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HIV: implication in Burkitt lymphoma

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The risk of Burkitt lymphoma (BL) is increased in HIV-infected patients as compared to general population in Europe and in the US. This effect might be due to immune suppression and low CD4-cell counts associated with the development of AIDS. However, there is also evidence of a direct effect of HIV on B cell proliferation and differentiation, which may account for the development of B cell malignancies. We shall discuss possible mechanisms of implication of HIV in BL with a focus on the role of different viral components (Tat, Nef and gp120 proteins, viral envelope) in the c-myc/IgH translocation characteristic of BL.

Keywords: Burkitt lymphoma, lymphomagenesis, HIV-1.

Introduction. Burkitt lymphoma (BL) in African children is known to be associated with EBV infection. However, this is not always the case with the sporadic cases of BL in adults in other geographical areas [1, 2]. The incidence of sporadic BL is significantly increased in HIV-positive patients [3]. One of the EBV-encoded RNAs (EBER) characteristic of the latent viral cycle could be found only in about 30 % of HIV-related lymphoma cases [2]. Therefore, lymphomagenesis may be caused in these 30 % of cases by reactivation of EBV upon HIV infection, although these data are contested (compare [4], and [5]). At the same time, at least 70 % of cases of HIV-positive BL do not have a direct link to EBV infection.

The relative risk of various NHLs (Non-Hodgkin's lymphomas, to which BL pertain) in HIV-patients is clearly associated with immunodeficiency. Most of the lymphomas develop after the development of AIDS and the risk increases with the increase in viral loads and decrease in CD4-cell counts [6–8]. However, one cannot exclude the role of HIV itself in lymphomagenesis. In this review we are going to discuss mechanisms of HIV-associated BL, and various viral components that could be implicated in oncogenesis.

Molecular mechanisms of lymphomagenesis. The specific genomic trait of BL cells is a translocation of *c-myc* gene to imunnoglobulin gene loci, accompanied with *c-myc* oncogene overexpression [1, 9, 10]. In 80 % of BL cases B lymphocytes exhibit a translocation between the *c-myc* and *IgH* (immunoglobulin heavy chain) genes on chromosomes 8 and 14, respectively. Other variants include translocation between *c-myc* and other immunoglobulin gene loci on chromosomes 2 or 22 (*IgK* and *IgL* genes, respectively) [10]. The translocation is caused by errors in DNA repair via Non-Homologous End Joining (NHEJ). This mechanism joins two ends of broken DNA located in the immediate proximity [10–12]. The translocation partners therefore should be located closely together so that translocation could occur.

In normal naïve B-lymphocytes, *IgH* and *c-myc* loci are colocalized only in 6 % of the nuclei in mouse and humans ([12], Klibi et al., unpublished results). However, 5 min after induction of B cell proliferation with IL-4 admixed with antibodies to IgM and CD40, *c-myc* rapidly relocates from the border of the nucleus to transcription factories, including those with actively expres-

sed *IgH* gene. This causes an about 3-fold increase in *IgH*/*c-myc* colocalization rates [12]. The increased *IgH*/*c-myc* colocalization may consequently increase the translocation rate.

HIV and B cell abnormalities All the viral components that may contribute to B cell activation and the subsequent colocalization of *c-myc* and *IgH* loci might play a role in HIV-associated lymphomagenesis.

HIV infection leads to multiple B cell abnormalities, including hyperactivation, immunoglobulin class switching and HIV-specific B lymphocyte maturation [13–15]. Moreover, there are data on the relation of increased risk of lymphomagenesis with B cell activation upon viral infection [16]. It should be noted that there are other data that argue against such correlation [6].

HIV virions, Tat, and Nef, and possible lymphomagenesis. HIV infects primarily macrophages and T lymphocytes, although infection of some B cell subpopulations is also possible at a very low rate [17]. However, the virus may attach to B cell surface [18, 19]. It is likely that such binding may somehow alter B cell function. For instance, it has been shown that HIV-1 envelope protein Gp-120 decreases human B cell chemotaxis and CD62 ligand expression, and increases CD95-mediated B cell apoptosis in B cells isolated from human tonsils [20].

