NKT CELLS –DOUBLE EDGED SWORD

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NKT CELLS

- **Innate immune cells having features of both T cells and natural killer cells**
- **CD1d-restricted T cells**
- **Co expressing semi-invariant T cell receptor and NK cell markers**

NKT CELL

- **Ability to rapidly secrete large amounts of cytokines upon activation**

  -Allows them to bridge the innate and adaptive immune responses

  -NKT cell activation leads to activation of dendritic cells, NK cells ,$CD4^+$ and $CD8^+$T cells

- **NKT cells develop in cortical thymus and undergo selection by CD1d molecules on cortical thymocytes**

CHARACTERISTICS OF TYPES OF NKT CELLS

	Type 1 NKT	Type 2 NKT	NKT-like
Other names	classical NKT invariant NKT (iNKT) Vα14i NKT (mouse) Vα24i NKT (human)	non-classical NKT diverse NKT	NK1.1$^+$ T cells CD3$^+$ CD56$^+$ T cells
Restriction	CD1d	CD1d	MHC, other?
α-GalCer reactivity	+	-	-
TCR repertoire	Vα14-Jα18: Vβ8.2, 7, 2 (mouse) Vα24-Jα18: Vβ11 (human)	diverse	diverse

- Playing a role in microbial immunity, autoimmunity, tumor immunity & a variety of inflammatory condition

- Potent immuno regulatory function

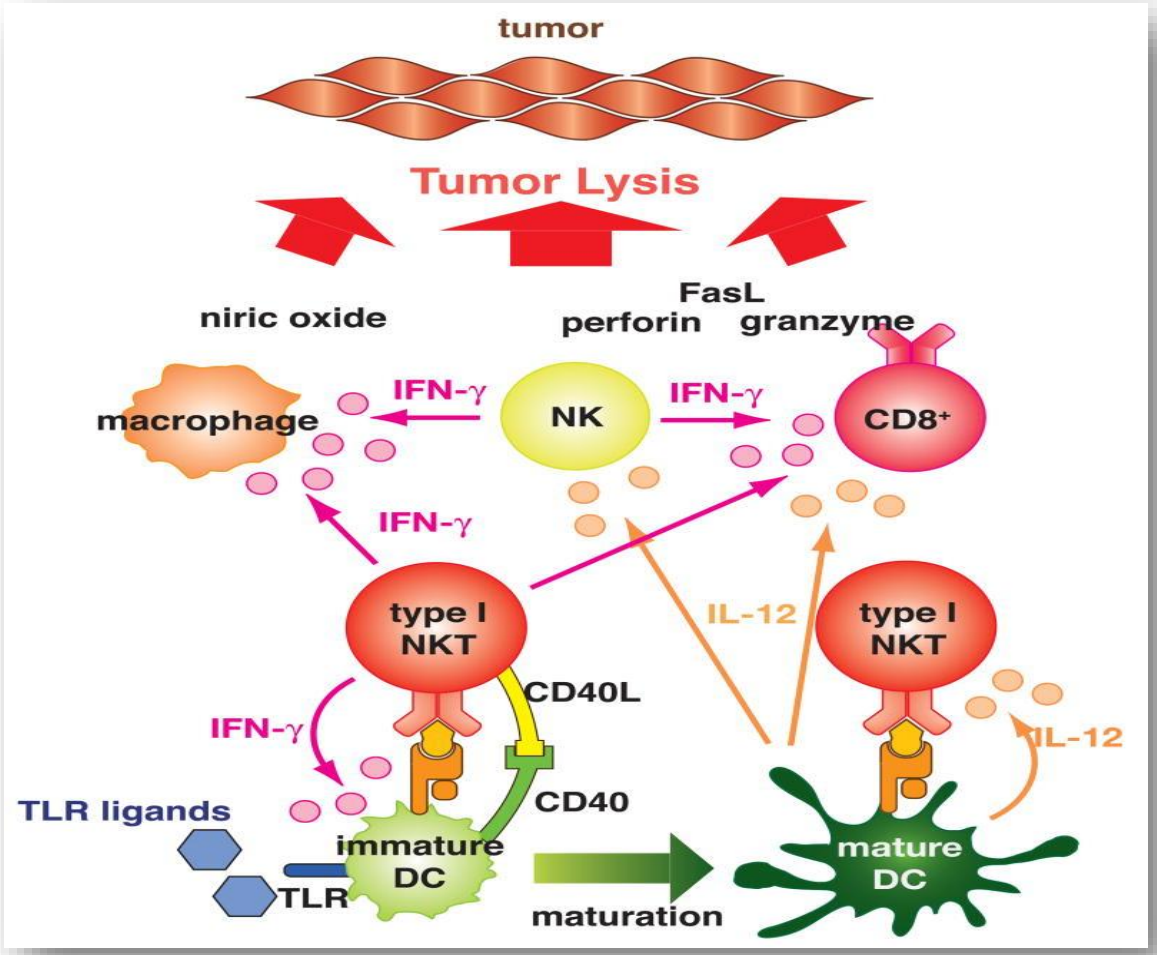
  -can promote cell mediated immunity to tumors and infectious organisms

