British Journal of Medicine & Medical Research
8(6): 541-543, 2015, Article no.BJMMR.2015.477
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Latent Viruses, Microcompetition, Transcription Factor Deficiency and the Cause of Acute Lymphoblastic Leukemia

Hanan Polansky[1*] and Adrian Javaherian[1]

[1]The Center for the Biology of Chronic Disease (CBCD), 616 Corporate Way, Suite 2-3665, Valley Cottage, NY. 10989, USA.

Authors' contributions

Both authors contributed equally to this work. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/18095
Editor(s):
(1) C. Cameron Yin, Department of Hematopathology, UT MD Anderson Cancer Center, Houston, TX, USA.
Reviewers:
(1) Anonymous, Unidad De Investigación , México.
(2) Golam Hafiz, Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University Shahbag, Bangladesh.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1118&id=12&aid=9168

Commentary

Received 2nd April 2015
Accepted 18th April 2015
Published 8th May 2015

ABSTRACT

The cause of B-cell Acute Lymphoblastic Leukemia (B-ALL) is unknown. Some studies suggested that the cause might be a deficiency in certain transcription factors due to a genetic deletion. We would like to propose a different event that might cause such deficiency. This event is the presence of certain latent viruses in infected cells. The event and its molecular, cellular and clinical consequences have been described by Hanan Polansky in 2003 in his book on Microcompetition.

Keywords: Microcompetition; transcription factor deficiency; latent virus; B-cell acute lymphoblastic leukemia; B-all; epstein-barr virus; cytomegalovirus.

1. INTRODUCTION

The cause of B-ALL is unknown. Some studies suggested that the cause might be a deficiency in some transcription factors due to a genetic deletion. For instance, Xu et al. [1] discussed PU.1 deletions that lead to B-ALL. Other studies mentioned genetic deletions that code for the transcription factors PAX5 and Ikaros. These studies showed that the resulting deficiencies

**Corresponding author: Email: hpolansky@cbcd.net;*

cause the disease. McClellan et al. [2] also showed the reverse, that ectopic expression of cytokines or transcription factors, specifically C/EBPα or PU.1, recovers the healthy phenotype. We would like to propose a second event that might cause a deficiency in a transcription factor. This event is the presence of certain latent viruses in infected cells. This event has been described by Hanan Polansky in 2003 in his book on Microcompetition [3].

Many viruses include a cis-regulatory element called N-box. When such a virus establishes a latent infection, the viral N-boxes bind the GABP·p300 transcription complex. Since this complex is limiting, the viral N-boxes decrease the availability of the complex to cellular genes. As a result, the cellular genes that are transactivated by the GABP·p300 complex produce fewer proteins and the genes that are suppressed by this complex produce more proteins. The abnormal levels of these cellular proteins cause a disease. Polansky used the term "Microcompetition" to describe the relationship between viral and cellular regulatory elements.

It is interesting that many common viruses that establish a latent infection have strong N-boxes in their promoters/enhancers. They include the Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and the Human Papillomavirus (HPV). In fact, the CMV has the strongest promoter/enhancer known to science. Liu et al. [4] showed that the CMV promoter/enhancer, which includes the N-box, is more than 150-fold stronger than the promoter of the platelet-derived growth factor-b chain (PDGF-b) gene. During latency, an infected cell harbors about 10 copies of the CMV. [5] Multiplying 10 copies of CMV per cell during latency, by a 150-fold stronger promoter/enhancer, suggests that a latent infection with CMV has a similar effect on the PDGF-b promoter and hence, its transcription, as the introduction of 10×150 or 1500 copies of additional PDGF-b genes into the cell. Since PDGF-b is susceptible to microcompetition with CMV, the Microcompetition theory predicts that a latent infection with CMV will cause a decrease in PDGF-b transcription followed by a decrease in the concentration of the PDGF-b protein and ultimately disease [6].

In support of a viral induced transcription factor deficiency, some studies showed that many B-ALL patients are infected with the Epstein-Barr Virus (EBV). For instance, Sehgal et al. [7] showed that 32% of children with B-ALL had evidence of active EBV replication. In another study, Ahmed et al. [8] found that 42.6% of B-ALL cases showed evidence of active EBV infection. Since only some latent viruses are active, it is expected that the percentage of B-ALL cases that harbor a latent EBV is even higher. Other studies showed that EBV infects greater than 90%-95% of the world's adult population, preferentially infecting B lymphocytes [9]. Based on these studies we conclude that it is highly likely that many of the cells that McClellan et al. [2] used in their study harbor a latent EBV infection.

Furthermore, because PAX5 significantly contributes to EBV latency, deletion of PAX5, as observed in a majority of BCR-ABL1+B-ALL cells, results in an increase in EBV genome copy number in infected cells, which subsequently increases microcompetition between the EBV genomes and the cellular genes and contributes to the development of B-ALL [10,11].

