Diagnostics and biomarkers

OC - (8405) - IDENTIFICATION OF AN MTB-SPECIFIC SOLUBLE HOST SIGNATURE FOR RISK OF DEVELOPMENT OF ACTIVE TB IN HIV+ MTB-EXPOSED CONTACTS

Mendy, Joseph (Gambia); Chegou, Novel (South Africa); Mayanja-Kizza, Harriet (Uganda); Stanley, Kim (South Africa); Thiel, Bonnie (United States of America); Ottenhoff, Tom (Netherlands); Kaufmann, Stefan (Germany); Boom, Henry (United States of America); Walzl, Gerhard (South Africa); Sutherland, Jayne (Gambia)

1 - MRC Unit The Gambia at LSHTM; 2 - SUN; 3 - MAK; 4 - CWRU; 5 - LUMC; 6 - MPIIB

Background: With 2 billion people infected with Mycobacterium tuberculosis (Mtb) worldwide, identification of those most at-risk of progressing to active disease would provide a targeted, cost-effective approach for preventative therapy strategies. The GC6-74 project recruited Mtb-exposed HIV-positive (HIV+) contacts from 5 African countries with the aim of identifying molecular and protein signatures for identification of ‘at-risk’ subjects by comparing those who progressed to active disease (progressors) to those who remained asymptomatic (controls).

Methods: For this arm of the project, we analysed longitudinal samples from 12 HIV+ progressors and 28 HIV+ matched controls from Uganda (Makerere University, MAK) and South Africa (Stellenbosch University, SUN). Diluted whole blood was stimulated for 7 days with 7 Mtb-specific antigens plus controls. Supernatant was collected and a 38-plex multiplex assay performed following identification of confirmed progressors and controls.

Results: The median time to progression to active disease was 510 days for SUN and 425 days for MAK participants. Baseline CD4 counts were 163 cells/μl for progressors and 154 cells/μl for controls. Baseline responses showed significantly lower IL-4 production in progressors following ESAT-6/CFP-10 (EC) stimulation (p=0.0309) and significantly higher macrophage-derived chemokine (MDC) following both Rv3019 and TB10.4 stimulation. For the time-point closest to progression, IL-10 production following EC stimulation and IFN-γ production following Rv3019 stimulation were significantly higher in progressors than controls (p=0.0024 and p=0.0028 respectively). A combination of 12 analytes following EC and TB10.4 stimulation gave 84.4% and 91.1% correct classification respectively.

Conclusions: We have defined a soluble signature for detecting likely progression to active TB in HIV+ subjects 1 year prior to progression. Following validation in other cohorts, this could be exploited for development of a field-friendly test for targeted interventional therapy.