Another crucial viral component that can greatly influence B cells is the HIV-Tat protein, a small hydrophobic protein that is excreted by virus-infected cells and can penetrate through the membrane of other cell types [21]. Treatment of peripheral blood mononuclear cells with recombinant Tat protein at 12–24 nM (0.15 0.28 mg/ml) up-regulated Fas expression in B cells, which is a sign of B cell activation [22]. Conversely, addition of extracellular Tat at 0.5–1 mg/ml decreased the proliferation of tonsillar B cells stimulated with anti-IgM antibody and IL-4 or anti-IgM and CD40 antibodies [23]. Thus, Tat could be a potent modulator of B cell proliferation, which may lead to B cell malignancies. Consistent with this hypothesis, transgenic mouse lines expressing Tat exhibited increased rates of malignant lymphoma of B-cell origin one year after birth [24]. However, histological features of lymphoma cells of these mice differed from those characteristic of human BL.

Nef protein also released by HIV-infected cells was recently shown to penetrate B cells and to alter B cell response via direct and indirect mechanisms. Swingler et al. presented evidence that HIV-1 Nef induces ferritin secretion from infected macrophages via activation of NF B, which causes B cell activation and hypergammaglobulinemia [25]. Recent work by Xu et al. showed that HIV-infected macrophages were able to connect to B cells via nanotubes, which induces transfer of Nef protein to B cells [26]. It should be noted that soluble Nef was also shown to enter B cells *in vivo* and *in vitro* without any nanotubes [27]. In the same study Nef was shown to suppress CD40-dependent immunoglobulin class switching in B cells, which leads to B cell dysfunction and might influence the likelihood of lymphomagenesis.

Conclusions. The majority of HIV-related Burkitt lymphomas are not associated with EBV infection. HIV was shown to activate B lymphocytes and alter B cell response *in vitro* and *in vivo*. Various viral components, such as viral envelope, Tat and Nef proteins can come in contact with B cells or penetrate them and have been shown to be implicated in B cell activation and misregulation of B cell functions. All these factors may contribute to prolonged relocalization of *c-myc* to transcription factories and, therefore, to the proximity of *IgH* gene, which may cause subsequent *c-myc*/*IgH* translocation followed by B cell immortalization and cancer.

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ВІЛ: зв’язок з лімфомою Беркітта

Резюме

Лімфома Беркітта з високою частотою зустрічається серед ВІЛ-інфікованих пацієнтів порівняно зі здоровими людьми. Така закономірність може бути пов’язана з імуносупресією і значним зменшенням кількості CD4-клітин у людей, хворих на СНІД. Однак є відомості і щодо прямого впливу вірусу на проліферацію та диференціювання В-клітин. Можливі механізми асоціації ВІЛ з лімфомою Беркітта можуть включати як взаємодію самого вірусу з В-клітинами, так і роль різних компонентів віріона і вірусних білків (Tat, Nef, gp120, оболонка вірусу). В міногляді обговорюється вплив ВІЛ і білків ВІЛ на транслокацію c-myc/IgH, характерну для клітин лімфоми Беркітта.

Ключові слова: лімфома Беркітта, утворення лімфом, ВІЛ-1.

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ВИЛ: связь с лимфомой Беркитта

Резюме

Лимфома Беркитта встречается с большей частотой среди ВИЧ-инфицированных пациентов по сравнению со здоровыми людьми. Эта закономерность может быть связана с иммуносупрессией и значительным уменьшением количества CD4-клеток у людей,

больных СПИДом. Однако есть данные и о прямом влиянии вируса на пролиферацию и дифференцировку В-клеток. Возможные механизмы ассоциации ВИЧ с лимфомой Беркитта могут включать в себя как взаимодействие самого вируса с В-клетками, так и роль различных компонентов вириона и вирусных белков (Tat, Nef, gp120, оболочка вируса). В миниобзоре обсуждается влияние ВИЧ и белков ВИЧ на транслокацию c-myc/IgH, характерную для клеток лимфомы Беркитта.

