Retrovirus: Protein Reawakens

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Abstract

The amino acid sequences ARG of gag proteins of HTLV1, HTLV2, STLV1 and STLV2 match with its primer binding site GGGGGCT CG in the 3'-to-5' direction, and the amino acid sequences SPR of gag proteins of HIV1, HIV2, SIV and FIV match with its primer binding site GGCGCCCGA in the 3'-to-5' direction, and gag, gag-pol and gag-pro-pol proteins are promising for reawaken dormant retrovirus infection. The latency-reversing drugs were involved in the process of transcription of cancer, the genome which they actually reawaken is just happened to be contained genome of the retrovirus, they are essentially false reawaken. Use proteins of retroviruses to reawaken themselves are more reliable, just like androgen receptor activates IGF1R genome.

1. Introduction

"Drugs fail to reawaken dormant HIV infection." An article of Science Daily reported [1]. "Scientists at Johns Hopkins report that compounds they hoped would 'wake up' dormant reservoirs of HIV inside immune system T cells, a strategy designed to reverse latency and make the cells vulnerable to destruction, have failed to do so in laboratory tests of such white blood cells taken directly from patients infected with HIV."

Therefore, I have to ask, can latency-reversing drugs actually reawaken the sleeping retrovirus?

2. Contain ≠ Equal

Let's design an experiment. First of all, prepare several T cells and the HIV1 double-stranded DNA which converted by reverse transcribed. HIV genome contains at least nine genes, such as gag, pol, and env [2]. IGF1R genome is on the human chromosome 15, which contains at least 21 exons, such as ENSE00003838363 and ENSE00001316091 [3]. In mathematics, a set is a collection of elements, so the genome can be defined as a set by listing its elements between curly brackets, separated by commas:

$$H = \{\text{gag, pol, env}\}\$$
 $I = \{\text{ENSE00003838363}, \text{ENSE00001316091}\}\$

Where H is the set of HIV genome, and I is the set of IGF1R genome. Next, use CRISPR-Cas9 enzyme [4,5] to copy HIV genome into the IGF1R genome of T cells. The form can be rewritten to:

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I = \{ENSE00003838363, gag, pol, env, ENSE00001316091\}
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One of the known target genes of androgen receptor activation is IGF1R genome [6]. In mathematics, a function from a set X to a set Y is an assignment of an element of Y to each element of X, so the process of transcription can be written in the form:

$$f(x) = y$$
 $f(A) = I$ $A = \{androgen, androgen receptor\}$

Where f is the function of RNA polymerase II, and A is the collection of androgen and its receptor. Python ^[7] is one of the most popular programming languages, which can be used to check the accuracy of mathematical formulas:

Then, injected androgen and its receptor into the T cells. After IGF1R genome is transcribed by RNA polymerase II $^{[8]}$, HIV will also 'wake up' $^{[9]}$. Can I claim that androgen reawakens the sleeping HIV? Of course not. The androgen reawakens IGF1R genome which contains HIV genome, not the retrovirus directly, even the python program returns a result of *False*.

```
9 print(H <= f(A)) #True</pre>
10 print(H == f(A)) #False
```

As you can see, the collection of elements returned by the method includes the HIV collection, which doesn't mean that two collections are equal. In mathematics, their relationship is:

$$H \subseteq f(A)$$
 $H \neq f(A)$

Several studies funded by NIH claim that AZD5582 can reawakens the sleeping HIV and SIV, but they also claim that its effective rate only has 42%: "SIV levels increased in five of 12 monkeys (42%) overall." [10,11,12] And most importantly, the AZD5582 was used for the treatment of cancer: "This compound causes cIAP1 degradation and induces apoptosis in the MDA-MB-231 breast cancer cell line at subnanomolar concentrations in vitro." [13] The AZD5582 was involved in the process of transcription of cancer, the genome which it actually reawakens is just happened to be contained HIV genome, it is essentially a false reawakens.

3. Indirect \neq Direct

In fact, not only AZD5582, but enormous studies claim that their latency-reversing drugs can be used to reawaken the sleeping HIV, for example, Ciapavir [14], bryostatin-1 [15], disulfiram [16], ingenol-B [17], prostratin [18], HDACis and PKCms [19].

Figure 1. Latency-reversing drugs

How is that even possible? In molecular biology, a base pair is a fundamental unit of double-stranded nucleic acids consisting of two nucleobases bound to each other by hydrogen bonds, such as adenine-thymine and guanine-cytosine [20]. Hydrogen bonds are usually formed between atoms that are electronically complementary, that is, between a proton acceptor atom with partial negative charge and an opposing proton atom with partial positive charge [21].