  - Suppress cell-mediated immunity associated with autoimmune disease and allograft rejection

- NKT cells -development of vaccine , adjuvants &immunotherapies

- **NKT cells - tumor surveillance**

  - ability to activate NK cells upon binding with lipid based tumor antigens



Nature immunology 2000

EXOGENOUS LIGANDS OF NKT CELLS

- **α linked glycosphingolipids from Sphingomons**

  (Kinjo et al.2005)

- **galactosyl diacylglycerols from Borrelia burgdorferi**

- **lipophosphoglycan(LGP) on *Leishmania donovani***

  (Amprey et al.2004)

- **phosphatidylinositol tetramannoside (PIM4) from *Mycobacterium leprae***

  (Fischer et al.2004)

NKT CELLS IN MALARIA

ROLE OF NKT CELLS IN PROTECTIVE IMMUNITY AGAINST MALARIA

- **NKT cells do not have a clear physiological role against pre-erythrocytic stages of malaria**

  (Molano et. al ,2000)

- **NKT cells activated by artificial ligand α-Gal Cer, shown to display an inhibitory effect against the development of liver stages of malaria in vivo by IFN -γ**

  (Romero et. al ,2001)

- **C-glycoside analogue of α-Gal Cer, called α-C-Gal Cer, was shown to display superior anti-plasmodial activity against the liver stages than the parental**

  (Schmieg et .al ,2003)

- **NKT cells has role as helper T cells to assist anti malarial antibody production by B cells**

  (Hansen et.al,2003)

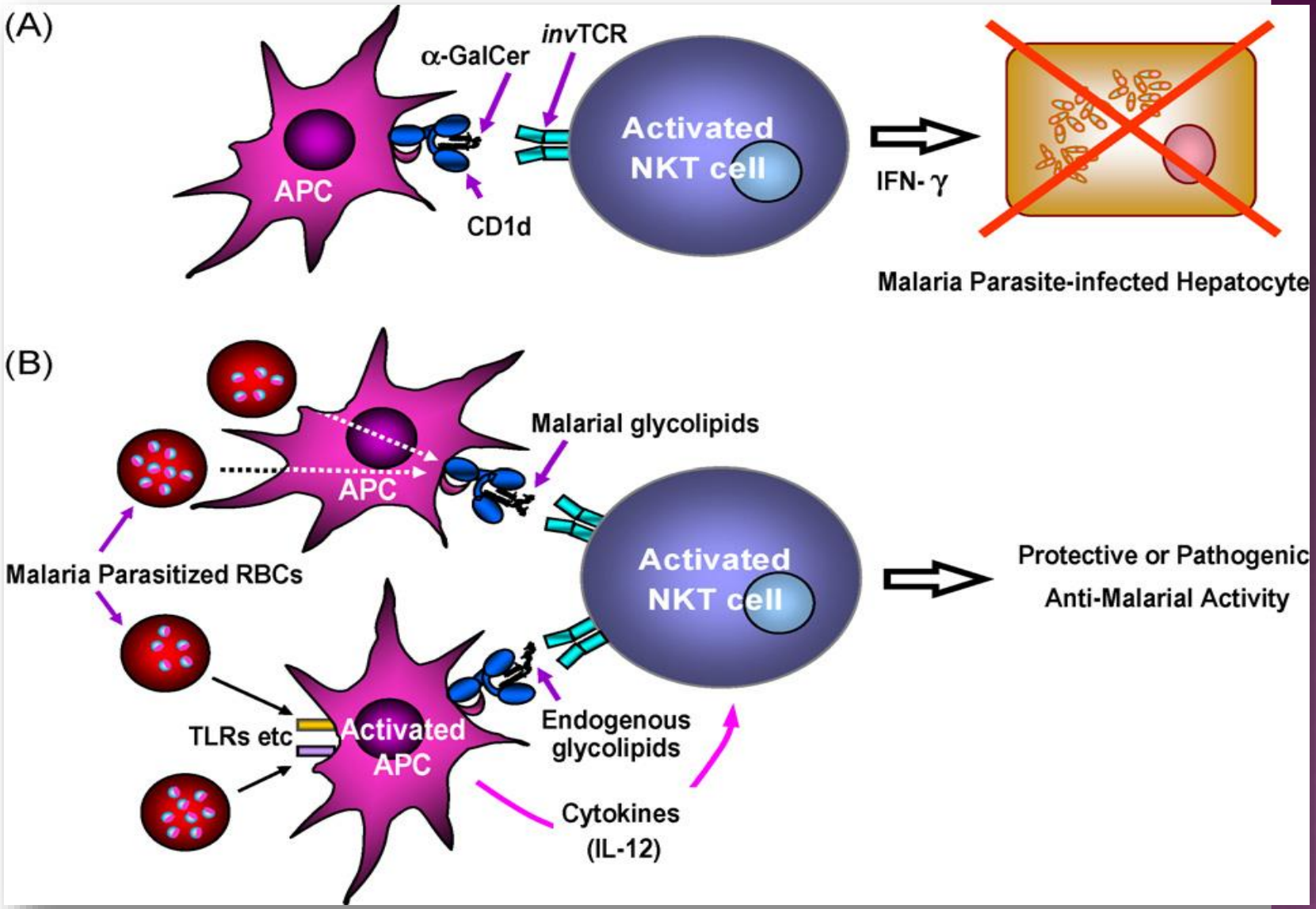
α Gal Cer and its analogue –not adequate to use as therapy

