

C.77-CD4/CD8 ratio decrease in AIDS

Written by Administrator

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There are no translations available.

C.77-CD4/CD8 ratio decrease in AIDS, explained by a molecular mimicry between African HIV-1 Nef and Notch-1: Nef as a target for vaccine and NF-kB inhibitors (salicylate, resveratrol, curcumin, epigallocatechine-3-gallate).

Guy Mong Ky TRAN^{1,2}, Adrien CAPRANI², Laurent GERBAUD¹

¹ Auvergne University, Hospital Hotel-Dieu, Public Health Department, 63 000 Clermont-Ferrand France(mkg_tran@yahoo.fr).

² Association « Positifs », Paris Cedex 18, France(positifpresident@yahoo.fr).

BACKGROUND

The AIDS hallmark is the simultaneous fall in CD4 and rise in CD8 T lymphocytes. Interestingly, this very pathognomonic but unexplained decrease of CD4/CD8 ratio is also characteristic of a member of the EGF family, Notch-1 function (Fowlkes BJ, 2002). Notch is defined in Drosophila development as inducing a notched wing. Calenda V (1994) found that Nef hampered drastically bone marrow progenitor cells functionality. African HIV-1 NDK strain (Spire B, 1989), which induced a fulminant AIDS killing the patient in only 15 days, decreases dramatically CD4 counts. Nef is the most abundant HIV-1 protein in infected cells (85% of mRNA). Nef is a superantigen, its action is amplified 1,000 times compared to a common antigen.

OBJECTIVE

We found previously Notch-1 in the 3'ORF (Open Reading Frame) or Long Terminal Repeat (LTR) of another retrovirus [Mouse Mammary Tumor Virus (MMTV)] (Tran MKG, Eurocancer, Paris 1998):

MMTV LTR 3'ORF (222-227)□□□ PLPYTG

Notch-1 (repeat 21)□□□□□□□□ PLPYTG

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We prolonged this alignment by using a chimera of Notch-1 (EGF repeats 1, 21, 22, 23, 27, 36) and Notch Drosophila (EGF repeats 22, 30):

MMTV LTR 3'ORF (213-236) PYIYRPTDA PLPYTGRY-DLNFNRW

Notch chimera ██████████PF-YRCTNA PLPYTGRYCDLNINRW

36 |23 |21 |1| 21 |Drosophila22|Dro30|22| 27

As Nef is located also in HIV-1 LTR, we looked for Notch-1 in Nef.

METHODS

Amino Acid (AA) alignment [by manual alignment, associated with Basic Local Alignment Search Tool Protein (BLASTP) on mouse Notch-1] between Epidermal Growth Factor (EGF) family members and Nef (Los Alamos HIV sequences Database, 2002, 2009). The EGF repeats of the following proteins were screened : Notch-1 (mouse, rat, Xenopus) -2, -3, -4 (Int-3), Notch (Drosophila, Leishmania), Lin-12, Slit, Cripto, Delta, Heregulin α , EGF (rat, mouse, guinea pig, human, rabbit, sea urchin), uromodulin (Tamm-Horsfall), TGF α , Cowpox Vaccinia virus, Shope Fibroma virus, Plasmodium Falciparum Pfs 25, factor X (Stuart), factor IX, factor XII, ELAM 121, MEL-14, Fibrillin, LTBP, WI-1 Adhesin, PAS-6/7, Schwanomma SDGF, Epiregulin, β -cellulin, Amphiregulin, HB-EGF, TPA, Urokinase, Protein C, Protein Z, Protein S, LDLR, Thrombomodulin. As I κ B α contains a Notch-like repeat (or Ankyrin repeat outside the EGF repeat), it was also included in the research list.

RESULTS

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Nef COOH-terminus of HIV-1 clade D African strains (from Congo Democratic Republic, Chad, Tanzania, Uganda, South Africa, Kenya), but not from other parts of the world (other clades A, B, C, E, M), was a perfect 100% molecular mimetic of Notch-1 (but not Notch-3 or other EGF family members): They shared a heptapeptide (7 AA) (Nef AA 187-191) SRLAFEH. The homology between Nef (Poon AFY, 2009) (AA 141-206) and Notch chimera (mainly Notch-1 + Notch Leishmania + Notch Drosophila + Notch-like repeat of IκBα) could be prolonged upstream and downstream of SRLAFEH to extend 68 AA long, with 4 His (166, 171, 192, 199), 1 Cys (206) and 1 Trp (143) (very highly significant):

