

Comment on: ‘Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors’ by Giannelou et al: mutations in TRNT1 result in a constitutive activation of type I interferon signalling

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Comment on: 'Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors' by Giannelou *et al*: mutations in *TRNT1* result in a constitutive activation of type I interferon signalling

We read with great interest the paper of Giannelou *et al*¹ reporting, for the first time, the efficacy of tumour necrosis factor (TNF) inhibitors in sideroblastic anaemia with immunodeficiency, fevers and developmental delay (SIFD). These authors also demonstrated high levels of interleukin (IL)-6, IL-12p40, IL-18, interferon (IFN)- γ and IFN-induced chemokines (IP-10 and MIG) in two patients. Herein, we wish to highlight that an activation of the type I IFN pathway may also be observed in SIFD.

Patient 1 (P1) was a 12-month-old girl referred because of recurrent attacks of fever from the age of 2 months, with or without documented infections, and failure to thrive. C-reactive protein (CRP) levels were elevated during each episode. Infections consisted of recurrent septicaemias. Aseptic febrile manifestations included vulvitis, parotiditis, adenitis and neutrophilic panniculitis. A chronic microcytic anaemia and low levels of serum IgG, IgA and IgM were noted from 2 months of age. She developed progressive lymphopenia with undetectable levels of B lymphocytes and CD27⁺ B memory cells by age 15 months, so that intravenous immunoglobulin (IVIG) (400 mg/kg/month) was initiated at this time. At last follow-up, aged 6 years, her height and development were normal and she was no longer subject to recurrent infectious episodes. However, she continued to experience three to four febrile attacks, lasting for 1–2 days, each month, associated with elevated CRP levels. Whole-exome sequencing identified compound heterozygous mutations in the *TRNT1* gene (c.1213G>A, p.G405R / c.1057–7C>G) encoding tRNA nucleotidyl transferase.

Patient 2 (P2), a girl born at term to first-cousin parents of African ethnicity, presented with intrauterine growth retardation (IUGR) and severe neonatal anaemia necessitating blood transfusion on the first day of life. During infancy, she required regular blood transfusions because of sideroblastic anaemia, which resolved spontaneously at the age of 4 years. She also demonstrated developmental delay and severe disease flares associated with fever, diarrhoea and dehydration. CRP levels were elevated during these episodes. Mild T CD8⁺ and natural killer lymphopenia, together with a profound B cell defect (B lymphocytes: $0.062 \times 10^9/L$, normal range $0.273–0.86 \times 10^9/L$), were evident at 4 years of age. Sanger sequencing of *TRNT1* identified a homozygous mutation in exon 7 (c.977T>C, p.I326T). The family history was notable for a first female child deceased at 29 weeks of gestation with IUGR, severe anaemia and respiratory and cardiac failure. Autopsy revealed pericardial effusion, cardiomegaly and congestion of the spleen and the liver. No DNA testing was performed.

Using an ultrasensitive digital ELISA combined with a high specificity pan-IFN- α antibody pair,² we observed an increased concentration of IFN- α protein in the serum from P1 (246.44 fg/mL, healthy controls <10 fg/mL) and P2 (108.18 and 38.05 fg/mL, healthy controls <10 fg/mL), comparable to the levels measured in certain monogenic type I interferonopathies.² Consistent with these data, we also recorded an increased expression of IFN stimulated genes (ISGs) in the whole blood of P1 and P2 on three occasions. Furthermore, in an *ex vivo* flow cytometry assay, STAT1 and STAT3 were constitutively phosphorylated in T CD3⁺ lymphocytes and monocytes from the whole blood of P2. Both patients also displayed a negative IFN score on one occasion,

suggesting a fluctuating biological process. A high daily variability of IFN scores has been reported in patients with mutations in the immunoproteasome.³

These observations indicate a constitutive activation of the type I IFN pathway in patients with biallelic mutations in *TRNT1* and thus suggest a possible role of type I IFN in the pathogenesis of SIFD. An increase in serum IFN- α protein, measured by standard ELISA, and an enhanced expression of ISGs have been previously reported in one patient with SIFD.⁴ Mitochondrial (mt) reactive oxygen species (ROS) have recently emerged as critical factors in the regulation of immune signalling pathways. By triggering NLRP3 inflammasome activation,¹ Giannelou *et al* suggest that ROS accumulation observed in cultured *TRNT1*-deficient fibroblasts might explain the associated autoinflammatory manifestations. Indeed, a high production of IL-1 in the supernatant of stimulated monocyte-derived macrophages and in colon biopsy tissue was observed in two patients. Of note, anti-IL1 agents were not tested in these patients, who responded to TNF inhibitors. Mitochondrial ROS impact immunoregulatory functions in plasmacytoid dendritic cells (pDCs), both in the early and late type I IFN response.⁵ Agod *et al* demonstrated that the RIG-I-mediated late phase of type I IFN production is intensified by elevated mtROS levels in pDCs.⁵ On the other hand, toxic ROS levels in mixed-Lineage-Leukemia-5 (MLL5)-deficient mice are critically dependent on type I IFN signalling, which triggers mitochondrial accumulation of full-length Bid.⁶ Thus, it might be hypothesised that a mutual activation of ROS and type I IFN results in type I IFN-mediated autoinflammatory disease. Moreover, NLRP3 recruitment via mitochondrial antiviral-signaling (MAVS)-RIG-I could occur in the mitochondrial outer membrane,⁷ suggesting that the autoinflammation ascribed to NLRP3 in SIFD may be initiated through the activation of RIG-I. RIG-I encodes a helicase, responsible for the recognition of foreign dsRNAs and the subsequent induction of a type I IFN response through MAVS, a facilitator of the activation of the TBK1 kinase and the IRF3 transcription factor after RNA detection. Overall, our data suggest that constitutive activation of the type I IFN pathway could be relevant to the pathophysiology of SIFD, although how aberrant tRNA processing secondary to *TRNT1* dysfunction might mediate enhanced type I IFN production and signalling is unclear at this time.

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