Primary immunodeficiency leading to mycobacterial disease

Esther van de Vosse

Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands

More than 150 different mycobacterial strains are known, of which only a few are considered pathogens in humans. The most pathogenic strains are the mycobacteria from the Mycobacterium tuberculosis complex which cause the globally spread disease tuberculosis and the Mycobacterium leprae and Mycobacterium leprae strains that cause leprosy. In addition to these well-known mycobacteria, there are many non-tuberculous mycobacteria (NTM) that are present in the environment and that seldom cause severe disease in healthy individuals.

NTM infection can lead to severe disease in individuals with a failing immune system due to a primary or secondary immunodeficiency. Mendelian susceptibility to mycobacterial disease (MSMD) is a rare primary immunodeficiency characterized by a predisposition to severe, sometimes lethal disease caused by otherwise poorly virulent NTM, as well as the vaccine strain Mycobacterium bovis BCG. In these patients the mycobacterial infection is often disseminated to various parts of the body and is difficult to treat. Interestingly, MSMD patients do not, in general, develop pulmonary tuberculosis. MSMD is usually caused by mutations in genes involved in the IL-12/IFN-γ pathway, such as: IL12RB1 which encodes the IL-12Rβ1 chain of the IL-12 and the IL-23 receptor, IL12B which encodes the IL-12p40 subunit of IL-12 and IL-23, IFNGR1 and IFNGR2 which encode the two chains of the IFN-γ receptor, and STAT1 which encodes one of the proteins that signal in response to IFN-γ.

The aim of our research is to identify the immunological and genetic defects in MSMD patients. Hereto the integrity of the IL-12/IFN-γ pathway is analysed in blood and isolated cells from the patients, as well as expression of receptor chains on the membrane of the cells. Mutations are subsequently identified by sequencing the genes involved. The effect of novel mutations that lead to amino acid changes can be analysed in retroviral expression models, as we have done for amongst others IL12RB1, IFNGR1 and IFNGR2.

To facilitate the analysis of variations identified by researchers around the world, databases have been set up that contain all reported MSMD patients and mutations (see for instance: www.lovd.nl/IL12RB1). Thus far, just over 400 patients have been reported worldwide with MSMD and this is probably only the tip of the iceberg. Also, other genes are still expected to be found to cause MSMD; no genes have been reported so far in which mutations specifically lead to susceptibility to tuberculosis.

© 2014 Asian-African Society for Mycobacteriology. Published by Elsevier Ltd. All rights reserved.