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Everything you Always Wanted to Know about the Biothermodynamic Background of Herpes Simplex Virus Type 1 – Host Interaction

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Abstract: Herpes simplex virus type 1 (HSV-1) is among the most widely spread viruses on the planet. However, the rate of binding to the receptor is not among the greatest ones. Gibbs energy of binding, which represents the driving force for antigen-receptor binding, of HSV-1 is less negative than can be expected. Furthermore, the Gibbs energy of biosynthesis of HSV-1 is among the most negative in nature. This implies high rate of multiplication of HSV-1. Obviously, HSV-1 uses specific strategy in virus-host interaction. While most other viruses increase infectivity through a high rate of antigen-receptor binding and cell entry/ highly negative Gibbs energy of binding, HSV-1 uses another strategy. It is related to a relatively slow reaction of antigen-receptor binding, which is followed by a higher rate of multiplication, which is a consequence of a highly negative Gibbs energy of biosynthesis. We can conclude empirically that both strategies are successful.

Keywords: Herpes simplex virus type 1 (HSV-1); antigen-receptor binding; equilibrium constant; Gibbs energy of binding; biothermodynamics

1. Introduction

Herpes virus is important due to its prevalence. It is the third most widely spread virus in the world population [Chayavichitsilp et al., 2009]. Herpes simplex virus type 1 (HSV-1) contains DNA, surrounded by an icosahedral protein to form a nucleocapsid [Mettenleiter et al., 2006]. The nucleocapsid is surrounded by a lipid envelope [Mettenleiter et al., 2006]. Herpes virions are amongst the most complex virus particles: they comprise in excess of thirty virally encoded proteins, and also contain cellular components [Mettenleiter et al., 2006].

Herpes virus, like other viruses represents a biological, chemical and thermodynamic open system [von Bertalanffy, 1950, 1971; Degueldre, 2021; Şimşek et al., 2021; Gale, 2018, 2019; Popovic and Minceva, 2020b; Popovic, 2018a, 2018b]. It is characterized by specific empirical formula and thermodynamic properties [Popovic, 2017]. Thus, it is important to know thermodynamic parameters that influence virus-host interactions [Mahmoudabadi et al., 2017; Head et al., 2022; Lucia et al., 2021, 2020a].

HSV-1 attaches to a specific receptor on the host cell's membrane surface. After attachment of the HSV-1 antigen to the host cell receptor, the envelope of the virus particle fuses with the host cell membrane, releasing the nucleocapsid into the host cell's cytoplasm [Riedel et al., 2019; Ojala et al., 2000]. The nucleocapsid travels to the cell's nucleus, where it attaches and releases the viral DNA directly into the nucleus [Riedel et al., 2019; Ojala et al., 2000]. The viral DNA is transcribed and viral proteins are expressed in steps: the immediate-early α, early β, and late γ proteins [Riedel et al., 2019]. The virions mature through budding of the nucleocapsids through an altered inner nuclear membrane, giving them an envelope [Riedel et al., 2019]. The virus exits the cell in the process of exocytosis [Liu et al, 2020].

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The binding of the virus antigen to the host cell receptor represents a chemical reaction, similar to protein-ligand interactions [Du et al., 2016; Popovic and Popovic, 2022]. HSV-1 has evolved an entry mechanism, which uses a receptor-binding protein to activate the membrane fusion process [Krummenacher et al., 2005]. This process also involves other glycoproteins [Krummenacher et al., 2005]. The gD protein of HSV-1 binds to either the HVEM receptor or Nectin-1, and is essential for virus entry into the host cell [Krummenacher et al., 2005]. An HSV-1 mutant without the gD protein is unable to enter into host cells [Krummenacher et al., 2005]. However, the mutant HSV-1 is able to enter into host cells in the presence gD306, a soluble version of gD (with residues 1-306) [Krummenacher et al., 2005; Cocchi et al, 2004]. This means that the gD also takes part in an entry step that differs from virus–cell attachment [Krummenacher et al., 2005; Cocchi et al, 2004]. The driving force for most chemical reactions is Gibbs energy [Demirel, 2014; Balmer, 2010; Atkins and de Paula, 2011, 2014]. Gibbs energy of binding is the driving force for antigen-receptor binding [Gale, 2022, 2021, 2020; Popovic and Popovic, 2022; Popovic, 2022a, 2022b, 2022c, 2022d, 2022e].

