Poster # 1044

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Enhanced Activation of Liver Infiltrating CD8+ T cells in HCV infected Patients with HIV Co-infection

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Background: HCV related liver disease contributes to the morbidity and mortality of persons with HIV infection. Some studies have shown an increase in the rate of progression of HCV related liver disease in persons with HIV co-infection compared with HCV mono-infected persons, but the mechanism of this enhanced liver injury in co-infected persons is poorly understood. HIV infection itself is associated with increased immune activation of peripheral blood T cells (bystander activation), so we hypothesized that liver infiltrating CD8+ T cells from patients with HIV/HCV co-infection would show increased activation in comparison with cells from persons with HCV mono-infection.

Methods: Eleven patients with HIV/HCV co-infection (on HAART) and 20 patients with HCV mono-infection undergoing liver biopsy were studied. We analyzed the frequency of liver infiltrating CD8+ T cells expressing the activation markers CD69, CD38, and HLA-DR, and the senescence marker, CD57 using FACS analysis. Unpaired T tests were used to compare the mean expression of each marker between the two groups. Additionally, tetramers were used to evaluate the expression of activation markers on liver infiltrating HIV and HCV specific CD8+ T cells from one patient with HIV/HCV co-infection and two patients with HCV mono-infection.

Results: A greater frequency of liver infiltrating CD8+ T cells from patients with HIV/HCV co-infection expressed CD38 (57% vs. 42%, p=0.03), HLA-DR (74% vs. 49%, p=0.02) and CD57 (28% vs. 17%, p=0.02) in comparison with HCV mono-infection. No difference in CD69 expression (p=0.2) could be detected. A majority of liver infiltrating HIV and HCV specific CD8+ T cells from HIV/HCV co-infected and HCV mono-infected patients expressed markers of activation, however, small numbers of patients with detectable liver tetramer responses precluded statistical comparison.

Patient Charcteristics

Pt #	Age	HIV	CD4	HIV VL	HCV VL	ALT	LBX Inflam	LBX fibros	HCV geno
109	79w	+	199	<50	23,250,000	79	1	2	1a,b
184	42m	+	888	<50	5,980,000	111	2	3	2b
185	54m	+	264	70	5,190,000	118	4	4	1
186	46m	+	595	660	19,860,000	244	2	2	1a
195	55m	+	830	<50	140,520,000	50	1	2	1
201	37w	+	242	1900	49,470,000	58	2	2	1
209	53m	+	673	70	2,130,000	27	2	0	1
210	71m	+	842	5800	5,610,000	73	2	3	1
216	53m	+	195	490	9,780,000	19	2	0	1
226	44m	+	543	16300	4,050,000	49	2	0	1
235	28m	+	646	<50	213,000	94	2	0	3
175	45m	-			29,890,000	135	1	4	1
179	54m	-			197,000	197	2	2	1
208	49m	-			5,080,000	45	2	3	1b
228	53w	-			494,000	67	2	2	1
232	52w	-			1,220,000	94	2/2	2	1a
601	60m	-			4,690,000	45	2/1	2	1b
602	48m	-			586,000	73	2/1	0	1a
617	57m	-			294,000	61	2	1	1a
618	44m	-			1,140,000	53	1	0	1a
619	53m	-			1,450,000	105	3/2	3	1a
633	52m	-			9,870,000	63	1/1	1	1a
637	58m	-			2,790,000	23	2/2	3	1a
640	56m	-			1,760,000	26	2/1	2	1a
641	52m	-			761,000	35	2/2	2	1b
642	62m	-			490,000	51	2/2	2	1a
643	54m	-			2,520,000	46	2/1	0	1
657	56m	-			47,300	59	1	2	1b
671	50m	-			1,060,000	50	2/2	1	1a,b
684	52m	-			4,910,000	54	2	3	1b
688	50m	-			16,800,000	64	2	2	1a

Table 1. Patient Characteristics. HIV viral load in copy/ml, HCV viral load in IU/ml, CD4 T cell count in cells/ml, liver biopsy inflammation and fibrosis score based on Scheuer grading. First number in inflammation score represents periportal inflammation and second if present, lobular inflammation.

