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### **NF- $\kappa$ B signaling pathways linked to autoinflammation and anti-TNF therapeutic response**

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is a chronic inherited autoinflammatory disorder. Typical features of TRAPS include recurrent fever, myalgia, rashes, and joint and abdominal pains. At the molecular level TRAPS is associated with autosomal dominant mutations in the gene encoding the 55 kDa TNF receptor (TNFRSF1A). In order to better understand the mechanisms of TNFR1 dysfunction we have undertaken a number of experimental strategies to begin to elucidate the basic biology underlying disease penetrance and pathogenesis, using peripheral blood mononuclear cells taken from patients with a number of different TRAPS-associated TNFRSF1A gene mutations. Our results show that whilst TRAPS is associated with activation of the transcription factor, NF- $\kappa$ B, individual mutations result in increased activity of specific NF- $\kappa$ B subunits, with both p65 and c-Rel subunit activity driving inflammatory response. Importantly, we also find that the two subunits trigger secretion of different pro-inflammatory cytokines, indicating that two distinct but complementary pathways generate the inflammatory features of TRAPS. Studies of TRAPS mutations can also help provide important information upon which to base therapeutic intervention strategies, with data from this laboratory indicating a mechanistic link between the anti-inflammatory anti-TNF biologic, infliximab, and pro-inflammatory response in patients with certain TRAPS mutations. Based upon these findings we continue to advise caution when prescribing infliximab as anti-TNF therapy to TRAPS patients.

#### **Biography**

After completing his PhD in Medicine at the University of Liverpool, United Kingdom, Turner moved to the USA to undertake postdoctoral studies at The Scripps Research Institute, Harvard Medical School, and Albert Einstein College of Medicine. He then returned to the UK to take up a faculty appointment at Bart's and The London School of Medicine and Dentistry, before then moving to his current position of Associate Professor at Nottingham Trent University. He has published over 30 papers in reputed biomedicine journals and currently sits on the Editorial Board of *Biochimica Biophysica Acta* – Molecular Cell Research, Bioscience Reports, and Biochemical Society Transactions.

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