Pathway-Centric analysis of rare autoinflammatory diseases (AID) and drug repurposing

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The rare hereditary autoinflammatory periodic syndromes are the result of specific mutations in a range of genes ultimately affecting innate immune response mechanisms, yielding a pro inflammatory state. Despite single genes being causative, the inflammatory consequences are widespread. To better understand the underlying mechanisms associated with TNF receptor-associated Periodic syndrome (TRAPS), as a prototypic model of an AID, we have undertaken extensive examinations of intracellular signalling pathways and cytokines associated with inflammatory responses in such patients, and then applied this roadmap of a perturbed, generally overactive signalling network to seek existing pharmacological drugs which can suppress one or more of the affected pathways, with the goal of repurposing existing drugs for the benefit of TRAPS patients. Several classes of small molecule compound have been identified which show potential benefits, and further classes of small compounds have been derived from in-silico structure and functional comparisons to existing chemical library data.

Biography

Dr Paddy Tighe is Associate Professor of Immunology within the School of Life Sciences, The University of Nottingham. Dr Tighes laboratory studies dysregulated immune function and biomarkers associated with a range of chronic diseases with immune system involvement focusing on the orphan autoinflammatory syndromes, and TNF-receptor-associated periodic syndrome (TRAPS) in particular. We were first to report the ligand-independent signaling processes triggered by intracellular accumulation of mutant TNFR1 in TRAPS and our MRC –funded development of high-throughput, high-content methods for intracellular signaling analysis has provided insight into the underlying mechanisms and potential targets for novel therapeutic agents for TRAPS. Current interests are comprehensive mapping of the TRAPS-associated inflammatory phenotype for improved diagnostics and identification of novel therapeutics and associated research into drug-repurposing for TRAPS treatment.

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