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Commentary

How can the latent cytomegalovirus cause an increase in all-cause mortality? An answer based on the microcompetition model

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Many studies showed the existence of a positive association between cytomegalovirus (CMV) seropositivity and all-cause mortality. In this paper, we use the microcompetition model to explain how the latent CMV sequesters the limiting GABP·p300/CBP transcription complex, which causes abnormal cellular gene expression, a chronic disease and mortality. Since most people harbour the latent CMV, we urge further research on this topic.

The presence of immunoglobulin G (IgG) antibodies against a particular virus indicates that the virus is in the latent phase [1]. IgG antibodies against the cytomegalovirus (CMV) are found in approximately 60% of adults in developed countries, and virtually 100% of adults in developing countries. Gkrania-Klotsas *et al.* [2] showed that individuals with CMV seropositivity have higher all-cause mortality compared with uninfected individuals. They also showed that an increase in the concentration of the CMV IgG antibodies increases all-cause mortality in infected individuals. Mathei *et al.* [3], in a later study, report that a positive CMV serostatus is not linked to an increased risk of all-cause mortality in their elderly cohort, which they explained is probably due to a survival effect. Rather, they observed that higher anti-CMV IgG titre was correlated with higher all-cause mortality. Studies [4–6] showed that higher copy number of the virus during the latent phase is correlated with higher IgG titre. Therefore, the observation of Mathei *et al.* [3] suggests that higher viral copy number during latency is associated with higher all-cause mortality. In this paper, we will use the microcompetition model to explain this association. This model was introduced in the book *Microcompetition with Foreign DNA and the Origin of Chronic Disease* [7].

Many viruses consist of an N-box, which is a core binding sequence found in their promoters/enhancers. After establishing a latent infection, the viral N-boxes bind and sequester the limiting GABP·p300/CBP transcription complex. Since the complex is limiting, the viral N-boxes decrease the availability of the complex to cellular genes. As a result, the cellular genes express an abnormal level of their protein. Those that are transactivated by the GABP·p300/CBP complex produce fewer proteins, and those that are transsuppressed by the complex produce more proteins. The abnormal levels of these cellular proteins cause a disease. Recently, the microcompetition model was used to explain how common latent viruses cause diseases, such as breast cancer [8], classic Hodgkin lymphoma [9], B-cell acute lymphoblastic leukemia (B-ALL) [10], Parkinson disease [11] and Alzheimer's disease (data not shown).

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), CMV, herpes simplex virus 1 (HSV-1), HIV and human T-cell lymphotropic virus (HTLV). It is interesting that 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.* [12] showed that the CMV promoter/enhancer, which includes the N-box, is more than 150-fold more powerful than the promoter of the cellular platelet-derived growth factor-b chain (PDGF-b) gene. Slobedman and Mocarski [13] showed that during latency, an infected cell harbours about 10 copies of the CMV. 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 the introduction of 10×150, or 1,500 copies of additional PDGF-b genes into the cell. Adam *et al.* [14] showed that PDGF-b is susceptible to microcompetition with CMV. Therefore, the microcompetition theory suggests

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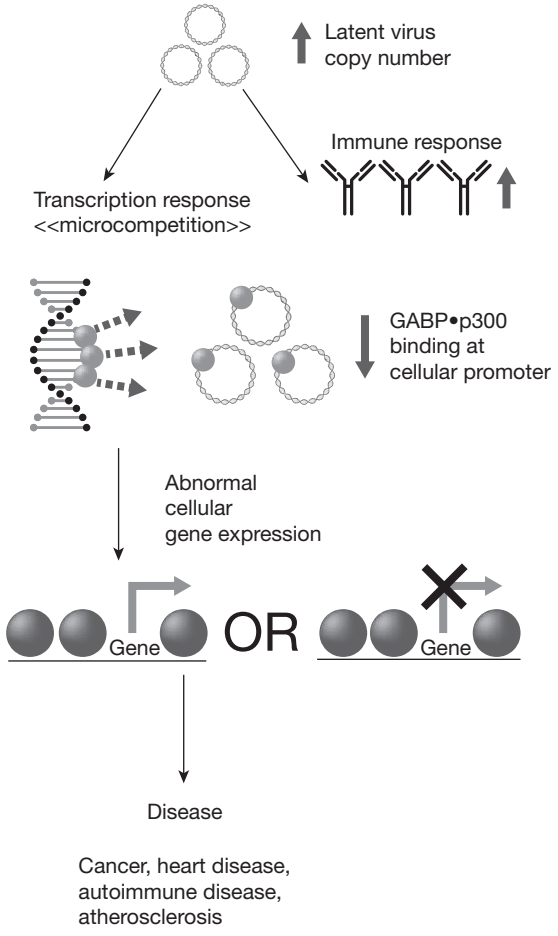
Figure 1. The microcompetition model: how latent viruses sequester GABP·p300 away from cellular genes and cause disease



