IMMUNE CHECKPOINTS AND PANCREATIC BETA CELL DYSFUNCTION IN HIV

680

Luke A. Pryke, Ziyue Liu, Alka K. Khaitan, Emily K. Sims, Samir K. Gupta

Indiana University School of Medicine Indianapolis, IN, USA

BACKGROUND

- ART-naïve people with HIV (PWH) and people without HIV (PWOH) have higher HOMA-B and lower PI:C (markers of pancreatic beta cell function and stress, respectively) compared to PWH receiving ART.
- This suggests lack of ART and impaired T cell function is associated with less beta cell injury.
- We hypothesized that immune dysregulation, and specifically increased immune checkpoints, in ART-naïve PWH is protective against beta cell impairment similar to type 1 diabetes mellitus (DM) and immune checkpoint inhibitor induced DM.

METHODS

- Soluble immune checkpoints (ICs) were measured in serum samples from study volunteers using a bead based multiplex assay.
- HOMA-B and PI:C ratio were calculated using serum glucose, insulin, pro-insulin and c-peptide.
- ANOVA was used to compare mean soluble ICs controlling for age, race, sex, smoking status and BMI.
- Pearson correlations were calculated to assess relationships between IC levels (PD-1, CD27, CD40, TIM-3, CTLA-4) and markers of beta cell function and stress among the separate groups.

The soluble immune checkpoint TIM-3 was found to be correlated with better pancreatic beta cell function and decreased beta cell stress among people with HIV. Immune dysregulation in people with HIV, and specifically heighted immune checkpoints, may be protective against beta cell impairment similar to type 1 diabetes mellitus (DM) and immune checkpoint inhibitor induced DM.

RESULTS

- PWH were found to have higher levels of circulating ICs PD-1, CD27 and CD40 ($p<0.001$).
- PWH receiving ART had higher levels of TIM-3 compared to the other groups ($p=0.037$).
- TIM-3 was found to be positively correlated with HOMA-B ($p=0.22$), and inversely correlated with PI:C ($p<0.05$) in the entire study population.
- Stronger correlations were found in the ART-treated group between TIM-3 and PI:C and between CTLA-4 and HOMA-B.

CONCLUSIONS

- In the entire study population higher TIM-3 was found to be correlated with better beta cell function and reduced beta cell stress.
- The soluble IC TIM-3 may, therefore, play a role in preservation of beta cell function in HIV.
- The ICs PD-1, CTLA-4 and CD27 were found to correlate with either HOMA-B or PI:C, but not both markers, making their role in beta cell protection inconsistent.
- There was no significant correlations with the IC CD40.

LIMITATIONS

- We investigated soluble ICs in this study, but it is unclear how findings may differ when measuring cell bound ICs.
- Patients in this study were not using newer INSTI based ART, so future studies should confirm our results in PWH taking INSTI medications.
- Findings should ideally be reproduced using a longitudinal prospective approach in the future.

ADDITIONAL INFORMATION

Contact information:
Luke Pryke, MD | lpryke@iu.edu
635 Barnhill Drive
Van Nuys Medical Science Building 116
Indianapolis, IN 46202

TABLE 1. DEMOGRAPHICS OF THE STUDY POPULATION

Parameter	HIV-negative controls (n=39)	HIV+/ART-; CD4≥350 cells/µl (n=28)	HIV+/ART-; CD4M<350 cells/µl (n=15)	HIV+/ART+ (n=23)
Age	34(10)	35 (11)	37 (12)	53 (3)
Gender (% male)	76.92	78.57	73.33	86.96
Race (% Black)	66.67	42.86	26.67	43.38
BMI (kg/m2)	27.72 (7.12)	26.71 (4.97)	27.27 (7.04)	28.93 (5.14)
Smokers (%)	19 (48.72)	14 (50.00)	7 (46.67)	6 (26.09)
CD4 (cells/µL)	887.76 (321.46)	556.71 (149.63)	138.93 (109.64)	661.00 (200.83)
HIV RNA (log copies/mL)	N/A	9.64 (2.24)	11.03 (2.24)	3.16 (0.33)

TABLE 2. SOLUBLE ICS AND HOMA-B/PI:C LEVELS

Parameter	HIV-negative controls (n=39)	HIV+/ART-; CD4≥350 cells/µl (n=28)	HIV+/ART-; CD4M<350 cells/µl (n=15)	HIV+/ART+ (n=23)
PI:C	0.0221	0.0215	***0.01385****	0.0210
HOMA-B (%)	115.42	110.17	124.20	***77.77****
PD-1	148.06	***588.88****	***478.66****	***267.12**
TIM-3	1802.63	2404.5	2337.77	***2934.26**
CTLA-4	7.54	7.85	5.74	9.06
CD27	962.72	***3785.55****	***3591.87****	***2290.65****
CD40	392.38	***543.50****	***539.83****	***509.49**

*p<0.05; **<0.01; ***p<0.001; †0.05 <p<0.10, p values compared to HIV negative controls
Soluble immune checkpoints: PD-1, Programmed cell death protein1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; CD27, Cluster of differentiation 27; CD40, Cluster of differentiation 40.

TABLE 3. ICS AND PANCREATIC FUNCTION CORRELATIONS

Correlation	HIV-negative controls (n=39)	HIV+/ART- (n=43)	HIV+/ART+ (n=23)	Entire study population
PD-1/HOMA-B	-0.20	-0.21	-0.02	-0.11
PD-1/PI:C	0.18	-0.18	-0.29	***-0.26****
TIM-3/HOMA-B	0.17	***0.29****	0.40	***0.24****
TIM-3/PI:C	0.37	***-0.27**†	***-0.43**†	***-0.21****
CTLA-4/HOMA-B	0.14	0.10	***0.51****	***0.19**†
CTLA-4/PI:C	0.14	-0.01	-0.03	0.03
CD27/HOMA-B	0.31	0.01	0.07	0.11
CD27/PI:C	0.17	-0.22	-0.23	***-0.24****
CD40/HOMA-B	-0.06	0.06	0.18	-0.01
CD40/PI:C	0.27	-0.13	-0.32	-0.15

Acknowledgements:
Parent studies supported in part by grants from the NIH K08DK103983, R01HL095149 UL1TR001108; Diabetes Research Center P30 DK097512; and National Center for Research Resources RR020128.