HIV in Israel, CCR5-Δ32 Mutation and Circumcision

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Some Statistics

Western European country	HIV diagnoses in 2007	Rate per million in 2007	Cumulative total, end 2007	Adult HIV prevalence 2007[3]
Denmark	306	56	5,076	0.2%
Finland	187	35.4	2,263	0.1%
France††	4,075	64.1	26,331	0.4%
Germany	2,752	33.5	31,403	0.1%
Greece	456	40.7	8,680	0.2%
Ireland	362	82.9	4,412	0.2%
Israel	358	50.3	5,358	0.1%
Italy‡	(1,460)*	(74.4)*	(6,322)*	0.4%
Luxembourg	34	70.8	818	0.2%
Netherlands	1,035	63.2	14,666	0.2%
Norway	248	52.7	3,787	0.1%
Portugal	894	84.3	28,851	0.5%
Spain‡‡	1057	76.4	5,785	0.5%
Sweden	425	46.5	8,017	0.1%
Switzerland	765	101.3	30,153	0.6%
United Kingdom	7,734	126.8	94,864	0.2%
Total	21,769	-	282,797	0.3%

HIV in Israel

- By the end of 2007 Israel had had a cumulative total of 5358 HIV cases.
- Among the HIV cases with a known mode of transmission, the majority (61%) have been infected heterosexually, followed by intercourse between men (18%) and intravenous drug use (15%).
- There were 336 new cases of HIV reported in Israel in 2006.
- Almost half of all new HIV cases in 2006 were found in persons originating from a country with a generalized HIV epidemic.

Circumcision and HIV

- Circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%.
- No direct protection against transmission from male to female.
- Recent American study showed that there is negligible protection for men having sex with men.
- WHO recommends circumcision for all males in regions where HIV by heterosexual transmission is endemic.

Mechanism of HIV protection of Circumcision

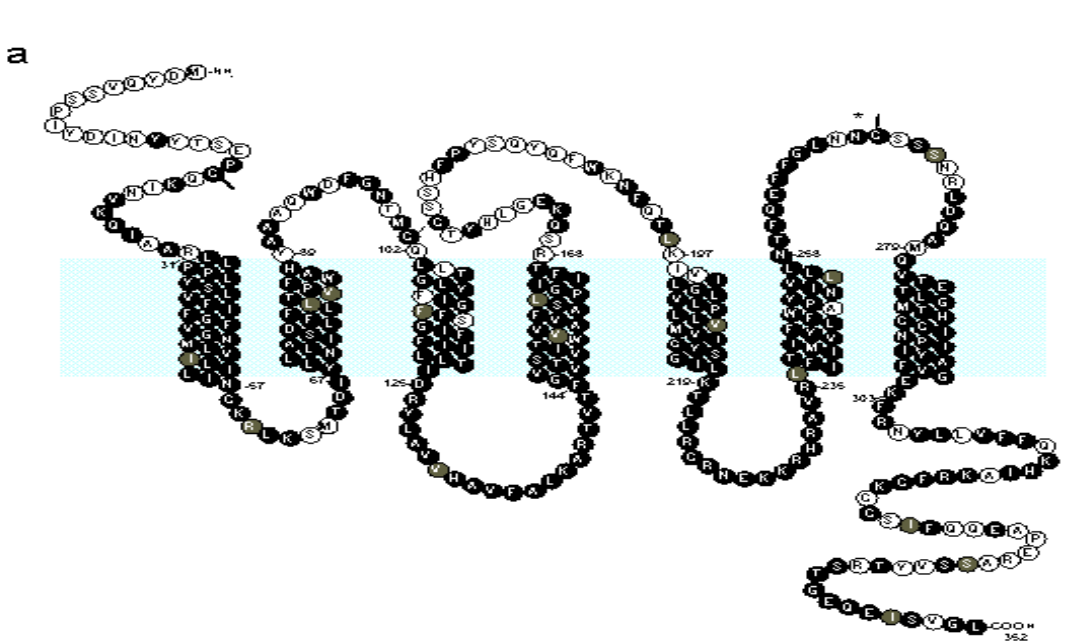
- The internal surface of the foreskin contains a higher density of Langerhans cells than any other tissue in the human body.
- Langerhans cells are most likely the primary site of viral entry (“Szabo and Short”, 2000).

