Detectable CSF Tat Despite Dual Compartment HIV Viral Suppression with cART

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Introduction

•HIV associated neurocognitive disorders (HAND) persist despite HIV suppression in both the blood and cerebrospinal fluid (CSF)

•Antiretroviral drugs do not prevent post integration transcription of viral components, such as tat

•Tat is known to be neurotoxic and able to exit the infected cell

Hypotheses

•The presence of HAND, in the context of HIV suppression in both blood and CSF, is related to the presence of tat in the CSF

•The putative HIV latency biomarker BCL11b will be elevated in samples where tat is not detectable

Methods

•30 CSF samples from virally-suppressed (<20cpml in blood and CSF) HIV+ men were studied

•Subjects were enrolled in an HIV and ageing prospective study involving medical and neuropsychological (NP) assessment (see Table 1)

•Presence and amount of tat in CSF was assessed using ELISA assay

•CSF BCL11B was detected by immunoblot assay using anti-BCL11b antibody and expression was quantified by computing the integrated intensity of the fluorescence signal

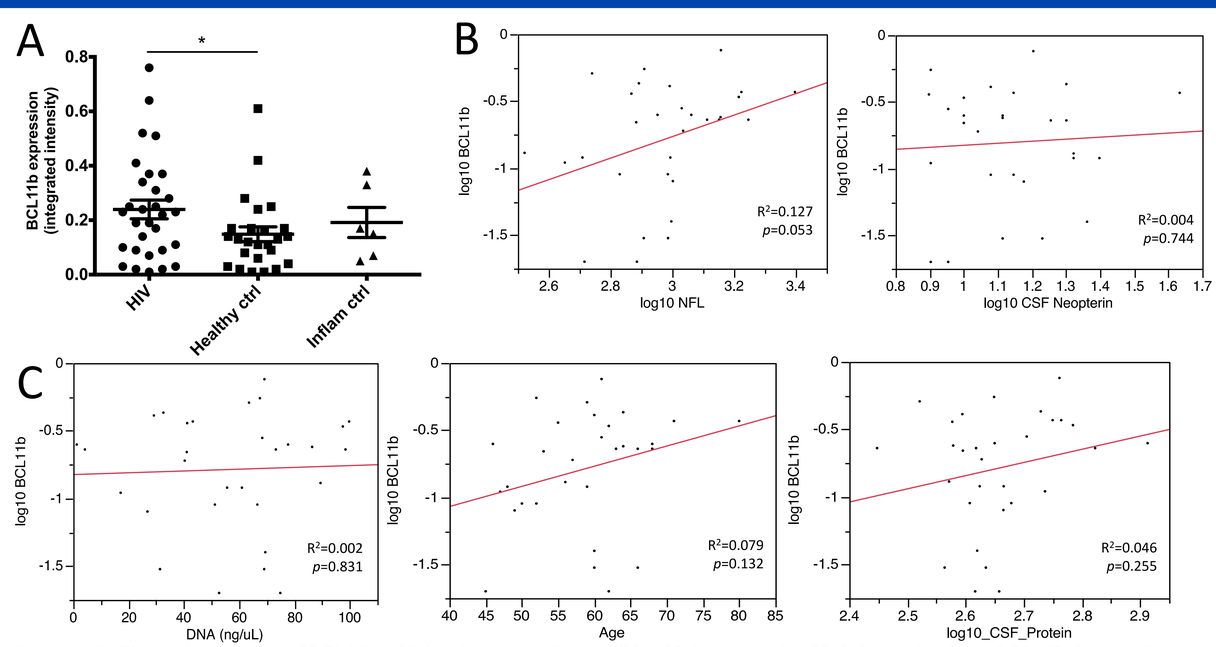

Figure 1. (A) Elevated expression of BCL11b in HIV and control patients (HIV *n*=30; Healthy ctrl *n*=25; Inflam ctrl *n*=6, **p*<0.05); (B) No significant relationship between BCL11b and NF-L or the inflammatory marker neopterin in the CSF; (C) Elevated expression of BCL11b is independent of age, total CSF DNA and total CSF protein

Table 1. Sample Characteristics

	NP-Normal	HAND	*p*
n	10	20	
Age (y) (M,SD)	56.8 (6.5)	59.8 (8.8)	.35
Education (y) (M,SD)	13.1 (2.6)	15.2 (2.7)	.06
Nadir CD4 (Med,IQR)	53.5 (206.5)	202 (253.3)	.07
Current CD4 (Med,IQR)	435 (294)	628 (539.8)	.41
HIV duration (y) (Med,IQR)	21.1 (9.0)	20.5 (12.8)	.77
cART duration (months) (Med,IQR)	48.0 (71.5)	22.5 (37.5)	.08
AIDS (Y:N)	9:1	12:8	.20

Table 2. CSF tat and BCL11b are independent of HAND status (Mean±SEM)

		HAND		
	NP-Normal	ANI	MND	HAD
n	10	11	6	3
CSF tat	46.3±37.1	2.5±2.5	0.0±0.0	21.8±21.8
CSF BCL11b	0.19±0.05	0.29±0.07	0.18±0.05	0.23±0.08

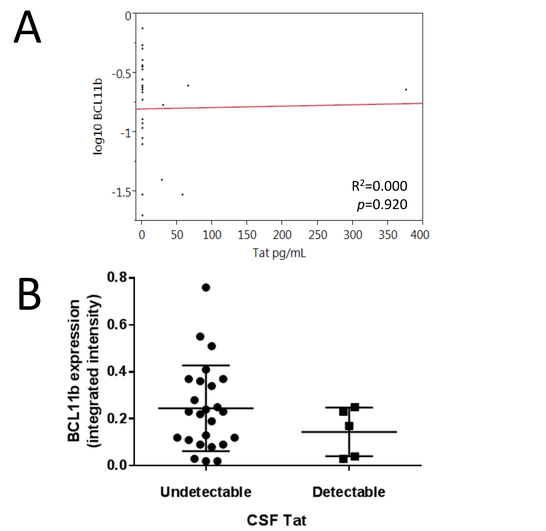

Figure 2. (A) No significant relationship between BCL11b and Tat in in the CSF; (B) Elevated expression of BCL11b is independent of CSF Tat detection.

Results

•Using standard criteria, neuropsychological (NP)-HAND was present in 67% of subjects

•CSF tat was found in 5 of 30 samples (range: 27-375pg/ml)

•There was no correlation with HAND: 3 of 5 were NP-normal, 1 had ANI and the other had HAD

•BCL11b integrated intensity levels were 0.23 ± 0.03 (*M±SEM*)

•There was no correlation between CSF tat and BCL11b

Conclusion

•CSF tat was detectable in 16.7% of dual compartment virally suppressed patients

•The lack of correlation with HAND may be related to intermittent tat production, tat polymerization rendering the current assay insensitive, or other causal factors for HAND (e.g. other transcripts such as *vpr*, *nef* or drug toxicity, inactive HAND)

•Nonetheless, the presence of tat despite viral suppression has implications for eradication strategies especially those involving cART

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