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HIV in Human Genomes and Therapeutics

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Abstract

One of the most interesting topics in the field of HIV/AIDS study is the possible relationship between HIV genetic penetrations and disease stages. One decade before, this kind of genomic information is difficult to achieve. Yet, the innovations of next generation sequencing (NGS) have changed this landscape. At present, new generations of bio-therapies target this undesired pathogenic pathways. In this article, we address the relationships between HIV-induced genomic changes across the history and different types of therapeutics have been testified since last decade—including integrate inhibitors, genome editing agents and therapeutic schedules. Future perspectives are also given.

Keywords: Human genome; Next generation of sequencing; Pathogenic pathways; Genomic editing; Experimental model; HIV-induced pathology; Viral therapeutics; Integrase inhibitors

Historic Overview

Current therapeutic limitation

Thanks for the HAART utility, we are currently not so horrified for HIV/AIDS [1-3]. Despite great diagnostic and therapeutic advancements, a significant drawback exists in HIV/AIDS therapeutics (incurable for HIV/AIDS patients). Several pathological pathways have been contributed for this key drawback. One of the challenges in HIV/AIDS study is the possible relationships between HIV genetic penetrations and disease pathogenic progresses (human mortalities) [4-6].

Problem origins

A number of pathogenic properties are attributed to this therapeutic barrier—including HIV latency, HIV reservoirs, HIV-genomic integrations and so on [7]. Among all these unknown territories, the study of HIV-genomic integration is the relatively earliest one [4-6].

The initiations of HIV-integration into human genomes study were started amid 2000. In these researches, physical states of DNA polymers were used as substrates for integrase activity evaluations and inhibitory efficacy comparisons [4]. Meanwhile, a series of integrase inhibitors have been verified and even licensed [4-6]. Shortly afterwards, a number of sophisticated scientific investigation roadmaps have been designed [8,9]. In this chapter, we address the relationships between HIV-induced genomic changes, rate of human mortalities and different types of therapeutics— intending to seek solutions from both chemical agents and biotherapies. It also highlights with new ideas and ways of clinical therapeutic improvements.

Next Generation Sequencing

One and half decade ago, animal and human genomic research is difficult to be accomplished and costs a fortune for a single genome. Yet, a great leap has been made approximately 2010. Genomic drafting technical innovation by next generation sequencing (NGS) [10-13] has changed the landscape greatly. It is 15,000 to 50,000-fold faster and costs less than 7,000 USD/per genome. This great genomic drafting protocol advancement has the capabilities of large-scale samplings and genomic data analysis, including HIV/AIDS studies. Following sections address these insights into the fields of HIV/AIDS studies and highlights with new ideas and clinical achievements.

Knowledge Evolution

Physical states of DNA polymers in pathologic and therapeutic studies

At the beginning of this millennium, genomic drafting was a huge task hardly finished by single lab or even an institute. Owing to this situation, physical states of DNA samples were used to identify small-segments of HIV genome integration into physical states of DNA polymers. In these initial studies, a great amount of HIV pieces can penetrate into DNA polymers as fast as 4 hrs [4]. By utility of this experimental model, a series of HIV/AIDS therapeutic agents (integrate inhibitors) have been developed and finally licensed [4-6,14-17].

Since integrase inhibitors were usually developed by DNA polymer substrate techniques, the situation of clinical therapeutic improvements were uncertainty. It means that DNA polymer conditions are not completely parallel with complicate conditions in living cells and bodies—including HIV infected patients. As a result, more sophisticate living conditions (*in vitro* or *in vivo* experimental models) must be established, and even utilized as HIV therapeutic drug evaluating systems.

Different types of animal models and human cell models

Before clinical human genomic pathological and therapeutic studies, *in vitro* or *in vivo* animal models for HIV genomic integration must be utilized first. In animal model studies, selections of animal genomic origin and human cell/tissue types are important.

There are similarity and diversity among different animal genomic origins and human cell types. These types of animal/human genomic studies generally needs less ethical requirements and can be studied in repeat ways comparing with clinical human investigations. In our opinions, these types of HIV genomic penetration studies should be emphasized now and in future. Similarly, these types of HIV animal

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models of genomic penetrations are also not 100% parallel to clinical human situation of HIV-infections, human mortality and therapeutics.

One of the most mortality impacts of HIV-induced pathogenesis might be virus-human genome penetrations in infected cells or tissues, which are irreversible by present clinical therapeutics [4-6]. But they are the targets of many biotherapies [17-20]. Despite great promises, this hypothesis has been just systematically studied. No marked breakthrough in terms of great survival benefits has been established. Generally speaking, studying the HIV-integrating to the genomes of different animals or cells/tissues can be enormously potentiality. Yet the achievement of this study is still not overwhelmed. New breakthroughs must be made in future.

