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A hub gene in a HIV-1 gene regulatory network is a promising target for anti-HIV-1 drugs

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Abstract

Any of the existing anti-HIV-1 drugs has tough problems: side-effects and development of drug resistance. From logical reasoning, the study concludes promising targets of anti-HIV-1 drug without the above problems should bear "hub" and "bottleneck" topological features in HIV-1 gene regulatory networks.

Keywords

Hub gene, Bottleneck gene, Anti-HIV-1 drug, Drug resistance, HAART

I Introduction

Topologies of gene regulatory networks of *Saccharomyces cerevisiae* and yeast were energetically analyzed [1][2]. The analyses revealed all of these networks were scale-free with power-law degree distributions. Further, it was shown that "hub" genes, which regulate multiple genes exist. The hub genes are evolutionary conserved; therefore it is thought that the genes assume important functions.

Recently, another topological feature of genes called "bottleneck" is noted [3]. The bottleneck gene is defined as a sort of a "main bridge" between highly connected sub gene networks (Fig. 1). Thus the bottleneck gene is considered to be requisite for sustaining interactions between sub networks; inhibiting the bottleneck gene leads to block the interaction between them. As an example of the bottleneck gene, Yu et al [3] take up Cak1p in yeast, and reveals Cak1p connects two signal pathways: cell cycle and sporulation.

Except biological networks, topological analyses of the Internet, where many computers are linked by wired or wireless connections have also been carried out. The analyses revealed the network topology of the Internet is the same scale-free as the gene regulatory networks are. Albert et al [4] investigated the scale-free network is immune or vulnerable to what kind of attacks. They demonstrated the scale-free network is fault-resilient against random faults; it receives a death stroke when hub routers or hub servers are taken a shot at.

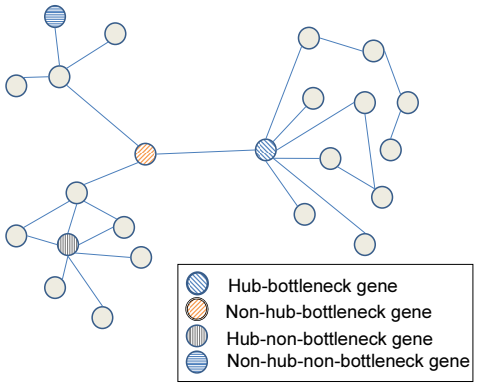

Fig. 1: Schematic view of hub-bottleneck, non-hub-bottleneck, hub-non-bottleneck and non-hub-non-bottleneck gene

With these research backgrounds, this study interests to determine topological features of anti-HIV-1 drug targets with no side-effects and no development of drug resistance.

HIV-1 which is a causal agent of AIDS only has 9 genes. However, functions of each gene are only partly revealed. One of the reasons is that HIV-1 replicates by manipulating intracellular agents so that a large number of interactions between HIV-1 genes and the agents form a web-like complicated pattern. For instance, Tat: the one of HIV-1 genes involves tran-

scriptional activation of HIV-1 gene expression, but actually its process looks very complex as follows (see. Fig. 2)[5]:

1. The nuclear factor NF-kB, NFAT and Sp1 bind to the long terminal repeat (LTR) region at the end of HIV-1 DNA.
2. By RNA polymerase II (RNAP II), short non-polyadenylated transcripts are synthesized.
3. A Tat protein and an intracellular Cyclin T1 bind to TAR segments of the short transcripts, thereby an intracellular Cdk9 is recruited and activated.
4. The activated Cdk9 phosphorylates the C-terminal domain (CTD) of RNAP II, which starts to elongate eukaryotic transcription.

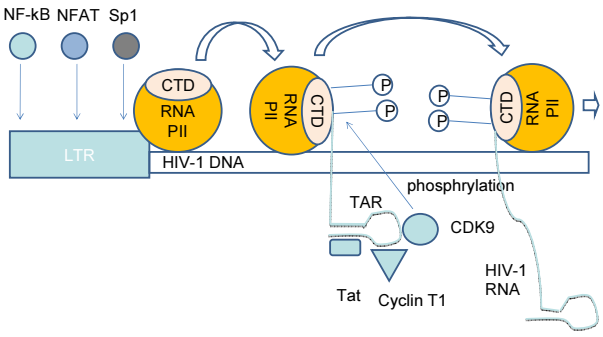

Fig. 2: Transcriptional process by cooperation between HIV-1 genes and intracellular agents

Even this scenario is so simplified that its perfect scenario is still incomprehensible. Actually HIV-1 gene regulatory networks are still not enough uunderstood. Therefore, from logical reasoning approach different from network analyses, the present study derives some topological conditions for anti-HIV-1 drug targets with no side-effects and no drug resistance to satisfy. This study concludes "hub-ness" and "bottleneck-ness" of HIV-1 genes are promising topological features of anti-HIV-1 drug targets.