Ключевые слова: лимфома Беркитта, возникновение лимфом, ВИЧ-1.

REFERENCES

1. *Bellan C., Lazzi S., De Falco G., Nyongo A., Giordano A., Leoncini L.* Burkitt's lymphoma: new insights into molecular pathogenesis // J. Clin. Pathol.–2003.–**56**, N 3.–P. 188–192.
2. *Bibas M., Antinori A.* EBV and HIV-related lymphoma // Mediterr. J. Hematol. Infect. Dis.–2009.–**1**, N 2.–e2009032.
3. *Engels E. A., Biggar R. J., Hall H. I., Cross H., Crutchfield A., Finch J. L., Grigg R., Hylton T., Pawlish K. S., McNeel T. S., Goedert J. J.* Cancer risk in people infected with human immunodeficiency virus in the United States // Int. J. Cancer.–2008.–**123**, N 1.–P. 187–194.
4. *Joab I., Triki H., de Saint Martin J., Perricaudet M., Nicolas J. C.* Detection of anti-Epstein-Barr virus trans-activator (ZEBRA) antibodies in sera from patients with human immunodeficiency virus // J. Infect. Dis.–1991.–**163**, N 1.–P. 53–56.
5. *Lennette E. T., Busch M. P., Hecht F. M., Levy J. A.* Potential herpesvirus interaction during HIV type 1 primary infection // AIDS Res. Hum. Retroviruses.–2005.–**21**, N 10.–P. 869–875.
6. *Engels E. A., Pfeiffer R. M., Landgren O., Moore R. D.* Immunologic and virologic predictors of AIDS-related non-Hodgkin lymphoma in the highly active antiretroviral therapy era // J. Acquir. Immune Defic. Syndr.–2010.–**54**, N 1.–P. 78–84.
7. *Guiguet M., Boue F., Cadranel J., Lang J. M., Rosenthal E., Costagliola D.; Clinical Epidemiology Group of the FHDH-ANRS CO4 cohort* Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study // Lancet Oncol.–2009.–**10**, N 12.–P. 1152–1159.
8. *Silverberg M. J., Chao C., Leyden W. A., Xu L., Horberg M. A., Klein D., Towner W. J., Dubrow R., Quesenberry C. P. Jr., Neugebauer R. S., Abrams D. I.* HIV infection, immunodeficiency, viral replication, and the risk of cancer // Cancer Epidemiol. Biomarkers Prev.–2011.–**20**, N 12.–P. 2551–2559.
9. *Grogg K. L., Miller R. F., Dogan A.* HIV infection and lymphoma // J. Clin. Pathol.–2007.–**60**, N12.–P. 1365–1372.
10. *Janz S. Myc* translocations in B cell and plasma cell neoplasms // DNA Repair (Amst).–2006.–**5**, N 9–10.–P. 1213–1224.
11. *Nikiforova M. N., Stringer J. R., Blough R., Medvedovic M., Fagin J. A., Nikiforov Y. E.* Proximity of chromosomal loci that participate in radiation-induced rearrangements in human cells // Science.–2000.–**290**, N 5489.–P. 138–141.
12. *Osborne C. S., Chakalova L., Mitchell J. A., Horton A., Wood A. L., Bolland D. J., Corcoran A. E., Fraser P. Myc* dynamically and preferentially relocates to a transcription factory occupied by *Igh* // PLoS Biol.–2007.–**5**, N 8.– e192.
13. *Moir S., Fauci A. S.* Pathogenic mechanisms of B-lymphocyte dysfunction in HIV disease // J. Allergy Clin. Immunol.–2008.–**122**, N 1.–P. 12–19.
14. *Moir S., Fauci A. S.* B cells in HIV infection and disease // Nat. Rev. Immunol.–2009.–**9**, N 4.–P. 235–245.
15. *Shen X., Tomaras G. D.* Alterations of the B-cell response by HIV-1 replication // Curr. HIV/AIDS Rep.–2011.–**8**, N 1.– P. 23–30.