- Malaria parasite resides within hepatocytes for only a brief period of time

- On α-Gal Cer activation NKT cells rapidly become into an anergic state that lasts a 4–6 weeks

(Parekh et al,2005)

- α Gal Cer had to be administered 2 days before sporozoite-induced infection



SEMINARS IN IMMUNOLOGY 2010

PATHOGENIC ROLE OF NKT CELLS AGAINST MALARIA

- **Infection by blood stages of *P .berghei* induces liver injury in mice**

- **DX5$^+$ NKT cells from the liver of CD1d-deficient mice infected with *P .berghei* blood stages cause liver injury by killing normal hepatocytes**

  (Adachi et al,2004)

- **Hepatotoxicity of these hepatic DX5$^+$ NKT cells**

  - MHC-unrestricted fashion

  - does not require TCR engagement

- **CD1d-deficient mice -considerably reduced splenomegaly**

- **CD1d-dependent NKT cells -development of splenomegaly induced by *P .berghei* blood stage infection**

  (Hansen et al,2003)

- **NKT cells influence the overall production of IFN-γ and TNF-α in vivo during malaria infection**

P. berghei ANKA INFECTION

- CD1d restricted NKT cells in BALB/c mice -resistance to cerebral malaria - Th2 response
- NKT cells induce early IFN- γ production and promote pathology in C57BL/6 mice
- Differential expression of molecules encoded by the natural killer complex (NKC) located on chromosome 6

(Hansen et al,2003)

- Partial protection or susceptibility depending on its genotype

- P . berghei K173 does not result in Cerebral malaria

- P. berghei K173 infection - increased plasma gamma interferon (IFN- γ) in spleen and liver at 24 h p.i.

P. berghei ANKA INFECTION

- ***Plasmodium berghei ANKA* –Cerebral malaria on day 6 p.i**
- **An absence of cytokine production at 24 h p.i.**
- **A surge of IFN-γ production at 3 to 4 days p.i.**

(Mitchell et al,2005)

Mice were co infected with both ANKA and K173

- **An early cytokine response, including a burst of IFN- γ at 24 h p.i., similar to animals infected with *P. berghei K*173 alone**
- **Absence of cerebral malaria**

(Mitchell et al,2005)

