


**Thesis Title: Understanding the mechanism of cancer progression in tumor hosts with type I diabetes with reference to the alteration in cancer immune-surveillance: Correction by NLGP**

**Abstract:**

Epidemiological studies suggest that patients with pre-existing type 1 diabetes (T1D) have a decreased risk of developing melanoma, prostate cancer, and breast cancer, although the underlying mechanism remains to be elucidated. In translational modelling, we observed that streptozotocin (STZ) induced T1D mice exhibited restricted melanoma and carcinoma (mammary, lung and colon) growth in association with extended overall survival. Tumor-infiltrating CD8<sup>+</sup> T cells were found to be responsible for tumor growth restriction. Tumor infiltrating CD8<sup>+</sup> T cells but not tumor cells themselves exhibited higher glycolytic and cytotoxic activities in T1D hosts. Such improved anti-tumor T cell function was linked to selective upregulated expression of insulin-like growth factor 1, insulin-like growth factor 1 receptor, and phospho-mTOR in CD8<sup>+</sup> T cells in the TME. T1D patient derived CD8<sup>+</sup> T cells displayed superior activation *in vitro* after tumor antigen stimulation vs. non-diabetic CD8<sup>+</sup> T cells. Activation of T1D patient derived CD8<sup>+</sup> T cells was sensitive to targeted antagonism of IGF1R and mTOR, supporting the operational involvement of the IGF1R-mTOR signaling axis. Our results suggest that selective activation of the intrinsic IGF1R-mTOR signaling axis in CD8<sup>+</sup> T cells represents a preferred endpoint to achieving more effective immunotherapy outcomes and improved cancer patient management. Neem leaf glycoprotein (NLGP) restricts immune dependent murine melanoma, carcinoma and sarcoma tumor growth control. However, therapeutic efficacy of NLGP in tumor hosts with pre-existing type 1 diabetes has not been studied yet. We found NLGP modulates the tumor microenvironment of type 1 diabetic hosts in favor of antitumor immunity. Further study showed NLGP reduces T1D associated hepatic inflammation irrespective of tumor burden. NLGP accelerates intra-tumor CD8<sup>+</sup> T cell oxidative phosphorylation in diabetic hosts, thereby improves glucose metabolism. Further, NLGP dampens glucose uptake by tumor cells in diabetic tumor microenvironment by downregulating glucose transporter 1 (*glut 1*) expression. Overall, NLGP positively influences immune microenvironment and metabolism in tumor bearing hosts with pre-existing type 1 diabetes.

  
(Signature of the candidate)

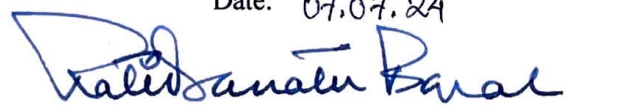
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