16. *Grulich A. E., Wan X., Law M. G., Milliken S. T., Lewis C. R., Garsia R. J., Gold J., Finlayson R. J., Cooper D. A., Kaldor J. M.* B-cell stimulation and prolonged immune deficiency are risk factors for non-Hodgkin's lymphoma in people with AIDS // AIDS.–2000.–**14**, N 2.–P. 133–140.
17. *Fritsch L., Marechal V., Schneider V., Barthet C., Rozenbaum W., Moisan-Coppey M., Coppey J., Nicolas J. C.* Production of HIV- 1 by human B cells infected *in vitro*: characterization of an EBV genome-negative B cell line chronically synthetizing a low level of HIV-1 after infection // Virology.–1998.–**244**, N 2.–P. 542–551.
18. *Malaspina A., Moir S., Nickle D. C., Donoghue E. T., Ogwaro K. M., Ehler L. A., Liu S., Mican J. A., Dybul M., Chun T. W., Mullins J. I., Fauci A. S.* Human immunodeficiency virus type 1 bound to B cells: relationship to virus replicating in $CD4^+$ T cells and circulating in plasma // J. Virol.–2002.–**76**, N 17.–P. 8855–8863.
19. *Moir S., Malaspina A., Li Y., Chun T. W., Lowe T., Adelsberger J., Baseler M., Ehler L. A., Liu S., Davey R. T. Jr., Mican J. A., Fauci A. S.* B cells of HIV-1-infected patients bind virions through CD21-complement interactions and transmit infectious virus to activated T cells // J. Exp. Med.–2000.–**192**, N 5.–P. 637–646.
20. *Badr G., Borhis G., Treton D., Moog C., Garraud O., Richard Y.* HIV type 1 glycoprotein 120 inhibits human B cell chemotaxis to CXC chemokine ligand (CXCL) 12, CC chemokine ligand (CCL) 20, and CCL21 // J. Immunol.–2005.–**175**, N 1.–P. 302–310.
21. *Debaisieux S., Rayne F., Yezid H., Beaumelle B.* The Ins and Outs of HIV-1 Tat // Traffic.–2012.–**13**, N 3.–P. 355–363.
22. *Huang L., Li C. J., Pardee A. B.* Human immunodeficiency virus type 1 TAT protein activates B lymphocytes // Biochem. Biophys. Res. Commun.–1997.–**237**, N 2.–P. 461–464.
23. *Lefevre E. A., Krzysiek R., Loret E. P., Galanaud P., Richard Y.* Cutting edge: HIV-1 Tat protein differentially modulates the B cell response of naïve, memory, and germinal center B cells // J. Immunol.–1999.–**163**, N 3.–P. 1119–1122.
24. *Kundu R. K., Sangiorgi F., Wu L.Y., Pattengale P. K., Hinton D. R., Gill P. S., Maxson R.* Expression of the human immunodeficiency virus-Tat gene in lymphoid tissues of transgenic mice is associated with B-cell lymphoma // Blood.–1999.–**94**, N 1.–P. 275–282.
25. *Swingler S., Zhou J., Swingler C., Dauphin A., Greenough T., Jolicoeur P., Stevenson M.* Evidence for a pathogenic determinant in HIV-1 Nef involved in B cell dysfunction in HIV/AIDS // Cell Host Microbe.–2008.–**4**, N 1.–P. 63–76.
26. *Xu W., Santini P. A., Sullivan J. S., He B., Shan M., Ball S. C., Dyer W. B., Ketas T. J., Chadburn A., Cohen-Gould L., Knowles D. M., Chiu A., Sanders R. W., Chen K., Cerutti A.* HIV-1 evades virus-specific IgG2 and IgA responses by targeting systemic and intestinal B cells via long-range intercellular conduits // Nat. Immunol.–2009.–**10**, N 9.–P. 1008–1017.
27. *Qiao X., He B., Chiu A., Knowles D. M., Chadburn A., Cerutti A.* Human immunodeficiency virus 1 Nef suppresses CD40-dependent immunoglobulin class switching in bystander B cells // Nat. Immunol.–2006.–**7**, N 3.–P. 302–310.

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