

Severe vs mild COVID-19 immunity and Nicotinamide pathway

The South African Immunology Society (SAIS) in collaboration with Immunopaedia hosted a webinar that featured talks by Prof Clive Gray and Dr Melinda Suchard on “What possible immune responses causes severe COVID-19 in some and recovery in most?” and “Macrophage activation and Nicotinamide pathways in COVID-19”

Prof Clive Gray gave a tour de force overview on what we currently know about COVID-19 immunology. His talk focused on 4 main areas:

- Lessons learnt from SARS-CoV (MERS and other respiratory viral) research (etiological agent for the 2003/4 SARS epidemic). He showed that high viral inoculum (exposure) is associated with hyper inflammation which if left unchecked causes detrimental pathology.
- the balance between inflammation and tolerance (read: [Tissue tolerance in COVID-19](#))
- An overview of multiple studies that hat demonstrates that hyper inflammation (increase in IL-8, TNF, IL-6, CXCL2) and infiltration innate cells (macrophages, monocytes and neutrophils) into the lung tissue results in tissue damage is associated with severe disease. Also read: [Multi-organ damage is a hallmark of severe COVID-19; Are Lung microbial products driving hyper inflammation in severe COVID-19?](#)

The emerging 1: Evidence for pre-existing immunity

- Preexisting T cell immunity existed to H1N1 in the adult population (Greenbaum et al 2009)
- The presence of cross-reactive T cells was found to correlate with less severe disease (Sridhar et al 2013; Wilkinson et al 2012)
- SARS-CoV and MERS-CoV protective cross-reactivity with bat CoVs (Zhao et al 2016)
- Cross-reactive T cell responses against spike or membrane proteins in 28% of unexposed healthy blood donors (Sekine et al 2020)
- Substantial cross-reactive SARS-CoV-2 CD4 and CD8 T cells have been observed (Grifoni et al 2020)
- Long-lasting T cell immunity (17 years) to SARS-CoV nucleoprotein (NP) that cross-reacted with SARS-CoV-2 NP (Le Bert et al 2020)
- SARS-CoV-2-specific T cells in individuals with no history of SARS, COVID-19 or contact with individuals who had SARS and/or COVID-19 (Le Bert et al 2020)

- He provided a summary of recent papers that suggest a role in T cell memory in reduced pathology. Also Read:

- [Is there a role of T cells in immune protection to SARS-CoV-2 infection and COVID-19?](#)
- [Inclusion of non-spike proteins in SARS-CoV-2 vaccines may be important for the induction of protective T cell memory.](#)
- [Do SARS-CoV-2-specific T cells confer long-lived protection?](#)

Melinda Suchard (SAIS President) began her talk with a brief introduction of the role macrophages play in hyperinflammatory syndrome (also known as “cytokine storm”) and the potential role of macrophage activation syndrome in patients with severe COVID-19. She then described the different pathways of macrophage activation (alternative vs classical macrophage activation) and metabolism (oxidative phosphorylation vs Warburg-like (aerobic glycosylation) metabolism). *Why was this important?* She described that upon during infection macrophages switch to a Warburg-like metabolism which results in an increase in TNF, while glycolysis is associated with an increase in anti-inflammatory cytokines like IL-10. Thus highlighting a role of macrophage metabolism in their effector function. For example indoleamine 2,3 dioxygenase (IDO) activity which catalyses nicotinamide is usually associated with alternatively activated macrophages. She then highlighted that COVID-19 risk factors: age, diabetes,

obesity, hypertension & gender are associated with disruption of the Nicotinamide adenine dinucleotide (NAD) metabolism. Based on this researchers hypothesise that “infectious pathogens (including SARS-CoV-2) may cause disruptions in the NAD pathway” and pre-existing disruptions in chronic diseases that also affect NAD metabolism such as the COVID-19 risk factors described above results in diseases severity upon infection. Finally, she ended her talk providing evidence from other viral diseases and sepsis and that support this hypothesis and the potential role of NAD metabolism in understanding pathology of COVID-19 and other viral associated Sepsis.

Summary by Cheleka Mpande