Evidence of HIV-1 Adaptation to HLA-Restricted Immune Responses at a Population Level

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This thesis is presented for the degree of Doctor of Philosophy of Murdoch University, 2002

I declare that this thesis is my own account of my research and contains as its main content work that has not previously been submitted for a degree at any tertiary education institution.

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Abstract

Selection of HIV-1 variants resistant to antiretroviral therapy is well documented. However, the selection *in vivo* of HIV-1 mutant species that can escape host immune system HLA class I restricted cytotoxic T-lymphocyte responses has, to date, only been documented in a few individuals and its clinical importance is not well understood. This thesis analyses the observed diversity of the HIV-1 reverse transcriptase protein in a well characterised, stable, HLA-diverse cohort of HIV-1 infected patients with over two thousand patient-years of observation. The results show that HIV-1 polymorphism is selected within functional constraints and is associated with specific HLA class I alleles. Furthermore, these associations significantly cluster along the sequence and tend to occur within known corresponding HLA-restricted epitopes. Absence of polymorphism is also HLA-specific and more often seen with common HLA alleles. Knowledge of HLA-specific viral polymorphisms can be used to model an individual's viral load from their HLA type and viral sequence. These results suggest that cytotoxic T-lymphocyte escape mutation in HIV-1 is critical to the host at an individual and population level as well as to short and long term viral evolution. This work provides new insights into viral-host interactions and has clinical implications for individualisation of HIV-1 therapy and vaccine design.

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Abbreviations

A	Adenine
Ab	Antibody
AH	Ancestral haplotype
AIDS	Autoimmune deficiency syndrome
APC	Antigen presenting cell
C	Cytidine
CCR	CC chemokine receptor
CDR	Complementary-determining region
cps	Copies
CTL	Cytotoxic T-lymphocyte
CXCR	CXC chemokine receptor
D	Diversity (gene segment)
DBMS	Database management system
df	Degrees of freedom
DNA	Deoxyribonucleic acid
DT	Decay time
EBV	Epstein-Barr virus
eCTL	Effector CTL
env	Envelope
ER	Endoplasmic reticulum
G	Guanine
gag	Group-specific antigen
HBV	Hepatitis B virus
HCMV	Human cytomegalovirus
HIV	Human immunodeficiency virus
HLA	Histocompatibility leukocyte antigen
HSV	Herpes simplex virus
IC	Inhibitory concentration
IDU	Immunodeficiency unit
IFN	Interferon
IL	Interleukin
IQR	Inter-quartile range
J	Joining (gene segment)
kDa	Kilo Dalton
LTNP	Long term nonprogressor
LTR	Long terminal repeat
MCMV	Murine cytomegalovirus
MHC	Major histocompatibility complex
MIP	Macrophage inflammatory protein
mL	Millilitre
M-tropic	Macrophage tropic
n	Number
NC	Non-conservative
nef	"Negative factor"
NK	“Natural killer”
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NS	Non-synonymous

NSI	Non-syncytium inducing
NtRTI	Nucleotide reverse transcriptase inhibitor
OR	Odds ratios
P	*P*-value
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PI	Protease inhibitor
RANTES	"Regulated on activation, normal T expressed and secreted"
RNA	Ribonucleic acid
RRE	Rev-responsive element
RT	Reverse transcriptase
SDF	"Stromal-derived factor"
SHIV	Simian-human immunodeficiency virus
SI	Syncytium-inducing
SIV	Simian immunodeficiency virus
STI	Structured treatment interruptions
T	Thymine
TAP	“Transporter associated with antigen presentation”
TCR	T-cell receptor
tRNA	Transfer RNA
T-tropic	T-cell tropic
V	Variable (gene segment)
WABMRDB	Western Australian bone marrow registry database
WAHIVCS	Western Australian HIV cohort study

For amino acid abbreviations see Figure 2.20 on page 35.

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