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Hanan Polansky*, Adrian Javaherian

The latent cytomegalovirus decreases telomere length by microcompetition

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Abstract: Reduced telomere length has been associated with aging and age-related diseases. Latent infection with the Cytomegalovirus (CMV) induces telomere shortening in the infected cells. Latent CMV infection may cause reduced telomere length via GABP transcription factor deficiency, according to the Microcompetition Theory. Microcompetition and viral-induced transcription factor deficiency is important since most people harbor a latent viral infection.

Keywords: Latent virus; microcompetition; transcription factor; telomere

Reduced telomere length has been associated with aging as well as age-related diseases including cardiovascular disease, diabetes and cognitive decline [1]. Telomeres, stretches of DNA at the ends of chromosomes, provide protection against inappropriate DNA repair, recombination and loss of genetic information after cell division. Van de Berg *et al.* measured the relationship between telomere length in T cells and CMV infection [2]. They report that one year post primary CMV infection, that is during the latent phase, the cells exhibited shorter telomeres. We would like to propose an explanation for the observed relationship between latent CMV infection and reduced telomere length. The explanation is based on the theory presented by Hanan Polansky in 2003 in his book on Microcompetition [3].

Many viruses contain an N-box, which is a core binding sequence found in their promoters/enhancers. After establishing a latent infection, the viral N-boxes bind the cellular 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 express abnormal levels of their proteins. Those that are stimulated by the GABP•p300 complex produce fewer proteins, and those 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 that establish latent infections 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 CMV has the strongest promoter/enhancer of these viruses. In order to estimate the strength 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 [4]. Slobedman and Mocarski showed that during latency, an infected cell harbors about 10 copies of CMV [5]. Now, let us multiply 10 copies by 150-fold. 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. Adam et al. showed that PDGF-b is susceptible to microcompetition with CMV [6]. Therefore, the Microcompetition theory suggests that a latent infection with CMV causes a decrease in PDGF-b transcription followed by a decrease

***Corresponding author: Hanan Polansky,** The Center for the Biology of Chronic Disease (CBCD), 616 Corporate Way, Suite 2-3665, Valley Cottage, NY 10989, USA, Tel: 585-250-9999, E-mail: hpolansky@cbcd.net
Adrian Javaherian, The Center for the Biology of Chronic Disease (CBCD), Valley Cottage, NY 10989, USA

in the concentration of the PDGF-b protein in the latently infected cell, and ultimately disease.

Yu *et al.* reported that GABP directly regulates genes involved in telomere maintenance [7]. Specifically, they determined the telomere repeat binding factor 2 (Terf2) gene to be a GABP-activated direct target gene. Terf2 belongs to a complex of six telomere-associated proteins, termed shelterin, which functions to protect chromosome ends from the DNA damage response (DDR) and to control telomere maintenance by telomerase.[8] Microcompetition with CMV decreases the availability of GABP to Terf2. This GABP transcription factor deficiency causes a downregulation of Terf2 expression, abnormal telomere maintenance, and a reduction in telomere length.

A number of studies have reported an association between short telomeres and increased risk for vascular diseases. Spyridopoulos *et al.* mention that individuals with shorter telomeres in leukocytes carry a higher risk for dying of cardiovascular disease [9]. A study by Van der Harst *et al.* that showed that telomere length is shorter in patients with congestive heart failure. Spyridopoulos *et al.* reported that the most pronounced degree of telomere shortening was in their CMV-seropositive coronary heart disease (CHD) patients. Furthermore, many research studies also suggest that shortened telomeres are associated with diabetes [10]. CMV infection is also associated with an increased risk for CHD [11]. Mendy *et al.* reported that CMV infection increased the risk of mortality from diabetes [12]. It is also interesting that in his book, Polansky explains how microcompetition between a latent virus, such as CMV, and certain cellular genes, could cause most major diseases. These genes include the tissue factor (TF), CD18, and CD49d, which are suppressed by GABP. According to the theory, microcompetition between CMV and these genes for GABP, increases their transcription, and increases the risk of atherosclerosis, stroke, and autoimmune diseases, including diabetes.

In their study, van de Berg *et al.* reported a correlation between T cell telomere length and T cell differentiation after infection with CMV, proposing an indirect causal relationship between latent CMV infection and the shortening of telomere length. We believe there is a direct causal relationship between latent CMV infection and reduced telomere length via GABP transcription factor deficiency, according to the Microcompetition Theory. Furthermore, we believe that microcompetition and viral-induced transcription factor deficiency is important since most people harbor a latent viral infection.

For instance, more than 90%-95% of people are infected with the EBV [13]. Seroprevalence of CMV is greater than 70-80% by the age of 50 [14]. HSV type 1 has an estimated seroprovalence of greater than 90% in many nations [15]. Therefore, most people struggle with microcompetition, and are at risk for a transcription factor deficiency, and the diseases that are triggered by such deficiency, including heart disease and autoimmune disease.

Conflict of interest statement: Authors state no conflict of interest.

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