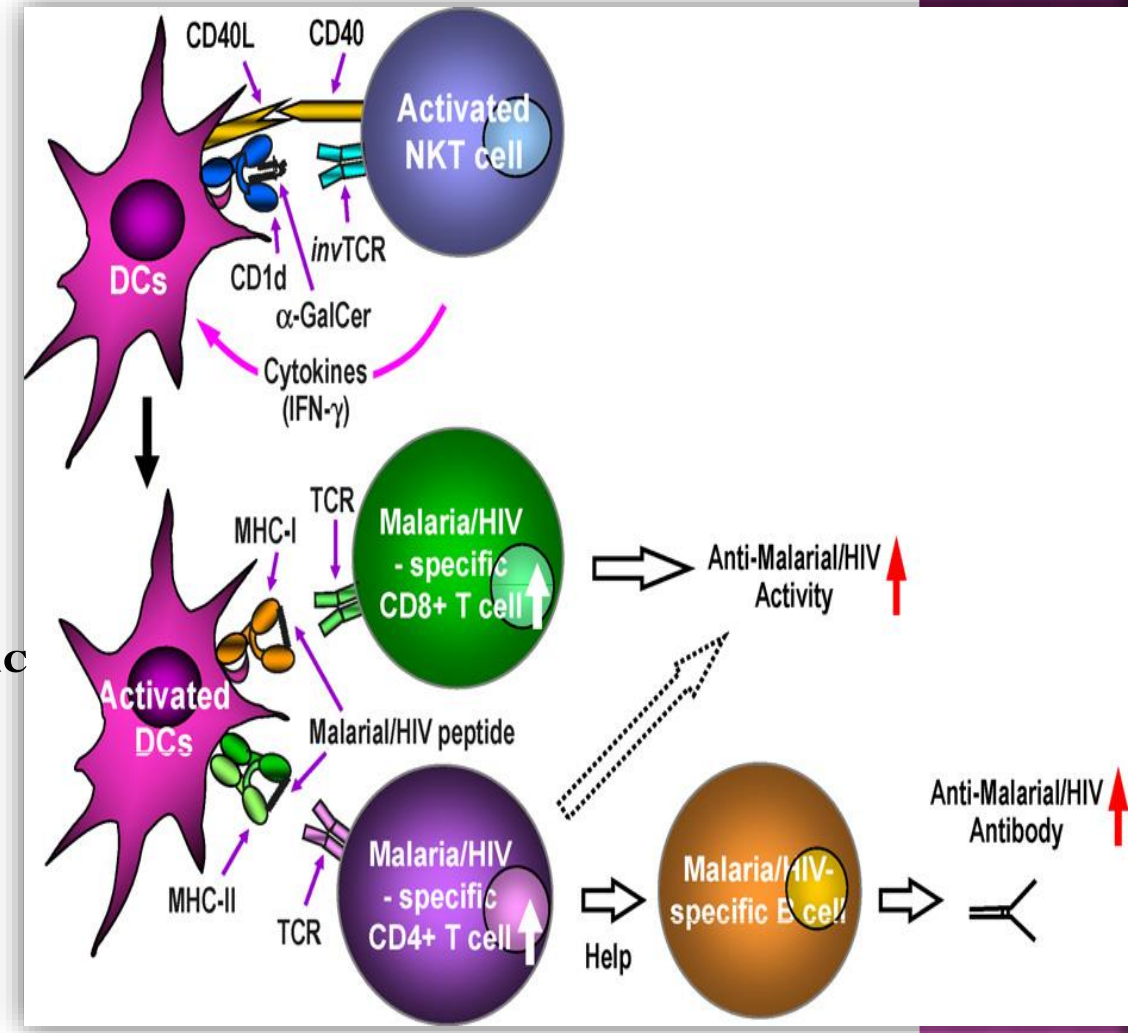
Absence of a regulatory pathway involving IFN-γ and $CD8^+$ T cells in *P. berghei ANKA* infection allows the development of cerebral immunopathology

ROLE OF NKT CELLS IN ELICITING ACQUIRED IMMUNITY AGAINST MALARIA AND HIV

- **Adjuvant effect of α - GalCer was dependent on CD1d/NKT pathway**

- **IFN-γ - the key mediator for the adjuvant effect**

- **CD40-CD40 ligand interaction is also dispensable forα -GalCer to induce activation of dendritic cells**