Figure 2. Watson-Crick base pair

Therefore, in order to transfer the electromagnetic interaction ^[22], the latency-reversing drugs also demand to be matched with the corresponding nucleobases. Unfortunately, the atoms that make up these drugs are completely different, even if their atoms are all matched with corresponding nucleobases, for example, an oxygen atom and a hydrogen atom as thymine, the sequences they form are still different, they cannot match with the same genome of the same virus at the same time, and disulfiram doesn't even have an oxygen atom.

Figure 3. Disulfiram

More importantly, which atom is the starting point, and which atom is the ending point? How does the RNA polymerase II read each atom, and in what kind of order? These drugs have no regular patterns of any kinds of structures, obviously, they cannot be directly identified by the RNA polymerase II. The one that actually identified by the polymerase definitely has a fixed structure, for example, the androgen receptor, which has proteins that can be read sequentially in a fixed order.

In addition, the shapes and sizes of these drugs are also completely different, and if two atoms are far away from each other, the electromagnetic interaction is negligible. The electromagnetic force that occurs between two electrically charged particles can be stated as a simple mathematical expression of Coulomb's law [23]:

$$F=k_{
m e}rac{q_1q_2}{r^2} \hspace{1.5cm} k_{
m e}=rac{1}{4\piarepsilon_0}$$

Where $k_{\rm e}$ is the Coulomb's constant, q is the signed magnitudes of the charge, r is the distance between two charges, and ε_0 is the vacuum permittivity. As you can see, when the distance is more than 1nm, the electromagnetic force between two atoms will be less than 1% of the force at the distance of 0.1nm. And androgen receptor, which made up of hundreds of proteins, is much bigger than the latency-reversing drugs.

If the connection in the molecular-level is magnified to the macro-level, it feels like those scientists are trying to put different types of plugs into one completely mismatched receptacle.

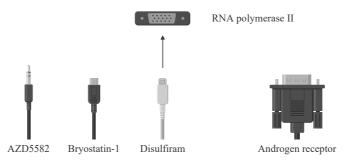


Figure 4. Drugs reawaken

In computer science, to make one receptacle match with different plugs, each of them requires an unique adapter to convert the electromagnetic interaction, just like the androgen adapted by its receptor. It is the androgen receptor that directly activates IGF1R genome, not the androgen.

Of course, there is no doubt that those studies funded by NIH is 100% accurate, so the blame is on the RNA polymerase II. The one that made the mistake must be the polymerase, it should come from Schrödinger's cat, and has countless protein structures in a superposition, which can automatically match with every latency-reversing drug, and accurately convert the electromagnetic interaction without the receptors.

By the way, those latency-reversing drugs were also used for the treatment of cancer [24,25,26,27], just like the AZD5582 [13].

4. Model

As we know, HIV recruits human uncharged tRNA to serve as the reverse transcription primer ^[28], HIV and IGF1R genomes are both transcribed by RNA polymerase II ^[8,9], one of the known target genes of androgen receptor activation is IGF1R genome ^[6], androgen receptor recruited by RNA polymerase II ^[29], a promoter is a DNA sequence that directs RNA polymerase II at the correct initiation site ^[30], adenine, cytosine and guanine are found in both RNA and DNA, uracil and thymine are both bind to adenine via two hydrogen bonds ^[31], and tRNA is serves as the physical link between the mRNA and the amino acid sequences of proteins ^[32].

Therefore, uncharged tRNA is serves as the physical link between the promoter and the protein receptors which recruited by RNA polymerase II.

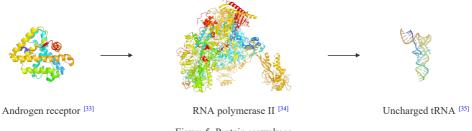


Figure 5. Protein reawakens

Retroviruses can accurately identify and replicate themselves, obviously, the things that can actually reawaken themselves are their own proteins, for example, gag, gag-pol and gag-pro-pol proteins.

5. Results

Although DNA is always synthesized in the 5'-to-3' direction, reverse transcriptase synthesizes negative-strand DNA in the 3'-to-

5' direction [36,37]. The androgen receptor recruited by RNA polymerase II may also be rotated 180 degrees, so uncharged tRNA may have 4 ways of matching with the primer binding site. Use the x-axis to represent the protein, and the y-axis to represent the primer binding site. Negative numbers means the protein or tRNA rotated 180 degrees, or synthesized in the 3'-to-5' direction when both values are negative. Represent different types of retroviruses with different patterns and colors, and matching their sequences around the primer binding site with their own proteins, their coordinates can be represented in the following figure:

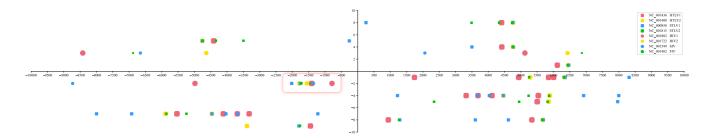


Figure 6. Coordinates of matched points

When there are 2 amino acid sequences of the matching points, there are so many possibilities that it is impossible to confirm which protein is matching the primer binding site, and when there are 4 amino acid sequences, no matching target can be found. But when there are 3 amino acid sequences, there is exactly one perfect matching region. Inside the red box, different colored circles and cubes overlap at the same y-axis, and their distances at the x-axis are close, which means that their gag, gag-pol and gag-pro-pol proteins match with the same primer binding site, even the viruses are highly different.