What is CCR5

- CCR5 is a cell membrane protein with 7 transmembrane domains.

- It is a CC chemokine (two adjacent cysteines near the end of the AA chain)

- It's found on T-Cells, Macrophages, Dendritic cells and Microglia.



Function of CCR5

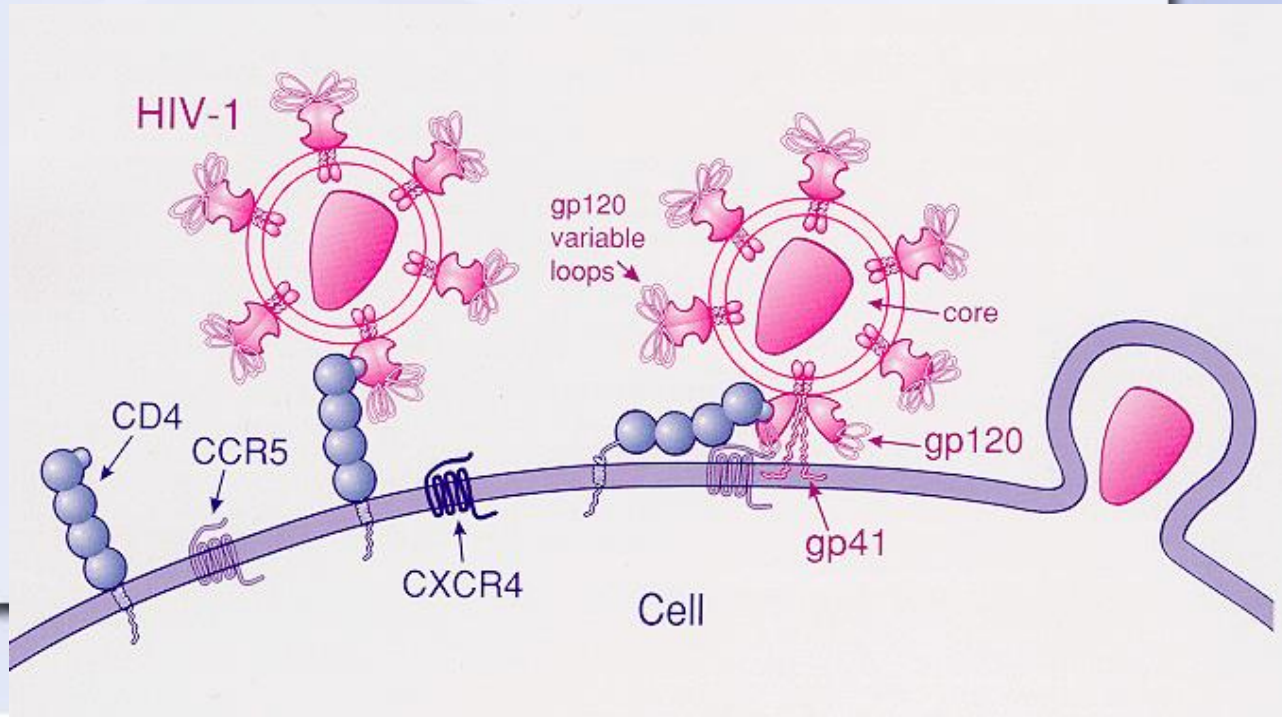
- It's exact role in normal immune function is unclear (plays a role in chemotaxis).

- It's natural ligand is CCL5 (RANTES), which is released from CD8+ T-cells and is known to have a suppressive effect on HIV propagation.

Function of CCR5, cont.

- The HIV-1 virus uses CCR5 as a coreceptor to enter target cells.

