Multi-compartment dissemination of genome-intact HIV-1 reservoir clones

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Background

Latently infected CD4 T cells provide a highly durable reservoir for HIV-1, but the ability to support viral persistence appears to differ considerably among different CD4 T cell populations. Here, we used single-template near full-length viral deep sequencing to map proviral sequences across nine different CD4 T cell subsets from blood and lymph nodes (LN).

Methods

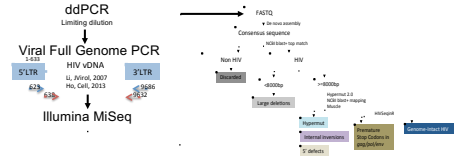
Table 1. Patient characteristics (n=3)

Patient ID	Duration of HIV infection (years)	Time on HAART (years)	Duration of suppressive therapy (years)	CD4 Cell Count at enrollment (cells/ul)	Viral Load at Enrollment (copies/ml)
MP082-2	23.5	Unknown	2.7	1093	<20
MP131	25.8	19.3	4.7	1114	<20
MP133	7.3	6.5	3.7	686	<20

Table 2. CD4 T cell populations in this study.

PBMC	CD3+ CD4+	CD45RA-	Total Memory
		CXCR3+CXCR5-	Th1-enriched
		CCR4+CCR6-	Th2-enriched
		CCR4+CCR6+	Th17-enriched
		CXCR3-CXCR5+	Circulating Tfh-like
		CXCR3+CXCR5+	Th1/Tfh-like-cells enriched
Lymph node	CD3+ CD4+	PD-1- CXCR5-	Double Negative (DN)
		PD-1- CXCR5+	CXCR5+
		PD-1+ CXCR5+/-	PD-1+ Tfh-enriched
		CD45RA+	Tnaive

Figure 1. HIV reservoir quantification and genotyping



Results

Table 2. A total of 312 HIV proviral genomes were detected across all patients and all CD4 T cell subsets. All subsets investigated in this study contains HIV DNA. In each patient, the subset with the highest calculated reservoir size (defined as intact-HIV/million cells) is highlighted in red.

	Full viral genome single-template amplification & sequencing					ddPCR
MP082 (n=87)	Number of Cells Sampled	Total HIV Genomes Detected	Intact HIV Genomes Detected	[Intact-HIV/million cells]	[ANY-HIV/million cells]	[LTRgag /million cells]
MP.01.Blood.TH1	5675	5	1	176	881	5461
MP.02.Blood.TH2	4682	1	0	0 (<192)	214	5934
MP.03.Blood.TH17	10414	13	1	96	1348	2756
MP.04.Blood.TFH	11345	9	0	0 (<79)	793	2090
MP.05.Blood.TH1TFH	17016	11	1	59	646	1783
MP.06.Blood.TotalMemory	6368	5	0	0 (<141)	785	4682
MP.07.LN.DN	15420	11	3	195	713	1944
MP.08.LN.CXCR5	15750	16	4	254	1016	1776
MP.09.LN.PD1	11357	2	0	0 (<79)	176	1881
MP.10.LN.Naive	62152	1	0	0 (<14)	16	0
MP.11.LN.TotalMemory	12853	13	0	0 (<70)	1011	2204
MP131 (n=65)						
MP.01.Blood.TH1	37083	5	2	54	135	1861
MP.02.Blood.TH2	51768	15	7	135	290	359
MP.03.Blood.TH17	10680	1	0	0 (<84)	94	1045
MP.04.Blood.TFH	48950	8	0	0 (<9)	163	1398
MP.05.Blood.TH1TFH	18690	7	2	107	375	2435
MP.06.Blood.TotalMemory	35303	5	0	0 (<25)	142	570
MP.07.LN.DN	21805	2	1	46	92	463
MP.08.LN.CXCR5	16762	3	0	0 (<54)	179	548
MP.09.LN.PD1	22398	12	4	179	536	1286
MP.10.LN.Naive	36342	1	0	0 (<25)	28	0
MP.11.LN.TotalMemory	27738	3	3	108	216	689
MP133 (n=160)						
MP.01.Blood.TH1	18245	10	0	0 (<49)	548	1716
MP.02.Blood.TH2	18987	10	1	53	527	2732
MP.03.Blood.TH17	23288	24	2	86	1031	2695
MP.04.Blood.TFH	41385	0	0	0 (<22)	0	216
MP.05.Blood.TH1TFH	NA	NA	NA	NA	NA	NA
MP.06.Blood.TotalMemory	18542	6	0	0 (<49)	324	850
MP.07.LN.DN	37973	24	1	26	632	734
MP.08.LN.CXCR5	48802	26	0	0 (<18)	533	955
MP.09.LN.PD1	43907	29	2	46	660	1281
MP.10.LN.Naive	37380	2	0	0 (<24)	54	194
MP.11.LN.TotalMemory	39753	29	2	50	729	1250

Figure 2. Frequencies of genome-intact sequences relative to defective copies did not significantly differ between blood and lymph nodes.

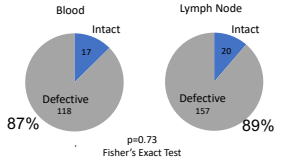


Figure 3. Proviral sequences from blood (red) and lymph nodes (blue) intermingled phylogenetically without obvious compartmentalization.

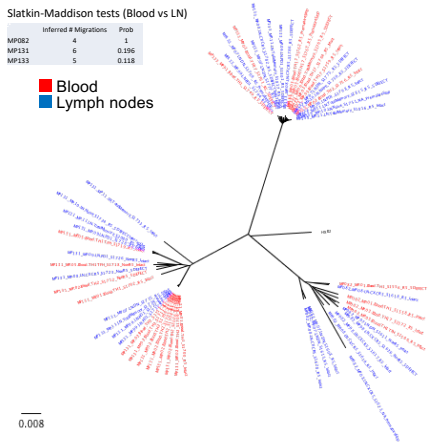
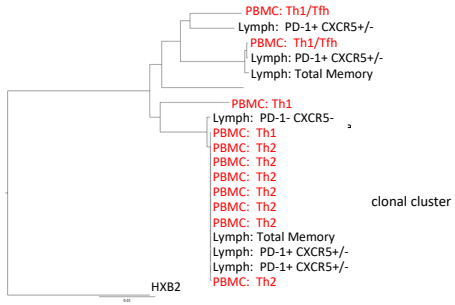


Figure 4. In a patient (MP131), a 10 member genome-intact clonal cluster was detected across CD4 T cell subsets in both PBMC and lymph node, indicating dissemination.



Conclusions

This study suggests dynamic interchanges between genome-intact viral reservoir cell populations from blood and lymphoid tissues. Clusters of clonally-expanded intact proviruses encompassing sequences from cells with distinct anatomic localization and functional polarization suggest infection of common precursor cells as a driving force for viral reservoir stabilization.

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