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High Mobility Group Box 1 (HMGB1) and HIV-Associated Kaposi's Sarcoma in Africa

Helen Byakwaga[1,2], Peter W. Hunt[2], Miriam Laker-Oketta[2,3], David V. Glidden[2], Conrad Muzoora[1], Albert R. Davalos[4], A. Rain Mocello[2], David R. Bangsberg[5], Edward K. Mbidde[6] and Jeffrey N. Martin[2]

[1]Mbarara University of Science and Technology, Mbarara, Uganda; [2]University of California, San Francisco; [3]Infectious Diseases Institute, Kampala, Uganda; [4]Buck Institute for Research on Aging, Novato; [5]Massachusetts General Hospital, Center for Global Health, Harvard Medical School, Boston, MA, USA; [6]Uganda Virus Research Institute, Entebbe, Uganda

Correspondence:
Helen Byakwaga
hbyakwaga@gmail.com

Background

- Other than Kaposi's sarcoma-associated herpesvirus (KSHV) and CD4+ T cell lymphopenia, the mechanisms responsible for KS are poorly understood.
- Additional mechanisms must exist in sub-Saharan Africa given that only a minority of individuals with advanced AIDS in that setting develop KS despite the high prevalence KSHV.
- High mobility group box 1 (HMGB1) protein is a host transcriptional regulator that promotes cell proliferation. It is actively secreted by senescent cells (resulting in decreased transcriptional activity and cell proliferation).
- HMGB1 is known to interact with KSHV *in vitro*.
  - Binds to KSHV latency-associated nuclear antigen (LANA) and stimulates replication and transcriptional activator (RTA) transactivation, facilitating KSHV replication.
  - May also block p53-dependent secretion of HMGB1, thereby increasing intracellular HMGB1 levels even in the setting of senescence.
- Increased secretion of HMGB1 (e.g., higher plasma levels) secondary to immune activation/senescence might be associated with:
  - Increased risk of KS to the extent it reflects inflammation and decreased immune surveillance.
  - Decreased risk of KS to the extent it suppresses KSHV replication and spindle cell proliferation.

Objective

To assess whether HMGB1 has a role in the development of KS in untreated HIV-infected African adults.

Participants

HIV-infected Ugandan adults, identified just prior to start of ART. Pregnant women were excluded.

Cases: Mild-moderate biopsy-confirmed KS and no urgent indications for chemotherapy, seen in preparation for the Antiretrovirals for Kaposi's Sarcoma (ARKS) clinical trial, based at the Infectious Diseases Institute in Kampala, Uganda.

Controls: No KS, derived from Uganda AIDS Rural Treatment Outcomes (UARTO), a clinic-based cohort of HIV-infected adults initiating ART in Mbarara, Uganda.

Measurements

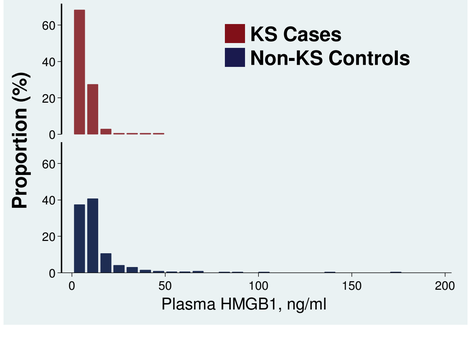
- Both ARKS and UARTO studies used the same instruments and labs for all study measurements.
- Plasma HMGB1 levels were measured in morning plasma by an enzyme-linked immunosorbent assay.

Characteristics of Participants

Characteristic	KS Cases (n=224)	Controls (n=450)
Age	34 (28-40)	35 (29-40)
Female Sex	44%	68%
BMI, kg/m^2	21.4 (19.4-23.1)	21.1 (19.4-23.4)
Hemoglobin, g/dL	11.6 (10.3-13.2)	12.2 (10.6-13.7)
Physical Health Status[a]	53.3 (36.4-58.2)	54.0 (45.0-58.6)
Mental Health Status[a]	48.6 (37.7-56.7)	52.6 (45.9-58.7)
Asset Index[b]	0.18 (-1.80-1.78)	-0.58 (-1.82-0.86)
HIV RNA, log$_{10}$ copies/ml	5.3 (5.0-5.6)	5.1 (4.6-5.6)
IL-6, pg/ml	4.60 (2.43-7.92)	2.58 (1.43-5.55)
CD4+ T cell, count/mm^3		
<50	35%	15%
51-100	11%	17%
101-200	23%	39%
201-350	18%	20%
>350	13%	9%
HMGB1, ng/ml, by Quartile		
Q1 (0.44-4.25)	46%	14%
Q2 (4.26-6.63)	29%	23%
Q3 (6.64-10.16)	17%	29%
Q4 (10.7-138.85)	8%	33%

All data as median (interquartile range) unless indicated.
[a] Scores derived using the Medical Outcomes Study HIV survey.
[b] Asset based measure of socioeconomic status (Pritchett et al).