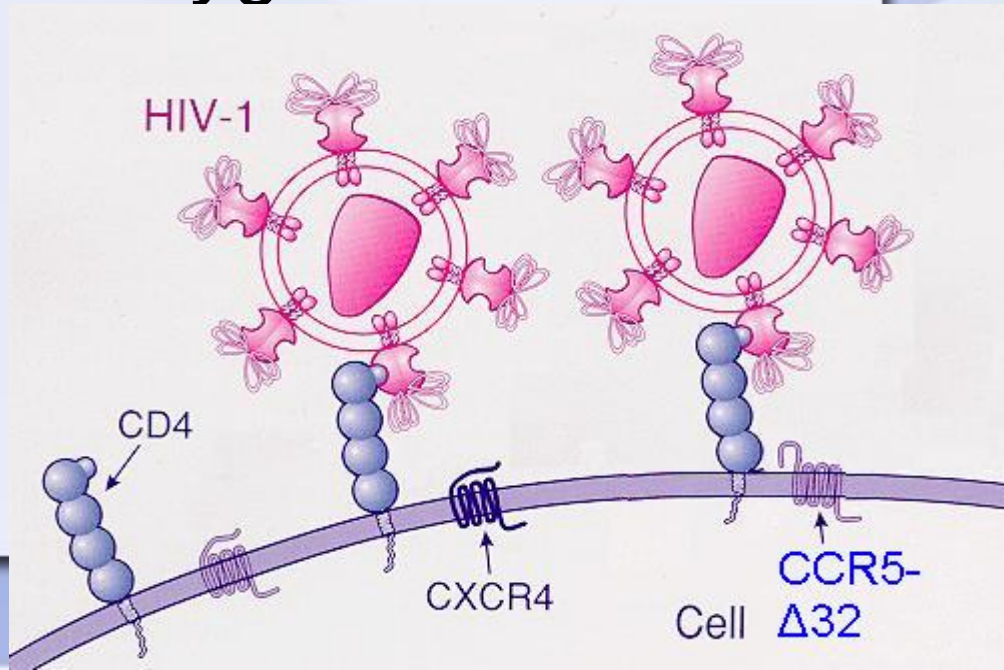
- There are other possible coreceptors, however CCR5 is by far the most important.



CCR5-Δ32

- CCR5-Δ32 is a deletion mutation of the CCR5 gene.

- This mutation results in a nonfunctional receptor, making HIV-1 unable to enter the cell, giving a very strong protection against HIV infection in monozygous individuals.



The beneficial effects of CCR5-Δ32

- Those monozygous for CCR5-Δ32 have a near immunity to HIV-1. Only 12 cases of HIV-1 positive individuals have been described world wide.

- Those heterozygous for CCR5-Δ32 have some level of protection against infection and have an average delay of 2 years in progressing to AIDS, compared to the average HIV infected population.

- One study showed 20% of exposed seronegative individuals had heterozygous CCR5-Δ32 genotype, compared to 7.5% of HIV-1 seropositive and 10% of individuals from the general population.

Prevalence of CCR5-Δ32 in Israel

- About 10% in Ashkenazi Jews.
- About 2,5% in Sephardic Jews.
- About 0,1% in Jews of Ethiopian decent.

CCR5 as a target in Therapy

The CCR5-Δ32 mutation has revealed the CCR5 receptor as one of the most effective targets for HIV therapy.

Entry inhibitors:

Agents that bind to CCR5, effectively blocking it.

- PRO140 (Progenics)
- Vicriviroc (Schering Plough)
- **Maraviroc** (Pfizer)
  - Clinical Trial:426 patients received optimized therapy plus 150 mg maraviroc once daily and 414 patients twice daily. At 48 weeks, 55% of the former and 60% of the latter, achieved a **viral load of less than 400 copies/mL** compared with 26% of those taking placebo; about 44% had a viral load of less than 50 copies/mL. In addition, they had a mean i**ncrease in CD4 cells of 110 cells/µL** compared to 56 cells/µL in the placebo group.

The «Miracle Case»

- November 2009 an article by Dr. Gero Hutter, of Charite Universitatsmedizin Berlin, appeared in the New England Journal of Medicine describing the case of a 42 y.o. leukemia patient with concomitant HIV infection.

- The patient received a bone marrow transplant from a donor monozygous for CCR5-Δ32.

- For 2 years since the transplant the patient has been HIV free. Both on serum analysis and on brain tissue biopsy.

Caveats

- HIV is an extremely adaptable and heterogenous virus and several HIV subtypes can use other coreceptors, and some are able to bind to other regions of CCR5.

- CCR5-Δ32 causes an increased susceptibility to the west nile virus

Other genotypes offering HIV resistance

- CCL3L1
- KIR3DL1 and HLA-B*57 (present in 12% of exposed, but noninfected, vs 2,7% of exposed and infected)

Conclusion

The low prevalence of HIV in Israel can be explained by two factors:

- the extremely high rate of male circumcision
- the relatively high rate of the CCR5-Δ32 mutation

THANK YOU FOR YOUR ATTENTION