II Hub-ness for anti-HIV-1 drug targets

II.1 About the drug resistance

Currently, there are 25 anti-HIV-1 drugs and they are divided into 3 classes. The most bothersome problem for the present anti-HIV-1 drugs is development of the drug resistance.The reason why the drug resistance is easy to emerge is HIV-1 is highly mutagenic in nature so that HIV-1 can evolve a virus enzyme's active site which an anti-HIV-1 drug targets; thereby HIV-1 can easily escape from that inhibition. In other words, the problem lies in each anti-HIV-1 drug can only inhibit just "one" active site (i.e. one specific function) of HIV-1 enzyme. For instance, the reverse transcriptase inhibitor which was developed as the earliest anti-HIV-1 drugs blocks a HIV-1 reverse transcriptase (RT)'s active site. Indeed, HIV-1 mutates an active site of RT, for instance, such as K65R, L74V, Y115F and M184V against "Abacavir"(RT inhibitor) [6], thereby the drug resistant strain appears in just two months. This problem is not limited to a particular HIV-1 drug. On "Alazanavir", which belongs in the class of a protease inhibitor, multiple mutations (L10IFV, G16E, K20RMI, L24I and so on) on the active site of its targeting protease are observed [6].

On the other hand, we can expect an anti-hub gene drug can cause a malfunction of all genes under the hub gene's regulation. Even though HIV-1 is highly mutagenic, it seems unlikely that all of the malfunctioning genes can evolve together to recover their functions. From this reasoning, we can conclude that anti-HIV-1 drugs targeting hub genes are immune to drug resistance. This conclusion is validated by the fact that "multiple drugs therapy (HAART)" targeting multiple HIV-1 functions is effective to suppress HIV-1 population growth.

Meanwhile, a hub gene must play a significant role in a HIV-1 gene regulatory network, thus we can expect that the hub gene have to be insusceptible to any mutations. Namely, any mutations to a hub gene to achieve the drug resistance must result in a suicidal action for HIV-1.

From these discussions, we think a hub gene in HIV-1 gene regulatory networks is a promising candidate as anti-HIV-1 drug targets to overcome the drug resistance.

II.2 About the multiple drug therapy

Next we discuss some important problems of multiple drug therapy for AIDS. The problems are 1) an increase of a treatment cost and of a daily dosage and 2) strong side-effects. First, we discuss the primary problem.

The multiple drug therapy produces a strong effect by simultaneously inhibiting multiple HIV-1 enzymic activities by plural anti-HIV-1 drugs. However, unfortunately the therapy just restrains AIDS progres-

sion and does not bring AIDS patients to recover fully. Therefore, the therapy forces them to continue to take the plural drugs for a long life, so the treatment cost will become high amount. This means that a quite number of AIDS patients in developing countries can not take this treatment by its cost.

On the other hand, as already mentioned, an anti-HIV drug targeting a hub gene can inhibit multiple genes under the hub gene's regulation. Namely we can expect the same effect as the multiple drug therapy by use of a single drug against a hub gene. Additionally we can reduce the treatment cost because the number of drugs necessary for our proposed therapy is the only one: anti-hub gene drug. Therefore AIDS patients in developing countries could use the drug.

Another problem of the multiple drug therapy is side-effects. In the therapy, patients have to take multiple drugs so that a very acute side effect by a synergetic effect of each drug's side-effect is brought into patients. Thereby, quite number of patients quit the treatment. Meanwhile if an anti-HIV-1 drug against a hub gene is used, just one drug suffices to take daily. Therefore, a side effect by the anti-HIV-1 drug targeting a hub gene must be reduced comparing with the one by the multiple drug therapy.

III Bottleneck-ness for anti-HIV-1 drug targets

In the previous section, as a topological condition for new targets of anti-HIV-1 drugs to satisfy, we have took up the "hub" feature of HIV-1 genes. However, the hub feature is not enough. We think the "bottleneck" feature is also important.

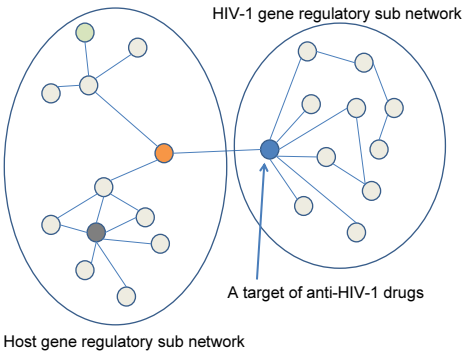

Fig. 3: A candidate of anti-HIV-1 drug targets

The reason why we have to consider the bottleneck feature is due to what HIV-1 replicates by using intracellular agents. Supposing that there exists a bottleneck HIV-1 gene connecting between a sub network composed of intracellular agents and the other sub network of HIV-1 genes, by inhibiting the bottleneck HIV-1 gene, HIV-1 could not utilize cellular agents belonging to the sub intracellular network. This means to block the HIV-1 replication. That is why we place equal importance on the bottleneck-ness and the hub-ness of anti-HIV-1 drug targets. Fig. 3 shows a "hub-bottleneck" HIV-1 gene which is considered to be ideal as an anti-HIV-1 drug target.

IV Conclusions

Based on logical reasoning, this study has concluded the hub-ness and bottleneck-ness are requisite topological features for anti-HIV-1 drug targets.

To demonstrate the validity of this study's discussions, we would require DNA micro-array time course data on the coexpression of HIV-1 genes and its host genes of each stage of HIV-1 virion synthesis [7]: the HIV-1 binding to the host cell, the HIV-1 uncoating, the reverse transcription from HIV-1 RNA to HIV-1 DNA, the nuclear import of HIV-1 DNA, the integration of HIV-1 DNA into the host DNA, the transcription from a pro-virus, the RNA export, the RNA translation, the assembly of HIV-1 elements, the virus RNA encapsidation, the budding of HIV-1 virions and the maturation of them. In the near future, we expect that these data will be provided in some public databases.

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