Distribution of Plasma HMGB1 in Cases versus Controls



Multivariable Logistic Regression for Determinants of KS

	Adjusted Model 1		Adjusted Model 2	
Characteristic	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Plasma HMGB1, ng/ml, by Quartile				
Q1 (0.44-4.25)	Ref		Ref	
Q2 (4.26-6.63)	0.36 (0.21-0.60)	<0.001	0.35 (0.20-0.60)	<0.001
Q3 (6.64-10.16)	0.18 (0.10-0.31)	<0.001	016 (0.09-0.29)	<0.001
Q4 (10.17-138.85)	0.08 (0.04-0.15)	<0.001	0.08 (0.04-0.15)	<0.001
IL-6, pg/ml, by Quartile				
Q1 (0.36-1.90)	Ref			
Q2 (1.91-3.38)	2.35 (1.24-4.46)	0.009	2.28 (1.16-4.46)	0.016
Q3 (3.39-6.54)	4.95 (2.63-9.31)	<0.001	4.62 (2.31-9.21)	<0.001
Q4 (6.55-333.69)	4.72 (2.49-8.96)	<0.001	4.29 (2.03-9.09)	<0.001
HIV RNA, log10 copies/ml				
≤10,000	Ref		Ref	
10,001-50,000	2.9 (0.9-9.5)	0.076	2.9 (0.8-9.8)	0.082
50,001-100,000	3.8 (1.2-12.0)	0.024	4.0 (1.2-13.0)	0.02
100,001-500,000	7.8 (2.6-23.5)	<0.001	9.0 (2.9-27.9)	<0.001
>500,000	3.8 (1.2-12.2)	0.027	4.1 (1.2-13.6)	0.022
CD4+ T cell count, cells/mm^3				
<50	Ref		Ref	
51-100	0.31 (0.16-0.59)	<0.001	0.26 (0.13-0.52)	<0.001
101-200	0.43 (0.25-0.73)	0.002	0.37 (0.20-0.66)	0.001
201-350	0.76 (0.41-1.40)	0.38	0.67 (0.35-1.27)	0.22
>350	1.72 (0.81-3.62)	0.16	1.70 (0.78-3.73)	0.19
Sex				
Men	Ref		Ref	
Women	0.33 (0.22-0.50)	<0.001	0.18 (0.11-0.30)	<0.001
Age, per 10 years	0.74 (0.58-0.96)	0.023	0.74 (0.56-0.96)	0.024
Hemoglobin, g/dL			0.81 (0.71-0.93)	0.002
BMI, kg/m^2			1.13 (1.07-1.21)	<0.001
Physical Health Status*			1.01 (0.991.04)	0.39
Mental Health Status*			0.99 (0.97-1.02)	0.70
Asset Index*			1.07 (0.97-1.18)	0.15

*Per unit increase in respective scale.
Adjusted model 1 and model 2: adjusted for all variables in each of the columns respectively.

Restricting to Participants without Report of Opportunistic Infections

	OR* (95% CI)	P value
Plasma HMGB1, ng/ml, by Quartile		
Q1 (0.44-4.25)	Ref	
Q2 (4.26-6.63)	0.37 (0.19-0.72)	0.003
Q3 (6.64-10.16)	0.17 (0.08-0.34)	<0.001
Q4 (10.17-138.85)	0.09 (0.04-0.19)	<0.001

*Adjusted for age, sex, CD4 count, plasma HIV RNA and IL-6 (N=394: 162 KS cases, 232 controls)

- Excluded those with the following self reported opportunistic infections in the previous 12 months: PCP, esophageal candidiasis, cryptococcal meningitis, cryptococcal pnuemonia, lymphoma, cryptococcal diarrhoea, recurrent typhoid, tuberculosis, CMV retinitis and shingles.
- We observed similar findings when we restricted analyses only to participants who did not report tuberculosis (pulmonary or extra-pulmonary) in the previous 12 months.

Conclusions

- Higher plasma HMGB1 levels are strongly associated with lower occurrence of KS, independent of CD4+ count, plasma HIV RNA and IL-6 levels.

Implications

- Our findings are consistent with the hypothesis that KSHV-mediated intracellular sequestration of HMGB1, reflected by lower extracellular levels, increases KSHV replication and subsequent KS.
- Active HMGB1 secretion by senescent KSHV-infected cells may be a mechanism that suppresses KS development in this setting.
- Some consequences of immune activation in HIV might suppress certain cancers.

Acknowledgements

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