23 COMPARATIVE CYTOKINE ANALYSIS ACROSS A SPECTRUM OF GENETICALLY AND/OR CLINICALLY DEFINED AUTO-INFLAMMATORY SYNDROMES

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Background/purpose Auto-inflammatory diseases constitute a group of disorders that manifest systemic inflammation in the absence of infection, auto-antibodies or auto-reactive T cells. A specific genetic mutation is identified in some of them, such as in neonatal onset multisystem inflammatory disease (NOMID) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, while in others such as Chronic Recurrent Multifocal Osteomyelitis (CRMO), and Adult onset Still's Disease (AOSD) a specific cause is yet to be elucidated. The rapid response to targeted cytokine blocking therapies suggests that these disorders are mediated by specific cytokines. Herein, the authors investigate whether each disease is characterised by a specific cytokine signature.

Method Serum samples, on visits when patients had clinically active disease, were collected and assayed by Luminex for the presence of 43 inflammatory cytokines at 9 timepoints. Disease groups (mutation positive and negative NOMID; CANDLE syndrome; CRMO; adult and pediatric Still's disease; rheumatoid arthritis, including juvenile idiopathic arthritis) were compared to normal controls whose assays were run at the same time. Ratios of patient values divided by the average of corresponding set of healthy control values were statistically tested for whether they significantly differed from 1 and also among the various disease groups.

Result A distinct cytokine profile is found in different auto-inflammatory diseases. Specifically, AOSD is characterised by markedly increased levels of Interleukin-18 ($p=0.005$, mean=3.068) and IL-1a ($p=0.032$, mean=1.5687) compared to controls. NOMID mutation positive patients had increased levels of IL-1a ($p=0.00078$, mean=1.7819), IL-6 ($p=0.001$, mean=1.5376) and IL-18 ($p=0.001$, mean=1.4924) compared to controls and NOMID mutation negative patients. IL-18 levels in AOSD patients were actually significantly higher than in patients with mutation positive and negative NOMID. CANDLE patients have highly increased IFN γ inducing protein 10 (IP-10) levels ($p=0.00053$, mean=3.9872) compared to controls and the other autoinflammatory diseases. CRMO patients had low levels of IL-8 ($p=0.005$, mean=0.1697), GM-CSF ($p=0.00684$, mean=0.0969) and MCP-1 ($p=0.002$, mean=0.0687) compared to controls and other diseases. These

differences in cytokine profiles disappeared when patients were on effective therapies.

Conclusion During active disease specific cytokine profiles may allow us to detect dysregulated cytokine pathways that discriminate between clinically different autoinflammatory syndromes. A comprehensive approach of cytokine profiling may be useful to develop a therapeutic plan. Further studies are needed to determine if this approach can be used to monitor therapy and help in the definition of inflammatory disease.