Seminars in immunology 2010

NKT cells in HIV

Depletion of NKT cells in early HIV infection

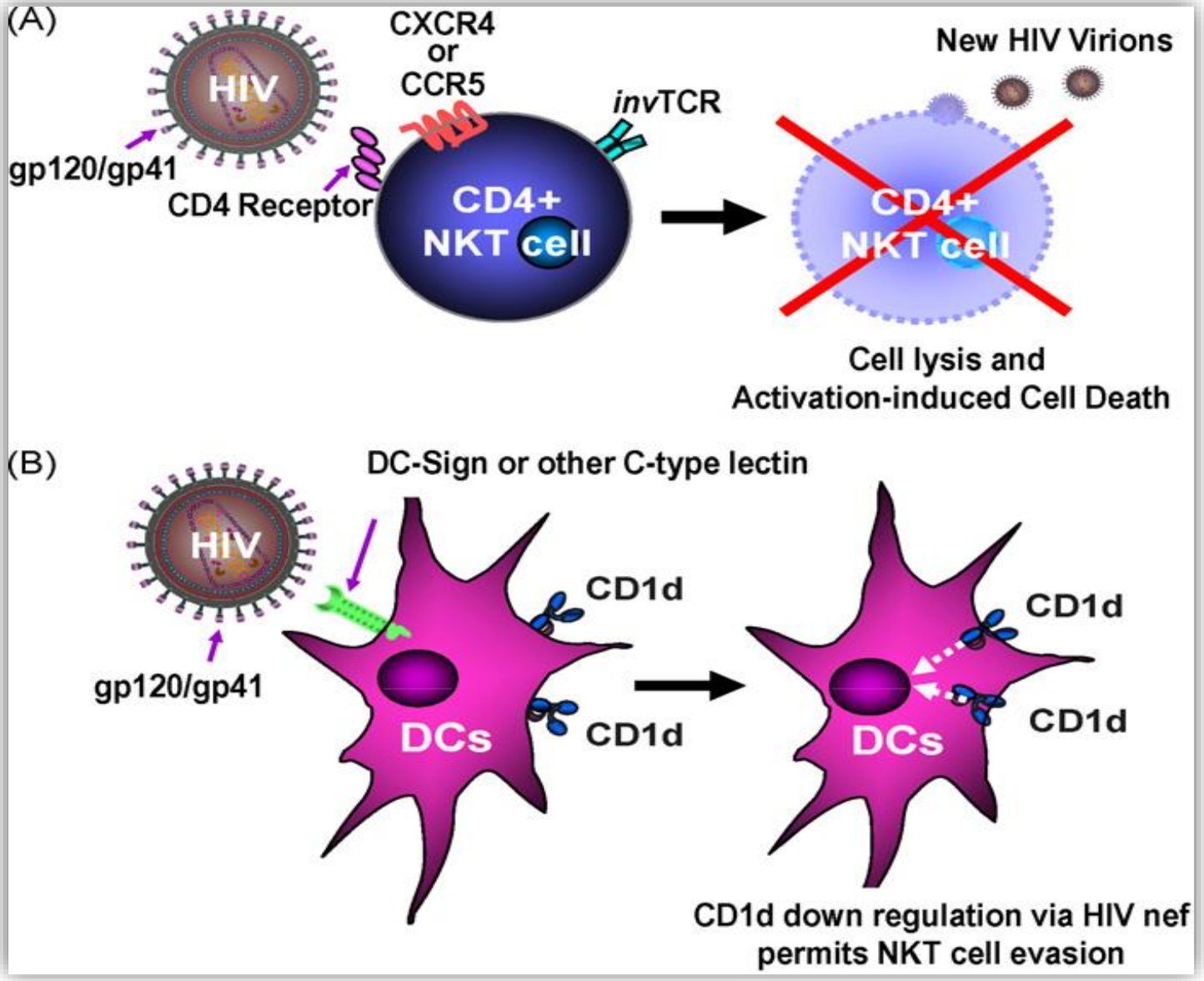
- **HIV causes AIDS primarily via infection of $CD4^+$ T cells, and the CCR5 or CXCR4 co-receptor**
- **Immune dysfunction and $CD4^+$ T cell depletion**
- **A subset of NKT cells express the CD4 receptor on their cell surface-vulnerable to direct infection by HIV**
- **NKT cell depletion in HIV-infected cases was limited to the $CD4^+$ NKT cells**

- **Only a small percentage of NKT cells expressed the $CD4^+$ receptor and the CCR5 co-receptor**

