**Objectives**:

The X-linked inhibitor of apoptosis protein (XIAP) and its defect has been well ascribed to susceptibility to Epstein-Barr virus infection in pediatric patients and development of lymphoproliferative syndrome. The multiple functions of the XIAP protein are being progressively uncovered beyond its said primary role in regulation of apoptosis, including its involvement in modulation of inflammation and immunity as well as being a ubiquitin protein ligase which is essential in regulating protein stability and degradation.

The extremes of clinical presentation provides the setting and opportunity to study, dissect and uncover new pathways mediating host defence against fungal pathogens. We worked up a previously well 27 years old Asian male presenting with chronic cough, haemoptysis with right lower lobe consolidation who was investigated and eventually diagnosed as fungal pneumonia with Aspergillus and Sacchromyces.

**Materials & Methods:**

To assess functional immune responsiveness, peripheral blood mononuclear cells (PBMC) were stimulated with lipopolysaccharide and fungal ligands. For whole exome sequencing (WES), libraries were prepared, hybridized and sequenced using Illumina Hiseq 4000 sequencing system and paired-end 151bp reads were generated for analysis. Identified candidate gene variants were amplified, cloned into peGFP-C1 backbone using Gibson cloning. Mutant alleles were introduced by Gibson Assembly via overlapping primers targeting the mutant site, then transfected into HEK293 or A549 cells to assay for expression, functional and infection studies.

**Results**:

The patient had normal white cell differential and lymphocyte subset including CD4 counts. Immunoglobulin levels were normal and he did not possess anti-cytokine autoantibodies. Assessment of the patient’s PBMC response revealed attenuated cytokine response IL6, IL1b, TNFa particularly against fungal ligands. Whole exome sequencing elicited a rare variant of XIAP: c.962C>G on exon 4 of X chromosome in the patient, resulting in alanine to glycine switch at position 321 (p.A321G) with high CADD Phred score of 32 and PolyPhene2 ascribing as probably damaging. Notably this lies adjacent to auto-ubiquination site at position 320.

The patient cells exhibited dimished XIAP expression compared to healthy controls; conversely capase 3 and caspase 9 activities through expression of their cleaved proteins were accentuated in response to zymosan and lipopolysacchride. Conversely there was reduced NFkB signalling in the patient cells. In XIAP A321G cells these immunophenotype were re-capitulated with enhanced caspase and attenuated NFKB2 expression, with effect seemingly more prononuced in zymosan-stimulated cells as compared to LPS-stimulated cells.

The addition use of MG132 proteosome inhibitor was able to reverse attenuated XIAP in patient cells. Using immunoprecipitation, we showed XIAP A321G resulted in increased XIAP ubiquination compared to its wild type.

**Conclusions**:

A novel facet of XIAP’s multi-functional role in immunity is being elicited. Altered ubiquination affecting its baculoviral IAP repeat 3 (BIR3) domain results in apoptosis and NFkB suppression, more pronounced against zymosan. This results in enhanced susceptibility to fungal pathogens.