Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Comprehensive Seminar

Investigating the defective immune phenotype in Syntaxin-11 deficient patients and mice

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Calcium is a universal secondary messenger in virtually all cells. Upon T cell activation, sustained cytosolic calcium is necessary to mount a robust immune response. The endoplasmic reticulum contains a limited amount of calcium, which upon emptying leads to the opening of CRAC (Calcium Release-Activated Calcium) channels and the phenomenon is termed as SOCE (Store Operated Calcium Entry). Several pioneering genome wide screenings identified Orai as the pore forming subunit and STIM as the ER calcium sensor that activates the CRAC channel upon store depletion. However, the exact composition of an active CRAC channel complex remains elusive till date. Ablation in the influx of calcium, due to loss of function mutations in these proteins, leads to altered immune phenotype that manifests as immunodeficiency, hyperinflammation and autoimmunity. We have found Syntaxin-11, a t-SNARE which is highly expressed in immune cells to be crucial for SOCE. Further, mutation in Syntaxin-11 leads to a hyperinflammatory and immunodeficient condition called Familial Hemophagocytic Lymphohistiocytosis-4 (FHLH-4). Patients with FHLH-4 present with persistent fever, hepatomegaly, splenomegaly, low blood cell (RBCs, WBCs & platelets) count and impaired lymphocyte cytotoxicity. We have found that Syntaxin-11 deficiency leads to impaired SOCE, impaired NFAT nuclear translocation and defect in downstream cytokine transcription. This points to a signalling defect which might provide possible mechanisms for FHLH-4 disease progression. My aim is to study mechanisms underlying FHLH-4 disease progression using mouse models and patient samples. We plan to do this by systematically identifying the specific T cell subsets and signalling pathways which are affected by the loss of STX11.

Monday, Dec 2nd 2024

09:30 Hrs (Tea / Coffee 09:15 Hrs)

Auditorium, TIFR-H