T Cell Subpopulation Profiles and Cancer Risk for HIV+ and HIV- Veterans

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INTRODUCTION

- Alterations in cell-mediated immunity have been associated with cancer risk for people living with HIV (PLWH).
- Circulating levels of T regulatory cells (Tregs), and activated and senescent T cells have been linked to cancer risk and outcomes in HIV uninfected persons but there has been limited study of T cell subset alterations and cancer development unique to PLWH.

OBJECTIVE

- To determine whether the proportions of select T cell phenotypes predicted the incidence of non-AIDS cancers that have been associated with responses to immunotherapy (lung, anus, kidney).

METHODS

Population

- We linked the Veterans Aging Cohort Study Biomarker Cohort (1,429 PLWH, 765 uninfected people, free of baseline cancer) to Veterans Affairs Cancer Registry data to identify 75 incident lung (n=46), anus (n=16), and kidney cancers (n=13; the most common cancers arising in the cohort with known immunotherapy links).

Outcome

- First incident lung, anus or kidney cancer

Primary Exposures of Interest

- Proportions of circulating T cell subpopulations:
  - Tregs (CD4+CD25+FOXP3+)
  - Activated (CD4+CD38+ and CD8+CD38+)
  - Senescent (CD4+CD28-, CD4+CD57+, and CD8+CD28-, CD8+CD57+)
- Covariates: age, sex, race/ethnicity, smoking status

Analysis

- Time-to-event analyses, following subjects from blood draw in 2005-2006
- Endpoint, earliest of: cancer incidence, death, lost to follow-up, or censoring (on 9/31/2017)
- Multivariable Cox regression models, each with a different T cell subpopulation proportion as the primary measure of interest

RESULTS

Table 1. Baseline Cohort Characteristics

Characteristic	HIV+ (n=1,429)	HIV- (n=765)
Age, Years, median	52.0	52.9
Male, n (%)	1,386 (97)	693 (91)
Race, n (%)		
Non-Hispanic White	264 (19)	156 (20)
Non-Hispanic Black	986 (69)	515 (67)
Hispanic/Other	178 (13)	94 (12)
Smoking, n (%)		
Current	734 (51)	366 (48)
Former	353 (25)	220 (29)
Never	339 (24)	177 (23)
Hepatitis C Status, n (%)		
Antibody Negative	801 (56)	496 (65)
Chronic HCV	507 (36)	171 (22)
Body Mass Index >30, n (%)	229 (16)	356 (47)
CMV Antibody Positive, n (%)	1,295 (91)	536 (70)
CD4 cell count		
<200 cells/mm3	261 (18)	
200-499 cells/mm3	652 (46)	
>500 cells/mm3	515 (36)	
HIV RNA >500 copies/ml	494 (35)	
Follow up time, years, media	10.9	11.0

Figure 1. Adjusted Associations of T cell Subset Proportions and Lung, Anus or Kidney Cancer Incidence

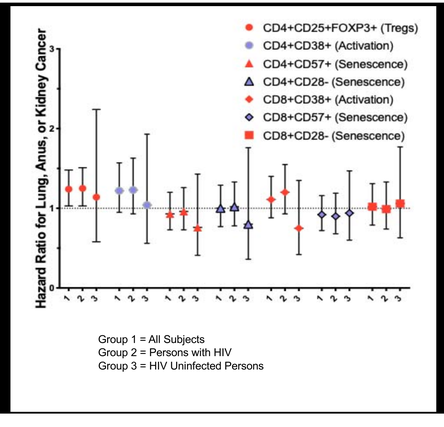

Table 2. Baseline Biomarkers by HIV Status

Biomarker		HIV+ (n=1,429)	HIV- (n=765)	P-value
CD4+	CD4+CD25+FOXP3+ (Tregs)*	5%	3%	<0.001
	CD4+CD38+*	43%	28%	<0.001
	CD4+CD57+*	26%	17%	<0.001
	CD4+CD28-*	13%	6%	<0.001
CD8+	CD8+CD38+**	36%	22%	<0.001
	CD8+CD57+**	53%	50%	<0.001
	CD8+CD28-**	56%	41%	<0.001
	Treg to Natural Killer Ratio	0.29	0.34	0.12

*Proportion of circulating CD4 cells, **Proportion of circulating CD8 cells

Table 3. Adjusted regression models measuring the association of proportion of T cell subsets and cancer incidence

Cell Subset (Phenotype)		All Subjects Hazard Ratio* (95% CI)	Persons with HIV Hazard Ratio* (95% CI)	Uninfected Hazard Ratio* (95% CI)
CD4+	CD25+FOXP3+ (Tregs)	1.24 (1.03-1.48)	1.25 (1.03-1.51)	1.14 (0.58-2.24)
	CD38+	1.22 (0.95-1.57)	1.23 (0.93-1.63)	1.04 (0.56-1.93)
	CD57+	0.93 (0.73-1.2)	0.96 (0.73-1.26)	0.76 (0.41-1.43)
	CD28-	1.00 (0.77-1.29)	1.02 (0.78-1.33)	0.80 (0.36-1.76)
CD8+	CD38+	1.11 (0.88-1.4)	1.2 (0.93-1.55)	0.75 (0.42-1.35)
	CD57+	0.92 (0.72-1.16)	0.9 (0.68-1.19)	0.94 (0.6-1.47)
	CD28-	1.02 (0.79-1.31	0.99 (0.74-1.33	1.06 (0.63-1.77)

*Hazard of lung, anus or kidney cancer per SD increase in measure; adjusted for age, sex, race/ethnicity and smoking status

CONCLUSIONS

- Among PWH increased circulating Tregs as a proportion of CD4 cells were associated with increased risk of lung, anus and kidney cancers.
- Correlation of these findings with the precancerous tumor microenvironment may provide greater insight into the role of HIV infection as an increased risk for some cancers.

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