Index No. 112/18/Life Sc./26

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 $CD8^+$ T cells were found to be responsible for tumor growth restriction. Tumor infiltrating $CD8^+$ 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 $CD8^+$ T cells in the TME. T1D patient derived $CD8^+$ T cells displayed superior activation *in vitro* after tumor antigen stimulation vs. non-diabetic $CD8^+$ T cells. Activation of T1D patient derived $CD8^+$ 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 $CD8^+$ 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 $CD8^+$ 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.

Anirban Sarkar.
(Signature of the candidate)
Mr. Anirban Sarkar
Date: 07.07.24

Anamika Bose 8/7/24.
Dr. Anamika Bose
Assistant Professor
Department of Pharmaceutical Technology (Biotechnology)
National Institute of Pharmaceutical Education & Research (NIPER), S.A.S. Nagar, Mohali
Punjab 160062

डॉ० अनामिका बोस / Dr. Anamika Bose
सहायक प्रोफेसर / Assistant Professor
फार्मास्यूटिकल टैक्नोलॉजी (बायोटैक्नोजॉजी)
Pharmaceutical Technology (Biotechnology)
राष्ट्रीय औषधीय शिक्षा एवं अनुसंधान संस्थान
National Institute of Pharmaceutical Education and Research
सेक्टर-67, एस. ए. एस. नगर-160 062, पंजाब, भारत
Sector-67, S.A.S. Nagar-160 062, Punjab, INDIA

Rathindranath Baral 8/07/2024
Dr. Rathindranath Baral
Former Head
Department of Immunoregulation and Immunodiagnostics
Chittaranjan National Cancer Institute
Room No. 601. 37, S.P. Mukherjee Road, Kolkata 700026

Dr. Rathindranath Baral
Former Head
Immunoregulation & Immunodiagnostics
Chittaranjan National Cancer Institute
Kolkata; India