GABP and PU.1 compete for binding to regulatory elements [12]. Hence, in infected cells, the ectopic expression of PU.1, described in McClellan et al. [2] releases the GABP·p300 complex from the viral elements. This increases the availability of the complex to cellular genes, which may lead to reprogramming of the cells into the myeloid lineage.

2. CONCLUSION

We believe that the viral-induced transcription factor deficiency is very important. The majority of the world's population harbor a latent viral infection. For instance, more than 90%-95% are infected with the EBV. Seroprevalences of CMV tend to be greater than 70-80% by age 50 [13]. Furthermore, HSV type 1 has an estimated seroprovalence of greater than 90% in many nations [14]. Therefore, most people are at risk for transcription factor deficiency and therefore, at risk for diseases that can be triggered by such deficiency, including cancer. This risk was observed in a study that showed an independent association between seropositivity for CMV and 14-year mortality among adult participants [15].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Xu LS, Sokalsi KM, Hotke K, Christie DA, Zarnett O, Piskorz J, Thillainadesan G, Torchia J, DeKoter RP. Regulation of B cell linker protein transcription by PU.1 and Spi-B in Murine B cell acute lymphoblastic leukemia. J. Immunol. 2012;189(7):3347-54.
2. McClellan JS, Dove C, Gentles AJ, Ryan CE, Majeti R. Reprogramming of primary human Philadelphia chromosome-positive B cell acute lymphoblastic leukemia cells into nonleukemic macrophages. Proc Natl Acad. Sci. U. S. A. 2015;112(13):4074-9.
3. Polansky H. Microcompetition with foreign DNA and the origin of chronic disease. New York: The Center for the Biology of Chronic Disease; 2003.
4. Liu BH, Wang X, Ma YX, Wang S. CMV enhancer/human PDGF-beta promoter for neuron-specific transgene expression. Gene Ther. 2004;11(1):52-60.
5. Slobedman B, Mocarski ES. Quantitative analysis of latent human cytomegalovirus. J. Virol. 1999;73(6):4806-12.
6. Adam GI, Miller SJ, Ulleras E, Franklin GC. Cell-type-specific modulation of PDGF-B regulatory elements via viral enhancer competition: A caveat for the use of reference plasmids in transient transfection assays. Gene. 1996;178(1):25-9.
7. Sehgal S, Mujtaba S, Gupta D, Aggarwal R, Marwaha RK. High incidence of epstein barr virus infection in childhood acute lymphocytic lukemia: A preliminary study. Indian J. Pathol Microbiol. 2010;53(1):63-7.
8. Ahmed HG, Osman SI, Ashankyty IM. Incidence of Epstein-Barr virus in pediatric Leukemia in the Sudan. Clin Lymphoma Myeloma Leuk. 2012;12(2):127-31.
9. Hall LD, Eminger LA, Hesterman KS, Heymann WR. Epstein-barr virus: dermatologic associations and implications: Part I. Mucocutaneous manifestations of Epstein-Barr virus and nonmalignant disorders. J. Am Acad Dermatol. 2015;72(1):1-19.
10. Raver RM, Panfil AR, Hagemeier SR, Kenney SC. The B-cell-specific transcription factor and master regulator pax5 promotes epstein-barr virus latency by negatively regulating the viral immediate early protein BZLF 1. J. Virol. 2013;87(14):8053-63.
11. Arvey A, Tempera I, Tsai K, Chen HS, Tikhmyanova N, Klichinsky M, Leslie C, Lieberman PM. An atlas of the epstein-barr virus transcriptome and epigenome reveals host-virus regulatory interactions. Cell Host Microbe. 2012;12(2):233-45.
12. Rosmarin AG, Caprio DG, Kirsch DG, Handa H, Simkevich CP. GABP and PU.1 compete for binding, yet cooperate to Increase CD18 (β_2 leukocyte integrin) Transcription. J. Biol Chem. 1995; 270(40):23627-33.
13. Reddehase MJ. *Cytomegaloviruses*: From Molecular Pathogenesis to Intervention. Volume 2. United Kingdom: Horizon Scientific Press; 2013.
14. Bernstein DI, Bellamy AR, Hook III EW, Levin MJ, Wald A, Ewell MG, et al. Epidemiology, clinical presentation and antibody response to primary infection with herpes simplex virus type 1 and Type 2 in Young Women. Clin Infect Dis. 2013; 56(3):344-51.
15. Gkrania-Klotsas E, Langenberg C, Sharp SJ, Luben R, Khaw KT, Wareham NJ. Seropositivity and higher immunoglobulin G antibody levels against cytomegalovirus are associated with mortality in the population-based European prospective investigation of cancer-norfolk cohort. Clin Infect Dis. 2013;56(10):1421-7.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=1118&id=12&aid=9168