that a latent infection with 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.

In his book, Polansky [7] explains how microcompetition between a latent virus, such as CMV, and certain cellular genes, can 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, such as lupus, diabetes and psoriasis. In contrast, the retinoblastoma (Rb) and BRCA1 genes are transactivated by the GABP transcription factor. Therefore, microcompetition between CMV and these genes for GABP, decreases their transcription. Since Rb and BRCA1 are tumour suppressors, the decrease in their transcription increases the risk of cancer.

The evidence that CMV is associated with increased risk of major diseases, such as cardiovascular disease (CVD), cancer, physical impairment and cognitive decline, and mortality is mounting. Simanek *et al.* [15] reported the highest hazard ratio (HR) for all-cause and CVD-related mortality among people who were both CMV seropositive and had high inflammatory marker C-reactive protein (CRP) levels (1.60 and 1.71, respectively). In another study, Wang *et al.* [16] determined the effect of latent CMV infection on incident frailty and mortality in immunocompetent older women and reported an increased prevalence of frailty with higher CMV IgG concentrations (5.6% among seronegative individuals and 18.4% among those in the highest quartile of CMV antibody concentration). Nikitskaya *et al.* [17] reported an increase in CMV levels in patients with acute coronary syndrome and stable coronary artery disease compared with the healthy control with a correlation as well to high-sensitivity CRP levels. Heybar *et al.* [18] found that the presence of CMV DNA in the aorta is over threefold more prevalent in atherosclerosis patients. Type 2 diabetes is also associated with CMV seropositivity [19]. Finally, Lepiller *et al.* [20] reported a significant increase in human cytomegalovirus (HCMV) seroprevalence in the group consisting of adult patients with hepatocellular carcinoma (HCC) and cirrhosis compared to the group of adult patients with cirrhosis but no HCC, and the group of patients with neither HCC nor cirrhosis (74% versus 54% and 57%, respectively).

This evidence promoted many scientists to suggest underlying mechanisms. Some suggested that social deprivation or inflammation might cause the observed relationships. However, Gkrania-Klotsas *et al.* [2] reported that both conditions do not contribute to the association between CMV and mortality. Another explanation centred on the negative effect of CMV on telomere length. This effect was observed by van de Berg *et al.* [21], and was mentioned in Gkrania-Klotsas *et al.* [2]. It is interesting that a substantial portion of genes involved in telomere maintenance are upregulated by GABP [22], and therefore are susceptible to microcompetition. For example, Terf2, which is involved in telomere maintenance, is transactivated by GABP. Hence, microcompetition with CMV decreases the concentration of GABP bound to Terf2, decreases its transcription, and ultimately decreases telomere length [23].

However, with latent CMV being so prevalent, why do only some develop chronic diseases? The answer centres on the viral copy number. The higher the number of the CMV genomes during latency, the stronger is the sequestering effect of the viral N-boxes on cellular gene transcription. Only a high enough viral copy number will cause over time the development of a disease. In support of this idea, Zuo *et al.* [24] found that the

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copy number of the EBV, another virus with an N-box, correlates with the clinical course of cancer.

The author believes that the sequestering effect of the viral N-boxes during latency on cellular gene transcription is important. Most people harbour a latent viral infection. For instance, more than 90–95% are infected with EBV. Seroprevalence of CMV is greater than 70–80% by the age of 50 [25]. HSV type 1 has an estimated seroprevalence of greater than 90% in many nations [26]. Therefore, most people are at risk of suffering from abnormal cellular gene expression, and the diseases caused by this sequestering effect.

Disclosure statement

The author declares no competing interests.

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