International Journal of Research in Medical Sciences
Polansky H et al. Int J Res Med Sci. 2015 Jun;3(6):1562-1563
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: 10.18203/2320-6012.ijrms20150193

Commentary

Microcompetition with latent Epstein-Barr virus causes a transcription factor deficiency, under-expression of retinoblastoma, and classic Hodgkin lymphoma

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Received: 26 April 2015
Accepted: 06 May 2015

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Classic Hodgkin Lymphoma (cHL) is characterized by the presence of Hodgkin/Reed-Sternberg (H/RS) cells, the malignant cells of the tumor.[1] H/RS cells show two kinds of changes in their retinoblastoma (pRb) tumor suppressor, inactivation through hyper-phosphorylation of the protein, and low concentration caused by under-expression or over-degradation. This commentary concentrates on the under-expression option.

Some studies showed that a latent infection with the Epstein-Barr Virus (EBV) is associated with a low concentration of the Rb gene.[2] One explanation offered to this low concentration is excessive degradation of the Rb protein.[2,3] We would like to propose another explanation that centers on reduced transcription of the Rb gene. The principles of this explanation have been described by Hanan Polansky in 2003 in his book on microcompetition.[4]

Many viruses have a core binding sequence in their enhancers, termed the N-box, which binds the cellular GABP·p300 transcription complex. Since the complex is limiting, by binding the complex, 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 the 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.

Many common viruses, which establish a latent infection, have a strong N-box in their promoters/enhancers. These viruses 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). It is interesting that the CMV has the strongest promoter/enhancer known to science. In order to estimate the power of the CMV promoter, we will combine the results from a few studies. Liu *et al*. showed that the CMV promoter/enhancer, which includes the N-box, is more than 150-fold stronger than the promoter of the cellular platelet-derived growth factor-b chain (PDGF-b) gene.[5] Slobedman and Mocarski showed that during latency, an infected cell harbors about 10 copies of the CMV.[6] Now, let us multiply 10 copies by 150-fold. We conclude that a latent infection with CMV has a similar effect on the PDGF-b promoter, and hence, its transcription, as an introduction of 10 × 150, or 1500 copies of additional PDGF-b genes into the cell. Adam *et al*. showed that PDGF-b is susceptible to microcompetition with CMV.[7] Therefore, the Microcompetition principle predicts that a latent infection with the CMV causes a decrease in PDGF-b transcription followed by a decrease in the concentration of the PDGF-b protein in the latently infected cell, and ultimately disease.

Since both the Rb gene and the EBV have N-boxes, microcompetition between the cellular and viral cis-regulatory elements down-regulates the transcription of the Rb gene. It is interesting that Al-Salam, *et al*. detected

EBV in 78% of pRb-negative cases. Furthermore, they also observed the opposite relationship, that EBV-negative cases were pRb-positive. The inverse relationship between the presence of EBV copies and Rb expression, mediated through microcompetition between the cellular and viral N-boxes, can explain the observed proliferation of the H/RS cells, and cHL.

We believe that the transcription factor deficiency caused by microcompetition with certain viruses during their latency phase, is a very important event. Since most individuals harbor a latent virus, most people might develop diseases resulting from such deficiency. One of these diseases is Classic Hodgkin Lymphoma.

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Cite this article as: Polansky H, Javaherian A. Microcompetition with latent Epstein-Barr virus causes a transcription factor deficiency, under-expression of retinoblastoma, and classic Hodgkin lymphoma. Int J Res Med Sci 2015;3:1562-3.