After entering the host cell, the nucleic acid is released into the nucleus and undergoes replication, transcription, translation and self-assembly [Riedel et al., 2019]. Replication, transcription and translation represent chemical reactions of biosynthesis of viral nucleic acids and proteins [Pinheiro et al., 2008; Lee et al., 2020; Johansson and Dixon, 2013; Dodd et al., 2020]. The nucleotides are polymerized into nucleic acids [Pinheiro et al., 2008; Johansson and Dixon, 2013; Dodd et al., 2020], while amino acids are polymerized into capsid proteins [Lee et al., 2020]. The driving force for the polymerization reaction is Gibbs energy of biosynthesis [Popovic and Minceva, 2020a; von Stockar, 2013a, 2013b; von Stockar and Liu, 1999]. Thus, to fully understand the virus-host interaction at the membrane and in the cytoplasm, it is necessary to know both Gibbs energies of binding and growth respectively. Gibbs energy of biosynthesis for HSV-1 has been reported in [Popovic and Minceva, 2020a]. Thermodynamic properties of other viruses are available in the literature [Popovic, 2022f, 2022g, 2022h]. Using phenomenological equations, which relate the rate of biosynthesis of virus particles with its driving force – Gibbs energy of biosynthesis, it is possible to estimate the kinetics of virus multiplication and compare it to other viruses [Popovic, 2022b].

The goal of this paper is to calculate the binding equilibrium constant and Gibbs energy of binding for Herpes simplex virus type 1 (HSV-1). The calculated values of Gibbs energy of binding will be compared to those of other viruses, to make a conclusion on the strategy used by HSV-1 in virus host interactions.

2. Methods

Antigen-receptor binding is a chemical reaction similar to protein ligand binding [Du et al., 2016; Popovic and Popovic, 2022]. It has the general form

$$(An) + (Re) = (An\text{-}Re) \tag{1}$$

where (An) is the virus antigen, (Re) the host cell receptor and (An-Re) the antigen-receptor complex [Du et al., 2016; Popovic and Popovic, 2022]. The antigen-receptor binding reaction is characterized by the dissociation equilibrium constant, K_d, defined as

$$K_d = \frac{[An][Re]}{[An - Re]} \tag{2}$$

where [An] is the concentration of the free virus antigen, [Re] the concentration of the free host receptor and [An-Re] the concentration of the antigen-receptor complex [Du et al., 2016; Popovic and Popovic, 2022]. The reciprocal of the dissociation equilibrium constant is the binding equilibrium constant, K_B [Du et al., 2016; Popovic and Popovic, 2022]

$$K_B = \frac{1}{K_d} \tag{3}$$

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The binding equilibrium constant can be used to find standard Gibbs energy of binding, $\Delta_B G^0$, through the equation

$$\Delta_B G^0 = -RT \ln K_B \quad (4)$$

where R is the universal gas constant and T temperature [Du et al., 2016; Popovic and Popovic, 2022].

3. Results

Based on the dissociation equilibrium constants, K_d, reported in the literature [Zhang et al., 2011; Willis et al., 1998; Krummenacher et al., 2005; Sprague et al., 2006; Chapman et al., 1999], binding equilibrium constants, K_B, and standard Gibbs energies of binding, $\Delta_B G^0$, were calculated. The interactions of virus antigens with host receptors and antibodies were analyzed. The antigen-receptor interactions included the interactions of HSV-1 glycoprotein D. The wild type version of glycoprotein D is labeled gD.

The K_B and $\Delta_B G^0$ values of antigen-receptor interactions of Herpes simplex virus type 1 (HSV-1) are presented in Table 1. The weakest antigen-receptor interaction is that between gD306 and HVEM. It is characterized by a binding equilibrium constant K_B = 2.50 $\cdot 10^5$ M^{-1} and standard Gibbs energy of binding of $\Delta_B G^0$ = -30.81 kJ/mol. The strongest antigen-receptor interaction is that between gD and Nectin-1 (three Ig domains). It is characterized by a binding equilibrium constant K_B = 5.85 $\cdot 10^7$ M^{-1} and standard Gibbs energy of binding of $\Delta_B G^0$ = -44.33 kJ/mol.

The K_B and $\Delta_B G^0$ values of antigen-antibody interactions of HSV-1 are presented in Table 2. The weakest antigen-antibody interaction is between gE and Fc at pH = 8. It is characterized by a binding equilibrium constant of K_B = 1.43 $\cdot 10^5$ M^{-1} and standard Gibbs energy of binding of $\Delta_B G^0$ = -29.42 kJ/mol. The strongest antigen-antibody interaction is between the gE-gI complex and hIgG4. It is characterized by a binding equilibrium constant of K_B = 5.03 $\cdot 10^6$ M^{-1} and standard Gibbs energy of binding of $\Delta_B G^0$ = -38.25 kJ/mol.

