IDA Highlight: TB is a complex disease

90% of people exposed to *Mycobacterium tuberculosis* (M.tb) clear infection or contain the infection (termed as latency). In some countries, predominantly those with very low incidence of TB, preventative TB therapy is given to individuals with latent M.tb infection. However, in South Africa TB preventative therapy is only given to HIV infected individuals and children under 5 years whom are exposed to (living with) a TB patient. M.tb is inhaled in an aerosol droplet (approximately 4um), these droplets are not captured by cilia and mucus, and make their way deep into the lung where they are phagocytosed by Alveolar Macrophages (AMs). These macrophages present antigens to T cells at the lymph nodes, where 14 days later the adaptive immunity controls infection. It is in these 14 days that M.tb replicates and establishes an infection. At this years Infectious Diseases in Africa symposium Thoma Scriba and Henry Mwanadumba presented their research that aims at understanding different aspects of the complexities of TB disease.

Thomas Scriba (University of Cape Town), presented some of his research that aimed at determine the kinetics that underlie progression from M.tb infection to TB disease. His research group enrolled adolescents (12-18 year olds) that were M.tb infected (determined by QuantiFERON assay), and followed them up for two years. Upon completion of follow-up, they compared longitudinal responses between individuals whom developed TB and controls (M.tb infected individuals with no sign of TB).

They observed increased transcriptomic levels of STAT1, GBP1, IL-6, MMP-9, ICAM1 and myD88 (among of other genes) in individuals who progressed to TB disease compared with controls. These genes were predominantly linked to interferon signalling and inflammation associated with immune pathology and myeloid cell markers as people progressed to TB diseases. They used some of these genes (and others) to develop a correlates of TB risk gene signature (Zak *et al.,* 2016). Over the years they have modified and improved this gene signature, and are currently testing whether this gene signature is able to identify individuals whom are at higher risk of TB progression and would benefit from TB preventative therapy.

One of Henry Mwandumba's (watch his video) research interests is investigating the reason for the rapid increase in M.tb, followed by a plateau when adaptive immunity is established. Srivastava *et al.*, (2014) and Huang *et al.*, (2018) described the time course and distribution of M.tb in lung cell subsets, they showed that M.tb infection induces a significant accumulation of AMs by two weeks. Based on this research, Henry together with David Russel (Cornell University) is investigating what is happening at the AM level in a mouse model. They showed that AM phagocytose M.tb but the phagosomes do not acidify (pH 4.5) and hydrolysis does not occur properly, shown also in Sturgil *et al.*, (1994). Therefore M.tb resides in non-acidified vacuoles in AMs during pulmonary TB. This result challenges the current M1-M2 macrophage dogma, and there are currently conducting research on whether disease progression is mediated by expanded permissive cells which allow proliferation of M.tb. In Malawi, they developed assays to investigate phagocytic function of macrophages isolated from bronchoalveolar lavage fluid, and the impact of HIV infection at a single cell level. They found that human AM are a heterogeneous population and are infected by HIV in vivo. Small and large AM exist, and HIV preferentially infects small AM, which express higher levels

of PD-1 than large AM. In their HIV studies they found that HIV infection is associated with disruption of the AM environment, as well as the CD4 environment, leading to immune dysregulation. All of which are prerequisites for TB disease. Future studies will include investigation of Host-directed therapies of permissive cells to become controller macrophages.

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