segregation in affected and non-affected. Clinical and molecular aspects were also evaluated. Protein modeling and other *in silico* tools were used to identify probable impact of genetic abnormalities on the structure and function of protein.
Result:
We identified a novel homozygous substitution mutation at **"c.379A>T:p.Iso127Val"** in CD40 Ligand (CD40LG) gene in diabetic siblings by WES. This change was found to be segregating in the affected and non-affected individuals by Sanger sequencing. Parents and non-diabetic siblings were found to be heterozygous carriers of the nucleotide change. The c.379A>T is located within evolutionarily conserved locus of human genome. Functional prediction by Gene Ontology term analysis suggested that immune functions of CD40LG are compromised by this genetic change. Further, by protein-modeling analysis we identified that structure of ligand-binding domain of CD40LG protein, with which it interacts with other immune cells, may also be affected. *In silico* analysis revealed significantly reduced spatial inter amino acid distance between the site of genetic change and the ligand binding domain in mutant CD40LG.
Discussion:
Apoptotic elimination of developing auto-reactive T-cells, having the potential to generate an autoimmune response against pancreatic cells, is critical to prevent T1D. This apoptotic removal mechanisms, occurs in thymus and is dependent on highly specific interaction of cell surface molecules as CD40LG on developing T-cells, and the corresponding cell surface molecules on Antigen Presenting Cells (APC). In the diabetic individuals investigated in our study, the mutation in CD40LG gene, caused significant structural damage to its protein, due to which these interactions between mutant CD40LG (present on T-cells) and the corresponding CD40 (present on APC) were probably affected. This loss of interaction between CD40LG bearing T-cells and APC, probably led to escape of auto-reactive T-cells in to immune system, which further generated autoimmune response against the pancreatic tissue, precipitating to T1D among these individuals.
Conclusion
Genetic investigation of cell surface proteins in autoimmune cells and understanding their mechanism for development of autoimmunity offers prospects for the development of new therapeutic strategies in the approach to probable early diagnosis of T1D.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Diagnostic Challenges Associated with the Rising Incidence of Endocrine Toxicity in the Era of Combination Immunotherapy

Anna Galligan, FRACP[1], Amir Iravani, FRACP, FRANZCR[2], Arian Lasocki, FRANZCR[3], Roslyn Wallace, MBBS[3], Alison Weppler, FRACP[3], George Au-Yeung, FRACP[3], Nirupa Sachithanandan, MD, phd[4], Cherie Ying Chiang, MBBS,FRACP,FRCPA[3], John Wentworth, FRACP, PHD[3], Peter Grahame Colman, MBBS,MD[5], Thomas William Kay, MBBS,PHD,MD[1], Balasubramanian Krishnamurthy, MD, DM, FRACP[1], Shahneen Sandhu, FRACP[6].

[1]ST VINCENT'S INST OF MED RSRCH, Fitzroy Vic, Australia, [2]Peter MacCallum Cancer Centre, Melbourne, Australia, [3]Peter MacCallum Cancer Centre, Melbourne, Australia, [4]St Vincents Health, Clayton South, Victoria, Australia, [5]Royal Melbourne Hospital, Parkville VIC, Australia, [6]Peter MacCallum Cancer Centre, Mebourne, Australia.

SUN-127

Background: Immune checkpoint blockade is now established as standard of care in several malignancies. Trials involving combined cytotoxic T lymphocyte associated protein 4 (CTLA4) and programmed cell death protein 1 (PD1) blockade demonstrate improved tumour responses in melanoma but at the cost of severe grade 3-4 immune related adverse events (irAEs) in 55%, and endocrine irAEs in up to 10% [1]. Immune-mediated damage to endocrine glands can be a diagnostic and management challenge. We aimed to review the incidence, biochemical evolution and imaging findings of endocrine toxicity related to combined anti CTLA-4 and anti-PD-1 therapy. Methods: We undertook a retrospective chart review of patients who received combined ipilimumab and nivolumab for metastatic melanoma at a tertiary referral centre between 2016-2019. We recorded onset and duration of abnormal biochemistry in endocrine irAEs, reviewed all available MRI images for pituitary size (mm) and appearance and 18-F FDG PET images for features of hypophysitis, thyroiditis and pancreatitis. Results: 162 patients received combination therapy. At least one irAE was recorded in 135 patients (83%), 100 (62%) required glucocorticoids, and 84 (52%) had an unplanned hospital presentation due to irAEs. Thyroiditis occurred in 50 (30.9%), with median time to onset of 30.9 days (range 1-234 days). 35 cases were identified with routine biochemistry performed every 4-6 weeks. TSH receptor antibody was measured in 13 patients and all were negative. 29 (58%) developed permanent hypothyroidism. Central cortisol deficiency was documented in 31 (19%) with a median time to diagnosis of 67.5 days (range 5-286). 4 cases were diagnosed on routine biochemistry and 14 presented with symptoms prompting investigation. 13 were diagnosed after routine neuroimaging demonstrated a pituitary abnormality, and a further 27 patients without the clinical syndrome had features of hypophysitis on neuroimaging. New onset diabetes occurred in 3 people, in which pancreatic inflammation on imaging was found in 2. A further 3/5 patients with an asymptomatic elevated lipase were found to have abnormal pancreatic imaging. In one patient with no features of endocrine or exocrine failure, there was a significant increase in FDG uptake and a subsequent loss of pancreatic volume. Conclusion: We report real world incidence of endocrine irAEs with combination immunotherapy. Routine biochemistry leads to the detection of some but not all cases. Early recognition and avoidance of unplanned presentations remains a challenge. Opportunistic assessment of endocrine gland appearance on routine imaging studies may provide useful early diagnostic information. Reference: Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. (2015) 1:23-34. 10.1056/NEJMoa1504030

Author/s:
Galligan, A; Iravani, A; Lasocki, A; Wallace, R; Weppler, A; Au-Yeung, G; Sachithanandan, N; Chiang, CY; Wentworth, J; Colman, PG; Kay, TW; Krishnamurthy, B; Sandhu, S

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