NC_001436 ^[38] HTLV1	400	CACAGT TGGGGGCTCGTCCGGGA TTCGAGC	429
	416	→ GCTCGGGGG	407
	317	Q K L L Q A R G H T N S P	319
	1383	CAAAAATTACTACAGGCCCGAGGGCACACTAATAGCCCT	1421
NC_001488 ^[39] HTLV2	760	AACAAT TGGGGGCTCGTCCGGGA TTTGAAT	789
	776	→ GCTCGGGGG	767
	323	Q K I L Q A R G H T N S P	325
	1758	CAAAAAATCTTACAAGCCCGCGGACACACTAACAGCCCC	1796
NC_000858 ^[40] STLV1	752	CACAGG TGGGGGCTCGTCCGGGA TACGAGC	781
	768	→ GCTCGGGGG	759
	317	Q K L L Q A R G H T N S P	319
	1735	CAGAAACTACTACAGGCCCGAGGACACACTAATAGCCCT	1773
NC_001815 ^[41] STLV2	709	A A C A A G T G G G G C T C G T C C G G G A T A C C T A C	738
	725	→ GCTCGGGGG	716
	322	Q K L L Q A R G H T N S P	324
	1704	CAAAAATTGCTGCAGGCCCGGGGCCATACTAATAGCCCC	1742

Figure 7. Deltaretrovirus

In GenBank database, the primer binding site of HTLV2 NC_001488 [39] genome is around 766 to 783, and the primer binding site of HIV1 NC_001802 [42] genome is around 182 to 199. As you can see, their primer binding sites start with TGG and end with GGGA, and after aligning the sequences, their matching points are in the same position.

NC_001802 [42] HIV1	176	TAGCAG TGGCGCCCGAACAGGGA CCTGAAA	205
	192	→ AGCCCGCGG	183
	148	V H Q A I S P R T L N A W	150
	762	GTACATCAGGCCATATCACCTAGAACTTTAAATGCATGG	800
NC_001722 ^[43] HIV2	853	GCAGGT TGGCGCCCGAACAGGGA CTTGAAG	882
	869	→ AGCCCGCGG	860
	150	V H V P L S P R T L N A W	152
	1535	GTCCATGTGCCACTGAGCCCCCGAACTCTAAATGCATGG	1573
NC_001549 ^[44] SIV	683	CAGCAG TGGCGCCCGAACAGGGA CTTGAGA	712
	699	→ AGCCCGCGG	690
	150	V H Q P L S P R T L N A W	152
	1329	GTACACCAGCCTTTGTCTCCGCGCACGTTAAATGCGTGG	1367

NC_001482 [45] FIV	352	C G C A G T T G G C G C C C G A A C A G G G A C T T G A T T	381
	368	→ AGCCCGCGG	359
	274	A I K A K S P R A V Q L R	276
	1432	GCCATAAAAGCTAAGTCTCCTCGAGCTGTGCAGTTAAGA	1470

Figure 8. Lentivirus

The amino acid sequences ARG of gag proteins of HTLV1, HTLV2, STLV1 and STLV2 match with its primer binding site GGGGGCT CG in the 3'-to-5' direction, and the amino acid sequences SPR of gag proteins of HIV1, HIV2, SIV and FIV match with its primer binding site GGCGCCCGA in the 3'-to-5' direction, and gag, gag-pol and gag-pro-pol proteins are promising for reawaken dormant retrovirus infection.

It is possible that other proteins are also involved in this process, but due to the lack of sufficient information, it cannot be determined at this time. What is certain so far is that "drugs fail to reawaken dormant HIV infection" [1], and it is more reliable to use proteins of retroviruses to reawaken themselves, just like "androgen receptor activates IGF1R genome" [6]. Latency-reversing drugs have failed in 40 years [48,49], and they will keep failing in the next 40 years.

Discussion

As of this writing, HIV/AIDS has not been cured yet.

Abbreviations

IGF1R: Insulin-like growth factor 1 receptor

HTLV: Human T-lymphotropic virus STLV: Simian T-lymphotropic virus HIV: Human immunodeficiency virus SIV: Simian immunodeficiency virus FIV: Feline immunodeficiency virus

Availability and requirements

Datasets were produced by python3, tool available at https://github.com/rheast/genome. Nucleotides were downloaded from NCBI https://www.ncbi.nlm.nih.gov/nuccore/. Samples nucleotides correspond to accession numbers: NC_001436, NC_001488, NC_000858, NC_001815, NC_001802, NC_001722, NC_001549 and NC_001482.

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