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THE INFLUENCE OF THE H2 COMPLEX ON MYCOBACTERIUM AVIUM INFECTION IN MICE

I.A. Linge¹, E.S. Petrova¹, E.V. Kondratieva¹, A.S. Apt^{1,2}¹Central Institute for Tuberculosis, Moscow, Russia; ²Lomonosov Moscow State University, Moscow, Russia

Mycobacterium avium is the opportunistic pathogen in humans, animals and birds and the most common cause of non-tuberculous mycobacterial lung infections worldwide. Analogously to other mycobacterial infections, its antigens are presented predominantly in the context of the Class II MHC molecules resulting in activation of CD4⁺ T cells producing IFN γ , the key cytokine in antimycobacterial response and infection control.

Addressing genetic control of *M. avium*-triggered disease, we compared two congenic strains of mice on the B6 genetic background established in our lab — B6.I-100 (H2-A^bE) and B6.I-139 (H2-A^bE) — that carry different alleles encoding the β -chain of the H2-A gene. After aerosol *M. avium* challenge, B6.I-139 mice died earlier and displayed more severe cachexia compared to B6.I-100 mice. Measurement of the CFU counts in lungs and spleens at weeks 8, 12 and 18 post infection, revealed significant differences in the lung phenotype at the early phase (more CFUs in the lungs of B6.I-100 mice). Assessment of lung pathology demonstrated diffuse inflammation in the lung tissue of B6.I-139 mice at week 8 post infection and granulomata containing foamy macrophages and necrotic zones during the chronic phase. Flow cytometry and immunohistochemical staining revealed higher neutrophil inflammation in the lungs of B6.I-100 mice, accompanied by an increased expression of genes involved in neutrophil attraction. The level of proinflammatory TNF α , but not IL-6 and anti-inflammatory IL-10 and TGF- β , was higher in the lungs of B6.I-100 at an early stage of infection. Importantly, lung CD4⁺ T cells from more resistant B6.I-100 mice were more activated (CD44^{hi}CD62L^{lo} phenotype) and produced significantly more IFN γ in response to mycobacterial antigens during chronic stage of infection. Higher numbers of lung CD4⁺ T cells in B6.I-139 mice in 8 weeks after challenge may reflect an attempt of the host to control infection early after challenge, apparently not successful. Of note, it is not clear whether interstrain differences in disease progression reflect differences in the efficacy of antigen presentation between H2-A^b alleles and subsequent T cell activation, or T cell exhaustion during chronic stage of the immune response. Overall, our data suggest that the allelic differences in the H2-A molecule are involved, albeit moderately, in control to *M. avium* infection.

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MYCOBACTERIUM AVIUM-TRIGGERED DISEASE: HOST GENETICS AND IMMUNITY IN MOUSE MODELS

I. Linge, E. Petrova, K. Majorov, E. Kondratieva, T. Kondratieva, A. Apt

Central Institute for Tuberculosis, Moscow, Russia

Mice of the I/St strain are extremely susceptible to *Mycobacterium tuberculosis* but resistant to *M. avium* infection, whereas B6 mice show a reversed pattern of susceptibility. By directly comparing: (i) characteristics of susceptibility to two infections *in vivo* (ii) architecture of lung granulomata and (iii) expression of genes encoding regulatory factors of neutrophil influx in the lung tissue, we demonstrate that genetic susceptibility of the host de-

termines the pattern of lung pathology. *M. avium*-infected B6 mice and *M. tuberculosis*-infected I/St mice are prone to develop necrotizing granuloma surrounded by hypoxic zones, massive neutrophil influx and B-cell follicles in the lung tissue. These mirror-type lung tissue responses demonstrate that the level of genetic susceptibility of the host to a given mycobacterial species largely determines characteristics of pathology, and emphasize the importance of host genetics in pathogenesis. Segregation genetic analysis and development of novel H2-recombinant congenic strains allowed dissection of genetic control of two infections. Regarding susceptibility to and severity of *M. avium*-triggered disease, involvement of two distinct genes was clearly demonstrated: the *Slc11a1* (former *Nramp1*) gene, acting as a major genetic factor, and the classic Class II MHC gene *H2-Ab*, a minor modifier of susceptibility pattern.

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EVOLUTION AND TRANSMISSION OF MYCOBACTERIUM TUBERCULOSIS RESISTANCE TO FLUOROQUINOLONES

T. Luo

Laboratory of Infection and Immunity, West China Center of Medical Sciences & Forensic Medicine, Sichuan University, Chengdu, China

Fluoroquinolones (FQs) have been widely used for the tuberculosis (TB) treatment for decades and *Mycobacterium tuberculosis* strains resistant to FQs have been reported globally. In the past few years, we had gained some insights into the evolution and transmission of *M. tuberculosis* FQ-resistance. Firstly, we found that FQ-resistance mostly appeared in multi-drug resistant (MDR) *M. tuberculosis* strains. We observed the emergence and transmission of FQ-resistance in clinical clustered (as defined by whole-genome sequencing) MDR cases and we speculated that the general inclusion of FQs in the first-line treatment regimen in western China may contribute to the high resistance rate among MDR cases. By studying the within-host heterogeneity of *M. tuberculosis*, we proved that the evolution of FQ-resistance is associated with the emergence and competition of several resistance related mutations in DNA gyrase genes, a process for selecting highly resistant and low-cost strains. Lastly, we studied the mechanisms of primary ofloxacin-resistant strains to acquire resistance to moxifloxacin (new generation FQ) and we found a secondary mutation in DNA gyrase associated with this process.

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EPIDEMIOLOGY OF EXTRAPULMONARY TUBERCULOSIS IN ALBANIA, 2010–2016

D. Mema¹, P. Kapisyzi¹, S. Tafaj¹, D. Mema², S. Bala¹, H. Hafizi¹¹University Hospital “Shefqet Ndroqi”, Tirana, Albania; ²Center of Primary Health Care No. 2, Tirana, Albania

Extrapulmonary tuberculosis (EPTB) is a therapeutic challenge. Possible reasons include ist under- and overdiagnosis/reporting. Here, we report results of the cross-sectional retrospective review of the epidemiology of EPTB in Albania from 2010 to 2016.

The objectives of the study were to find out epidemiological characteristics of EPTB and to explore risk factors, and challenges in the diagnosis and management of EPTB in Albania.