- **Majority expressed the fas molecules**

- **Depletion was largely due to a continuous process of fas-mediated activation-induced cell death, rather than direct infection by HIV**

(van der Vliet et al,2002)



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- Depletion of NKT cells by direct infection and cytolysis

- HIV also evades detection of NKT cells by direct downregulating CD1d cell surface expression on antigen presenting cells

- nef gene of HIV induces downregulation of the MHC-I expression- reducing presentation of HIV antigens to circulating T cells

DIRECT INFECTION OF CD4+ NKT CELLS BY HIV

- **CXCRX4-tropic HIV NL4-3** and **CCR5-tropic HIV BAL** able to infect **NKT cell lines**, in both **resting and active states**

- NKT cell lines were more susceptible to the **CCR5-tropic** strain- **higher levels** of CCR5 expression relative to CXCR4 expression

(Motsinger et al,2002)

- **α-GalCer-activated NKT cells** were more susceptible to HIV infection than resting NKT cells, possibly due to **upregulation of CCR5 expression** after activation

(Motsinger et al,2003)

- Accounts for the rapid depletion of NKT cells observed early in the course of HIV infection

Partial reconstitution of NKT cell levels with HAART

- Circulating NKT cell % in the peripheral blood increased significantly within 3 months of initiation of HAART, similar pattern of $CD4^+$ T cells

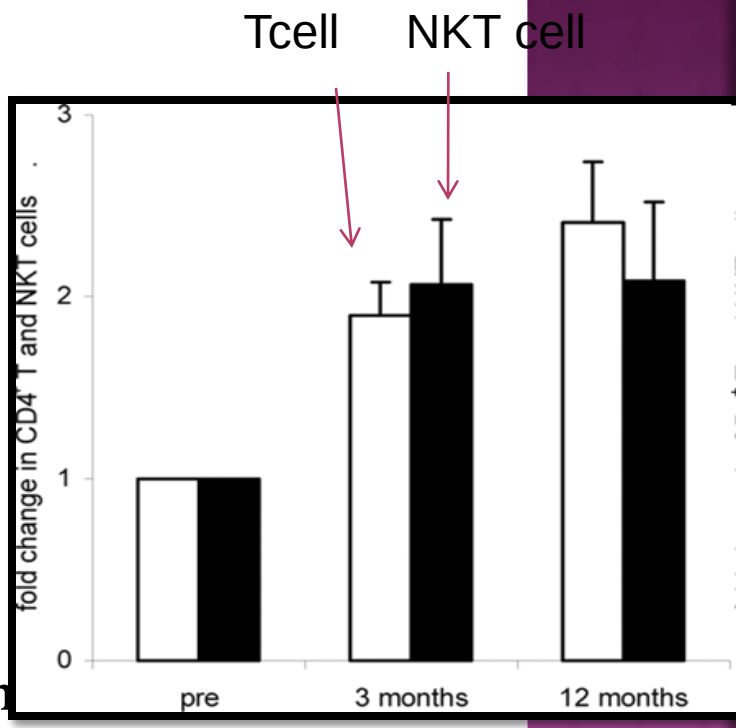
- Early rise of circulating NKT cells in HIV+ patients predominantly **CD4− NKT** cells

  (Van der Vliet et.al,2006)

- These cells were merely **redistributed from NKT cells sequestered in the periphery**

  (Pakker et.al,1998)

