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The immune response to HIV

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Since HIV was discovered as the causative agent of AIDS almost 30 years ago, HIV infection has become a devastating pandemic, with millions of individuals becoming infected and dying from HIV-related disease every year. A global research effort over the past three decades has discovered more about HIV than perhaps any other pathogen. Immunologists continue to be intrigued by the capacity of HIV to effectively knock out an essential component of the adaptive immune system — $CD4^+$ T helper cells. This Poster summarizes how HIV establishes infection at mucosal surfaces, the ensuing immune response to the virus involving DCs, B cells and T cells, and how HIV subverts this response to establish a chronic infection. Based on a clearer understanding of HIV infection and the response to it, the field has now entered an era of renewed optimism for the development of a successful vaccine.

Breaching the mucosal barrier

Vagina or ectocervix
Endocervix
Inserted HIV genome
Donor virus population
HIV-infected donor cell
HIV virion
Stratified squamous epithelium
Mucus layer
Lack of tight junctions between cells
Infected intraepithelial $CD4^+$ T cell
CD1a
$CD1a^+$ Langerhans cell
Langerin
Tear in the mucosal epithelium
Impermeable tight junctions between cells
Columnar epithelium
Transcytosis of HIV virions
Subepithelial DC
Infected $CD4^+$ T cell
Stroma
HIV penetration and infection

The DC response to HIV

Monocyte
IL-10
HIV uptake by langerin leads to virus degradation
HIV uptake by DC-SIGN blocks DC maturation
SAMHD1 and APOBEC3G restrict HIV replication
APOBEC3G
SAMHD1
TRIM5
CYPA
CYPA and TRIM5 recognize HIV capsid
Conventional DC
DC dysfunction
Lack of effective antiviral immunity
$CD8^+$ T cell
$CD8^+$ T cell response
Type I IFNs
IL-12, IL-15, IL-18
NK cell
NK cell activation
Inhibition of viral replication
CTLA4
IL-10
T_{Reg} cell
CD4
IDO
Viral RNA
pDC
TLR7
TRAIL
T_{Reg} cell differentiation promoted by IDO
IFN-induced T cell apoptosis
T cell-attracting chemokines
TRAIL-induced T cell apoptosis
Chemokine-mediated recruitment of new $CD4^+$ T cells for HIV to infect
Viral spread
Several years

A few hours

DC-SIGN
CD4
CCR5
Internalized virion
HIV-bearing stromal DC
Local amplification of initial founder virus(es) in a single focus of $CD4^+$ T cells
Infected $CD4^+$ memory T cell
T cell-attracting chemokines
pDC
Draining lymphatic vessels

Amplification in draining lymph nodes

1 week
HIV virions and HIV-bearing cells
Subcapsular sinus macrophage
$CD4^+$ T cell
T_{FH} cell
HIV-specific B cell and antibody response
MHC class II
$CD8^+$ T cell
TCR
MHC class I
Clonal expansion of HIV-specific $CD8^+$ T cells
HIV-bearing DC
Follicular B cell
Follicular DC
B cell follicle
T cell zone
Medulla
Efferent lymphatic
2–4 weeks
Systemic infection
HIV reservoirs in gut-associated and other lymphoid tissues

The B cell response to HIV

Advanced disease
$CD4^+$ T cell lymphopenia
IL-7
Increased number of immature transitional B cells
Chronic infection
Decreased response to antigens
Naive mature B cell
Decreased class-switch recombination (Nef-mediated)
Paucity of HIV-specific IgA at mucosal sites
Early infection
Immune activation (pro-inflammatory cytokines)
Follicular hyperplasia
Increased turnover and polyclonal activation of B cells
Activated mature B cell
Exhausted memory B cell
Increased in association with HIV viraemia
Short-lived plasmablast
Increased B cell apoptosis and GC destruction
Inadequate $CD4^+$ T cell help
Decreased number of resting memory B cells and splenic marginal zone B cells
Decreased natural immunity to secondary pathogens
Inadequate $CD4^+$ T cell help
Poor antibody response
Hypergammaglobulinaemia
Few high-affinity broadly neutralizing antibodies

Weeks	Months	Years	Several years
• Non-neutralizing • Lack of viral control	• Neutralizing, but limited breadth • Virus acquires escape mutations	• Neutralizing with wider breadth • ~20% of infected individuals	• Affinity matured, broadly neutralizing • ~1% of infected individuals

The T cell response to HIV

Several months
T_{Reg} cell
Galectin 9
TIM3
Suppression of $CD8^+$ T cell response
HIV-specific $CD8^+$ T cell
Cytokines and other soluble factors
TCR
MHC class I
Perforin and granzymes
Viral replication
Perforin pore
HIV-infected $CD4^+$ T cell
Apoptosis
$CD4^+$ T cell depletion and immunodeficiency
T cell-escape mutations in HIV
• First Env and Nef
• Later Gag and Pol
• ↓ MHC class I binding
• ↓ TCR recognition
• ↓ Epitope processing
$CD8^+$ T cell response insufficient to clear infection
Decreased T helper cell function
• Chronic infection
• Repeated T cell activation
Upregulation of inhibitory receptors on $CD8^+$ T cells
LAG3
TIM3
CTLA4
PD1
T cell exhaustion (loss of effector function and proliferative capacity)

Broadly neutralizing HIV-specific antibodies

Name of antibody	Source or approach	Target on HIV	Properties
2G12	B cell immortalization	Carbohydrates on gp120	Unique heavy-chain domain swap
IgG1 b12	Phage-display library	CD4-binding site of gp120	Long heavy-chain CDR3; heavy-chain-dominant binding
2F5 and 4E10	B cell immortalization	Membrane-proximal external region of gp41	Autoreactive; bind host lipids
PG9 and PG16	Large screen; cultured clone	gp120 conformational epitope in variable loops (V1–V2)	Dependent on quaternary structure; long heavy-chain CDR3
VRC01 and NIH45-46	Large screen; single-cell sort	CD4-binding site of gp120	Highly mutated; mimic CD4 binding to gp120
PGT121 and PGT125	Large screen; cultured clone	gp120 V3 carbohydrate-dependent epitope	Diverse, with similarities to 2G12
10E8	Large screen; cultured clone	Membrane-proximal external region of gp41	Binds cell-surface epitopes

Abbreviations

APOBEC3G, apolipoprotein B mRNA editing, catalytic polypeptide-like 3G; CCR5, CC-chemokine receptor 5; CDR3, complementarity-determining region 3; CTLA4, cytotoxic T lymphocyte antigen 4; CYPA, cyclophilin A; DC, dendritic cell; DC-SIGN, DC-specific ICAM3-grabbing non-integrin; GC, germinal centre; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; LAG3, lymphocyte activation gene 3; NK, natural killer; PD1, programmed cell death protein 1; PDC, plasmacytoid DC; SAMHD1, SAM domain- and HD domain-containing protein 1; TCR, T cell receptor; T_{FH} cell, T follicular helper cell; TIM3, T cell immunoglobulin domain- and mucin domain-containing protein 3; TLR7, Toll-like receptor 7; TRAIL, TNF-related apoptosis-inducing ligand; T_{Reg} cell, regulatory T cell; TRIM5, tripartite motif-containing protein 5.

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