

P005 IRAK-4 regulates transcriptional and post-transcriptional control of TLR/IL-1R responses by accessory pro-inflammatory signalling in a child with Q293X mutation.

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Innate immunodeficiency has been described in humans with *IRAK-4* mutation, as a consequence of defective TLR/IL-1R signalling. Using primary cells from a child with *IRAK-4* mutation (Q293X), we demonstrate that defective cellular responses are both cell-type specific and ligand specific, implicating differential roles for IRAK-4 in human peripheral blood mononuclear cells and primary dermal fibroblasts, and in LPS, IL-1 β and TNF- α signalling. We demonstrate cytokine response defects at transcriptional and/or post-transcriptional levels, despite functional NF- κ B signalling and intact MyD88-independent signalling, and propose that dysfunctional Complex 1 (IRAK1/TRAF6/TAK1) signalling, as a consequence of IRAK-4-deficiency, generates specific defects in mitogen-activated protein kinase activation that could underpin this patient's innate immunodeficiency.