4. Discussion

Antigen-receptor binding is the first step in virus-host interaction. It represents a biological interaction. Furthermore, antigen-receptor binding represents a chemical interaction similar to protein-ligand interaction [Du et al., 2016; Popovic and Popovic, 2022]. Moreover, antigen-receptor binding represents a biothermodynamic process [Popovic, 2022a, 2022c; Gale, 2018, 2019]. The driving force for this biothermodynamic process is Gibbs energy of binding. From experience, we know that antigen-receptor binding is a spontaneous process for a cell with an appropriate receptor. Indeed, Gibbs energy of binding of HSV-1 antigen to the host cell receptor is negative. The rate of entry of HSV-1 into host cells can be estimated based on the binding phenomenological equation, which belongs to nonequilibrium thermodynamics

$$r_B = -\frac{L_B}{T}\Delta_B G \quad (5)$$

where r_B is binding rate, L_B binding phenomenological coefficient, T temperature and $\Delta_B G$ Gibbs energy of binding [Popovic, 2022b, 2022i].

If we compare Gibbs energies of binding of HSV-1 with those of SARS-CoV-2, we will notice that Gibbs energy of binding of HSV-1 is much less negative. This leads to slower entry of HSV-1 virus into host cells, according to the binding phenomenological equation (5). This could be a reason for lower infectivity of HSV-1 compared to SARS-CoV-2. In case of simultaneous appearance of HSV-1 and SARS-CoV-2, SARS-CoV-2 will have an advantage in the competition for resources, which should lead to interference.

HSV-1 participates in virus-host interactions in the cytoplasm, as well. The rate of biosynthesis of virus components depends on Gibbs energy of biosynthesis. Gibbs energy of biosynthesis of HSV-1 nucleic acid and proteins was found to be -371.99 kJ/C-mol [Popovic and Minceva, 2022a]. The rate of synthesis of virus components in the cytoplasm is given by the biosynthesis phenomenological equation

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$$r_{bs} = -\frac{L_{bs}}{T}\Delta_{bs}G \quad (6)$$

where r_{bs} is biosynthesis rate, L_{bs} biosynthesis phenomenological coefficient and $\Delta_{bs}G$ Gibbs energy of biosynthesis [Popovic, 2022b, 2022i]. If we compare Gibbs energies of biosynthesis of HSV-1 and SARS-CoV-2, based on the biosynthesis phenomenological equation (6) we can conclude that the rate of biosynthesis of HSV-1 is significantly greater. The rate of biosynthesis of viruses is proportional to damage done to host cells and it can be concluded that HSV-1 can cause greater damage to host tissues than SARS-CoV-2. This does not mean that a more severe clinical picture will develop. The severity of clinical picture also depends on the type of target cells, as well as the type of life cycle (lysogenic or lytic), which HSV-1 will perform. However, the rate of biosynthesis indicates the potential of the virus to perform destruction of host cells and tissues. Based on Gibbs energy of biosynthesis, we can conclude that HSV-1 has a great potential (among the greatest among all viruses analyzed thus far).

HSV-1 has among the least negative Gibbs energies of binding. However, HSV-1 has among the most negative Gibbs energies of biosynthesis (-371.99 kJ/C-mol) [Popovic and Minceva, 2022a]. This leads to the conclusion that HSV-1 is the slowest to bind and enter host cells, but the fastest to multiply inside. Moreover, this means that all other viruses, like SARS-CoV-2, will have more negative Gibbs energy of binding and less negative Gibbs energy of biosynthesis than HSV-1. This balance should allow HSV-1 to perform coinfection with practically any other virus. HSV-1 uses the strategy of slow entry into host cells and fast multiplication. This is exactly the opposite of that used by SARS-CoV-2. SARS-CoV-2 during its time evolution has changed towards increasing infectivity (more negative Gibbs energy of binding), while maintaining a constant Gibbs energy of biosynthesis. Both strategies have proved themselves effective.

It is interesting to compare thermodynamic properties of human immunodeficiency virus type 1 (HIV-1) and HSV-1. Standard Gibbs energy of binding of HIV-1 is -46.90 kJ/mol [Popovic, 2022h]. In this research, the calculated standard Gibbs energy of binding for HSV-1 is -44.33 kJ/mol. The values of Gibbs energy of binding are similar for HIV-1 and HSV-1, differing by 5.5%. Thus, the rates of virus binding and entry onto host cell are very similar. It is most likely that HIV-1 and HSV-1 use similar strategies in virus-host interactions. HSV-1 is more widely spread than HIV-1, due to its method of transmission.

5. Conclusion

Herpes simplex virus type 1 (HSV-1) achieves a high frequency in the population, using a strategy of slow entry into host cells, followed by rapid multiplication of viruses in the lytic phase. This conclusion was drawn based on Gibbs energy of binding and Gibbs energy of biosynthesis of HSV-1.

HSV-1 is characterized by a very negative Gibbs energy of biosynthesis, compared to other viruses. The difference is up to 59.4%.

Due to its strategy, HSV-1 can perform coinfection with practically any other virus, since unlike other viruses, it uses a different strategy.

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