratory have identified that recombinant human IFN-y augments human macrophage anti Mtb activity. The developments in microbial genetics and immunology permit the first glimmer of hope for control of Tb.

"Studying is like rowing a boat upstream, If you are not going forward, You must be going backward." -- Old Chinese proverb.