- HAART stabilizes the rate of NKT cell depletion *(Vasan et.al,2007)*



Journal of Immunology , 2006

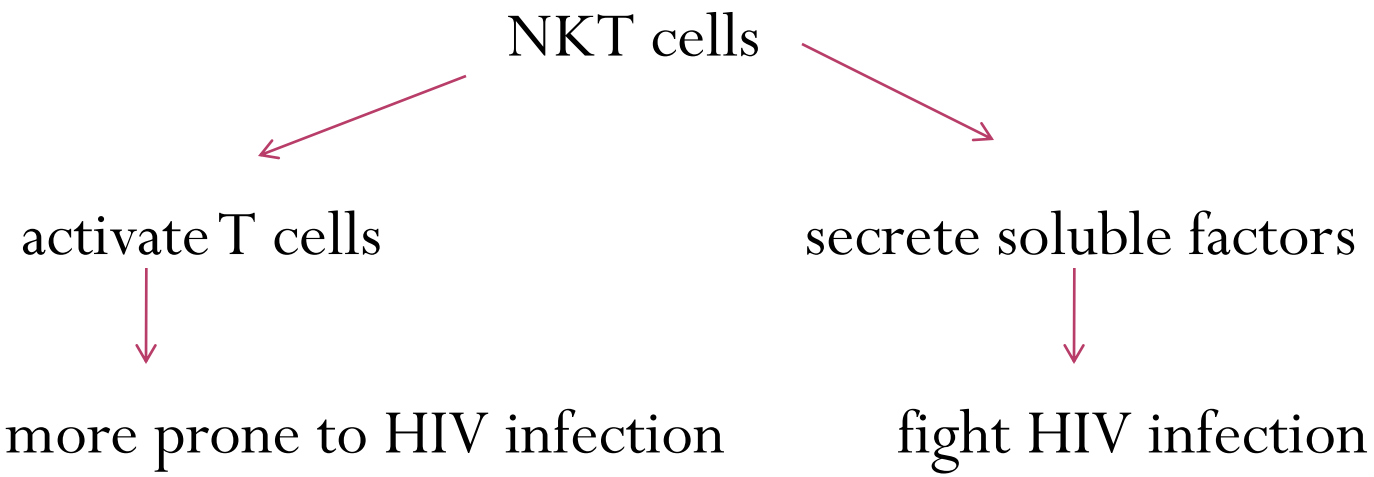
- Administration of IL-2 with HAART
- Expansion of both the $CD4^+$ and $CD4^-$NKT cell compartments *(Moll et.al,2006)*
- Again paralleling the $CD4^+$ T cell reconstitution of both naïve and memory cells

Restoration of NKT cell function by HAART during acute HIV infection

- NKT cell function - impaired during early HIV infection
- Significantly improved by effective treatment with HAART
- Preservation of NKT cell function may be important in HIV-infected individuals
- NKT cells display an **anti-HIV a**ctivity in vitro, mediated by IFN-γ secretion
- Chronic cases of HIV - NKT cells were unable to proliferate or produce IFN-γ in response to stimulation with α-Gal Cer

(Moll et.al,2009)

NKT CELL INTERACTION WITH HIV



- Effector mechanism for this anti-HIV suppression may be multifactorial

- Anti-HIV effect displayed by NKT cells is mediated by IFN- γ

(*Vasan et al.2007*)

- Anti-HIV effect of NKT cells- IFN-γ- invitro

- Combination of cytokine secretion, direct cytolysis, and secondary activation of other immune cells - invivo

CONSEQUENCES OF NKT CELL DEPLETION AND CD1D DOWN REGULATION DURING HIV

- Opportunistic infections

- NKT cells play protective role in host defense in a variety of bacterial, viral, and fungal pathogens -common in AIDS patients

- *Mycobacterium tuberculosis*, a bacterial pathogen causing - chronic respiratory and extra pulmonary disease

  (Snyder et.al,2007)

- *Cryptococcus neoformans* - fatal meningoencephalitis in end-stage AIDS patients

  (Kawakami et.al,2001)

- *Streptococcus pneumoniae* - cause recurrent, invasive, pneumonia

(Kawakami et.al,2003)

- Cytomegalovirus(CMV) - cause chorioretinitis, enterocolitis , pneumonitis, and radiculopathy

(Wesley et.al,2002)

- NKT cell depletion caused by HIV

  - general state of **immunocompromise**

  - eventual susceptibility **to opportunistic infections in AIDS**

NKT CELLS IN VACCINE DEVELOPMENT

- Vaccine against malaria and HIV - Difficult
- Co administration of α Gal Cer with vaccine enhance antigen specific $CD8^+$ T cell response and also improves protective immunity
- Glycolipids have the potential to boost T cell response and antibody response to vaccine antigen

CONCLUSION

- Role in preventing parasitic infection, protection from neoplasia, and fighting other viral, fungal infections
- Anti-HIV effect of NKT cells – non specific, the rapidity and magnitude of the cytokine response ensures that NKT cells are key players in the initial host immune response
- Important to preserve NKT cell number and function during HIV and other infections for improved long-term prognosis
- Glyco lipids that activate NKT cells have therapeutic potential in the treatment of infectious diseases, as well as adjuvants for vaccines against these pathogens


THANK YOU