R. A. de Paus

Congress report

Tuberculosis: Immunology, Cell Biology and Novel Vaccination Strategies.
15–20 January 2011 - Vancouver, Canada.

Roel de Paus, department of infectious diseases, LUMC, Leiden, The Netherlands.

This Keystone meeting focused on the immune responses, underlying pathology of, and protection against tuberculosis (TB). A better understanding of the host defense is needed to provide novel intervention strategies.

Antoni Fauci started with a keynote lecture. He pointed out challenges and opportunities to fight TB. TB is still a worldwide problem, with 14 million people infected and 1.3 million deaths in 2009. Over the past 30 years no new TB drugs have come to the market. Besides that, better diagnostics and vaccines are needed. Until now TB pathogenesis and latency is poorly understood. Because of the rising numbers of HIV-TB co-infections and a rise in the occurrence of multi-drug resistance TB, more and better TB control is needed. Antoni Fauci compared the amount of money spend on HIV and TB research. He stated that more anti HIV drugs were developed in recent years because 45 billion dollars were spent on HIV research and just a fraction of that on TB research. At this meeting some promising research results were presented. I will highlight some here.

Performing a good diagnosis, within a short time, can be a major issue in developing countries. Madhukar Pai gave an outline of the situation in India. For example, poorly informative antibody tests are used despite that there are no international guidelines supporting their use. And the interferon gamma release assays, intended to diagnose latent TB, are being misused for screening active TB. David Alland and colleagues developed a new promising assay. The Cepheid Xpert MTB/RIF assay can be used for easy screenings for the presence of mycobacterium tuberculosis (MTB) in sputum within a few hours. And in the same time information is obtained about resistance to the drug rifampicin. The assay can be performed at low costs in developing countries, when used on large scale. The assay will be further developed for screening for other drug resistances.

Mycobacterium species are intracellular pathogens, which can grow in the phagosome and can end up in the phagolysosome. Peter Peters showed that more virulent strains are in addition able to translocate to the cytosol, within two days after infection, and cause significant cell death after a week. The translocation process depends on the ESX-1 secretion system. Proteins of the ESX-1 system can induce a strong T cell response and are involved in host–cell lysis and represent key virulence factors (MTB may benefit from a strong T-cell response). A problem in vaccination strategies could be that the current live-attenuated BCG vaccine misses this secretion system and is relatively poor in presenting peptides in MHC class I. Currently vaccination strategies, using BCG transfected with the information for the ESX-1 secretion system, are developed and tested.

It is thought that MTB may profit from a strong T-cell response. However the mechanism needs more study. Some features from the tuberculosis bacteria may emphasize this. There are some regions in the DNA of MTB, carrying strong T-cell epitopes, which are highly conserved according to Joel D.Ernst.

Another remarkable story about the *LTA4H* polymorphism reveals two different mechanisms of pathogenesis. David Tobin studied *LTA4H* zebra fish mutants. They were highly susceptible for MTB infections. Studies, by T.R. Hawn and E.A. Misch, on polymorphisms in the *LTA4H* gene revealed that individuals who are heterozygous are less susceptible for meningeal TB and multibacillary leprosy. Low

LTA4H activity (when homozygous for the less active allele) results in low TNF production, which leads to more intracellular bacterial growth in the early phase of infection. High LTA4H activity (when homozygous for the other allele) results in high TNF production and results in initial control of the outgrowth of MTB, but in later stages there is excessive inflammation, more death of macrophages and more extracellular growth of the bacterium. Thus maybe we should distinguish a hypo- and a hyper-inflammatory state of immune response in the development of TB.

In the proper modulation of immune responses against MTB also neutrophils and B-cells may play a crucial role. Anne O'Gara found a typical interferon-α and interferon-γ transcript signature in neutrophils, which was very specific for TB patients. John Chan told that B-cells can regulate T-cell responses. B cells are found in granulomas in aggregates, with features of germinal centre B-cells in lymphoid tissue. These cells are required for an optimal granulomatous response.

Besides the interesting presentations, the meeting was very interactive, also at the breakfast and lunch table, with lots of opportunities to talk to well known researchers. I learned a lot. Until now I studied the susceptibility to non-tuberculous mycobacteria. The meeting gave me the opportunity to learn more about the current knowledge on the susceptibility to tuberculosis, which I will study in the near future. I would like to thank the NVVI for providing these opportunities by awarding a travel grant.