Abstract: ***Die Häufigen unter den Seltenen - was steckt hinter PFAPA bzw. SURF***

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Children with periodic fever syndromes not attributable to infections, rheumatic disorders, malignancies, or known monogenic autoinflammatory conditions fall outside established diagnostic categories and are commonly classified as “syndrome of undifferentiated recurrent fever” (SURF). Many patients show partial or temporary responses to empirical treatments like corticosteroids or colchicine, which underscores the unmet clinical need for new therapeutic strategies. To advance the molecular understanding and identify new therapeutic targets, we created the first large-scale single-cell RNA-seq immune cell atlas for SURF and analysed over 300,000 cells from 29 pediatric patients with SURF and 11 healthy controls. Our findings revealed a distinct cytokine signature and a pro-inflammatory transcriptional subnetwork culminating in elevated NAMPT expression. Modelling intracellular signalling suggests TLR4 activation via NAMPT, indicating a potential autocrine feedback loop. This study provides a key molecular resource for studying SURF that offers new insights into its immunopathology and can be instrumental in guiding future therapies to address the treatment gap.