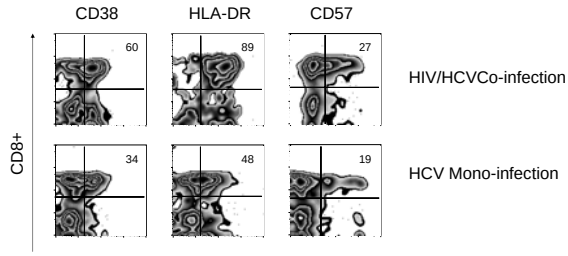

Figure 1. Representative FACS plots of liver infiltrating CD8+ T cells in HIV/HCV co-infected patient and HCV mono-infected patient. CD3+ gated. Frequency of activation marker positive CD8+ T cells is shown.

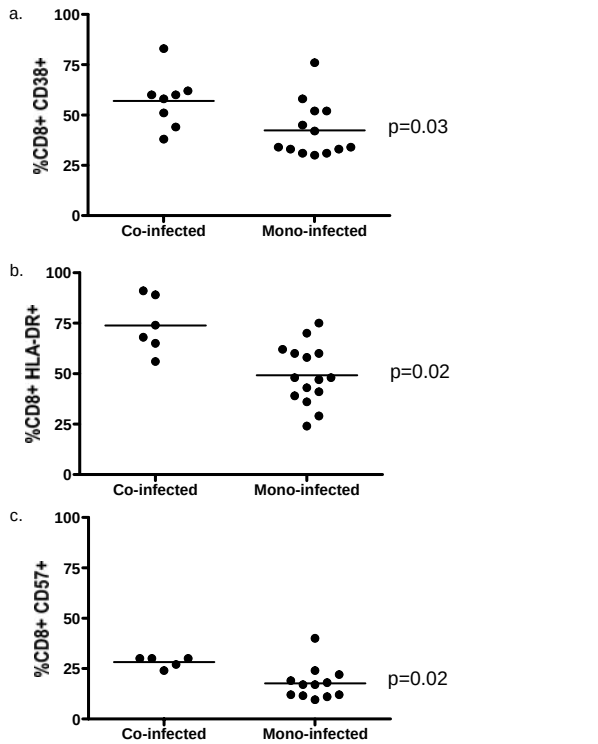

Figure 2. Summary plots of a) CD38, b) HLA-DR and c) CD57 expression on liver infiltrating CD8+ T cells in HIV/HCV co-infected patients compared with HCV mono-infected patients.

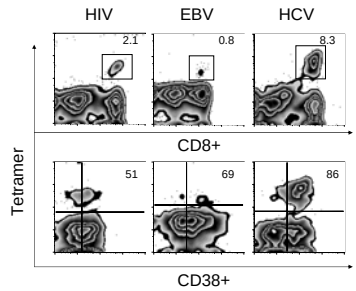

Figure 3. FACS plots of CD38 expression on liver infiltrating antigen specific CD8+ T cells in three patients with chronic HCV infection (HCV 216-HIV GAG response, HCV 688-EBV GLC response, and HCV 671-HCV NS3 tetramer response). Numbers show tetramer frequency in CD3+ lymphocytes and frequency of CD38 expression on antigen specific cells.

Conclusions: Liver infiltrating CD8+ T cells show greater activation in patients with HIV/HCV co-infection than in patients with HCV mono-infection. Greater expression of CD57 in the co-infected patients could represent a later stage of differentiation for these cells. This could contribute to the increased rate of liver disease progression in HIV/HCV co-infection if the cells expressing these activation and differentiation markers have greater cytotoxic effector potential and/or produce greater amounts of pro-inflammatory/pro-fibrotic cytokines.

Acknowledgements: The authors would like to acknowledge the support from EVC/CFAR P30 AI050409, Cancer Research Institute, Woodruff Fund (AG) and Public Health Service AI072191-01 (HR), AI070101 (AG).