Nef (<i>Poon's</i> number)	141 142 143 K IN 155 156 V S 164 165 166 S 171 174 175 R Q 187 191 192 Q 199
Nef Clade D	FGWCFELVPVDPQEEVEEDTEGETNCLLHPMCOHGMEDPERQVLVWRFNSRLAFEHKARLMHPEF
Notch-1 + <i>Droso</i>	GWLLD QGLS SNQSPPHLGIS QHA L AKPEMAALAGG K SRLAFEH PPPRLS HLQ
Notch Leishmania	FGWS...YR-VPQINP LQQV RWQL QHQ TH AVE-KARQMYH-
Notch-like repeat of IκB-α	QQLTEDGD SFLHLAI I H MEVIR

Characters of Notch *Droso* (=Drosophila) are *italicized*

It included the Nef **164-LL-165** and **174-ED-175** doublets precisely implicated in CD4 down-regulation and the **155-EE-156** in β-COP recruitment (*Benichou S, 1994*).

There is an homology of Nef with the Notch-like Ankyrin repeat of IκB-α.

Another short patch centered on a Cysteine was found between HIV-1 **clade O ANT 70** and **Notch-4 (1)/Notch-2 (25)**, as well as between Nef of SIV Syk and Notch Drosophila (14):

Nef HIV-1 clade O ANT 70

SEPCA PGVG

Notch-4 (EGF repeat 1)	EPCANGGTC
Notch-2 (EGF repeat 25)	SEPCKNGGT
Nef SIV Syk	QPCR-GGF
Notch Drosophila (EGF repeat 14)	QPCRNRGI
Notch Drosophila (EGF repeat 14)	QPCRNRGI

DISCUSSION AND CONCLUSION

This opens new avenues for a vaccine targeted to Nef-Notch specific to Africa, a continent devastated by AIDS and tuberculosis (in South Africa, about 60% HIV-1 infected patients had also tuberculosis). Notch-1 contains an Ankyrin repeat/Lin-12 homologous to I κ B- α , which is phosphorylated by IKK β kinase. Aspirin, an inhibitor of IKK β (Yin MJ, 1998), inhibits HIV-1 in vitro and has been claimed to be efficient against AIDS, but a preliminary clinical trial was stopped prematurely after appearance of some side effects (such as anemia and liver enzyme rise). We present here a biological basis for Aspirin (and Sodium Salicylate) as an anti-IKK β kinase, and hence anti-NF- κ B, namely an anti-NEF. This new mechanism of action revives this option of treatment and initiates a regain of interest on NF- κ B inhibitors as anti-NEF [resveratrol of red wine, EpiGalloCatechine-3-Gallate (EGCG) of green tea, curcumin of Turmeric (associated with pepper for absorption)]. A poster is presented in this ISHEID Conference (Caprani A et al., 2012) about the efficacy and non toxicity of this anti-NEF treatment.

BIBLIOGRAPHY

Benichou S, Bomsel M, Bodéus M, Durand H, Douté M, Letourneur F, Camonis J, Benarous R.

Physical interaction of the HIV-1 Nef protein with beta-COP, a component of non-clathrin-coated vesicles essential for membrane traffic.

J Biol Chem 1994, 269: 30073-6.

Calenda V, Graber P, Delamarter JF, Chermann JC.

Involvement of HIV nef protein in abnormal hematopoiesis in AIDS: In vitro study on bone marrow progenitor cells.

Eur J Haematol. 1994, 52:103-7.

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Fowlkes BJ, Robey EA.

A reassessment of the effect of activated Notch1 on CD4 and CD8 T cell development.

J Immunol. 2002, 169:1817-21.

Poon AFY, Swenson LC, Dong WWY, Deng W, Kosakovsky Pond SL, Brumme ZL, Mullins JI, Richman DD, Harrigan PR and Frost SDW.

Phylogenetic Analysis of Population-Based and Deep Sequencing Data to Identify Coevolving Sites in the nef Gene of HIV-1.

Mol Biol Evol 2010, 27: 819-32.

Spire B, Sire J, Zachar V, Rey F, Barré-Sinoussi F, Galibert F, Hampe A, Chermann JC.

Nucleotide sequence of HIV1-NDK: a highly cytopathic strain of the human immunodeficiency virus.

Gene 1989, 81: 275-84.

Tran MKG, Kirkiacharian S.

MMTV (Mouse Mammary Tumor Virus) 3' orf mimicks the EGF family: EGF, heregulin (c-ErbB2 ligand) , proto-oncogene Notch.

In: Boiron M & Marty M (Eds) Eurocancer 1998. Compte Rendu du XI Congrès, 3-5 Juin 1998. John Libbey Eurotext, Paris: 177, poster 20.

Yin MJ, Yamamoto Y, Gaynor RB.

The anti-inflammatory agents aspirin and salicylate inhibit the activity of I κ B kinase- β .

Nature 1998, 396: 77-80.

HIV-1 Nef

(Poon AFY, Mol Biol Evol 2010, 27: 819-32).

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