Finding therapeutic way to eradicate tuberculosis of the brain

Tuberculosis is one of oldest infectious disease in the world. It is caused by a bacterium called *Mycobacterium tuberculosis,* where it infects primarily the lung. Millions of individuals are infected with *Mycobacterium tuberculosis*. Even though we are all exposed to the bacterium that causes tuberculosis at most of the time, we only seldom develop active tuberculosis. This is because we are created with great immune (defence) system that is evolved and multi-facet with the ability to differentiate between self and non-self. But if an infection caused by tuberculosis is not treated quickly, the bacterium can circulate through the circulatory system of the blood, whereby it can infect other tissues. Bacteria of tuberculosis can travel to other organs including the brain, whereby the bacteria root itself to the brain parenchyma or infect the membrane surrounding the brain and spinal cord. Central nervous system tuberculosis is the most severe form of extra-pulmonary tuberculosis, characterised by the formation of rich foci a brain form of granulomas, and tuberculous meningitis. Granulomas contain mycobacteria by recruitment of immune cells that surround the bacteria.

Cytokine, a small protein secreted by cells, plays an important role in cell signaling, help cell to cell communication and stimulate cells to the site de of infection. It has been reported that cytokines tumour necrosis factor is involved in the recruitment of the immune cells and structure maintenance of granulomas. Tumour necrosis factor is a multifunctional proinflammatory cytokine which play a critical role in the initial and long-term host immune protection against *Mycobacterium tuberculosis* (*M. tuberculosis*) infection. This cytokine is synthesised by several cell types of hematopoetic origin, such as microglia/macrophages, neutrophils, dendritic cells and lymphocytes, and non-hematopoetic origin such as astrocytes and neurons. During central nervous system tuberculosis, excess of tumour necrosis factor has been implicated in persisting hyperinflammation, however, deficiency of tumour necrosis factor lead to uncontrolled bacterial growth; both phenomena causing necrotic lysis. Thus, a need exists to investigate the contribution of tumour necrosis factor by specific cell types in the control of cerebral *M. tuberculosis* infection and its protective immune response. Investigating the role of tumour necrosis factor derived from neurons in host immunity against *M. tuberculosis;* using an experimental murine model with cell type-specific gene targeting; we found that mice that is lacking a cytokine tumour necrosis factor in neurons ($NsTNF^{-/-}$) are not susceptible to *M. tuberculosis* infection with a phenotype similar to wild type mice*;* while those that completely lack cytokine tumour necrosis factor ($TNF^{-/-}$) mice died by 21 days post-infection. Thus, it seems that the resistance observed in $NsTNF^{-/-}$ mice may be caused by the compensation of TNF from other cellular sources.

Our data suggest that cytokine TNF produced by neurons have a very limited role in protective cerebral immune responses and once again we have demonstrated that TNF is required during central nervous system. Despite advances in tuberculosis care, long treatment period remains a major cause of patients not adhering or completing their course of treatment, which puts them at

risk of developing antibiotic resistance, that may in future lead to the end of antibiotic era. With the antibiotic resistance observed during tuberculosis treatment, therefore the immunomodulatory therapy is urgently needed for better control of infections to not proceed to disease state, or/and in the prevention of occurring secondary infections.

Publication

TNF-dependent regulation and activation of innate immune cells are essential for host protection against cerebral tuberculosis.
Francisco NM, Hsu NJ, Keeton R, Randall P, Sebesho B, Allie N, Govender D, Quesniaux V, Ryffel B, Kellaway L, Jacobs M
J Neuroinflammation. 2015 Jun 26