Genome-wide association study and new techniques

In human genomic studies, genome-wide associate study (GWAS) is widest utilized nowadays. Study GWAS for the relationships between human genomic makeup, virus-penetration loci and human mortalities are inevitable avenue for in-depth understanding of HIV/AIDS pathogenic processes, human mortality risks and related different types of therapeutics. These kinds of researches should not only study the biology or pathology of HIV infection and therapy, but also utility of innovative techniques such as NGS [9-12]. This dramatic technical improvement might finally assist us to solve enigma of HIV integration into human genomes by unprecedented speed and least amount of money.

In future, the heavyweight of genomic sequencing forces might generally participate with mathematics or physics major students or scholars because the laboratory protocols for computation or alignments of different DNA pieces into a whole genome will take longer times and efforts comparing with sequencing processes. For computational work, the mathematics or physics major students must be smarter and adept over biomedical major students [21,22]. So it is foreseeable that mathematics or physics major students might be at lease parts of working force suitable for genomic sequencing. The contributions by mathematics or physics scientists can be suitable for large scale genomic data analysis and need relatively less money by higher analytic efficiency [6].

New therapeutic paradigms

The ultimate goal of these genomic studies is for therapeutic purposes. Until now, we still do not know whether HAART should be given early or late because our understanding of the genetic pathogenesis and mortality of HIV in patients is lacking and incomplete. We do not know why patients are killed by HIV infections. Since previous hypotheses and preliminary studies suggested that penetration of HIV virus into human genome is possible in Table 1.

The blueprints for genomic HIV/AIDS studies

Whether genome-integration plays a key role for causing patient's mortality? We previously designed a series of experimental and clinical procedures to solve them up [8,9]. Table 1 represents the blueprint of next generation of genomic study on HIV infectivity, AIDS patient's mortality and new therapeutic means. If we can pinpoint the real causalities of AIDS patient's mortality, we then can decide whether HAART should be given early or late [23-25] (Table 1). Different styles of HIV-genomic interactions systems trigger and evaluate different types of therapeutic interventions against different forms of HIV infectivity, HIV-induced pathogenesis and human mortalities. For example, it was found that HIV was easily to integrate into pure DNA *in vitro* [4]. These experimental evaluating systems, nonetheless, cannot be directly translated into clinical applications. Only after genetic studies in animals, especially in HIV-infected patients, many experimental or clinical therapeutic intervention options can then be accomplished in HIV infected patients [26,27]. Likelihood, genetic or genomic studies in humans must be more relevant comparing with those in animals. In possible future human genomic studies, Figure 1 represents our visions on this matter.

Future trends

Apart from pathological HIV-genome interaction studies, HIV/AIDS therapeutics by every possible means is also important. Many other therapeutic investigation systems can be scientifically studied—including medicinal chemistry, pharmacokinetics, pharmacogenomics, modern drug delivery system utilities and so on.

Different avenues

To fully clearances of HIV from infected patients, priority goals of future HIV/AIDS treatments are to improve HIV/AIDS therapeutics in every detail. More efforts such as medicinal chemistry, pharmacogenomics, new technical or treatment patents, up-to-date clinical HIV infection diagnostics and integrase inhibitors are potential avenues to testify possible mechanisms or pathways relating to the roles of HIV persistence in infected patients. Some important topics and key elements for HIV/AIDS treatments must be emphasized first. Possible roadmaps and new alternative interventions are outlined in followings.

Key pathway discovery and useful therapeutic updating

- Scientific study of HIV vaccines, especially targeting at the heterogeneity and diversity characteristics of HIV viruses and other unknown biological and pathologic mechanisms.
- Clarify the role of HIV-penetration into human genome—possibly main cause of chronic characters of HIV infections.
- Develop more effective and less toxic antiviral chemical or biotherapy intervention systems and next generation of anti-HIV drugs of both chemotherapeutic agents and biotherapies.
- Find ways of excellent clinical HIV diagnostics for viral mutations and drug-resistance, which may cause potential global outbreak for HIV/AIDS epidemics and treatment failures.

Methods	Possible evaluation	Ref
Biophysically monitor the interactions between pure DNA or extracted host genome and HIV	Integrase inhibitors	4
In vitro pathogenesis and bioinformatics study of HIV in infected animal and human cells and against by different types of therapeutics	Biotherapy and other therapy	6
In vivo genomic or bioinformatics study of HIV and its relationship between viral vaccine/drugs and disease progresses and animal survival/mortalities	Evaluations of different vaccines and antiviral drugs	8-9
Establishments of the relationships between HIV and human genome changes for susceptible and infected patients	HIV-induced pathogenesis and therapeutic studies	7
Remedy inserted HIV segments by biological means, such as recombinases	Therapeutic options	17
Genome edition of infected genome	Zinc finger nuclease, TALEN, Cas9 and meganucleases	18

Table 1: Different levels of genomic study for HIV infection, pathogenesis and therapy.

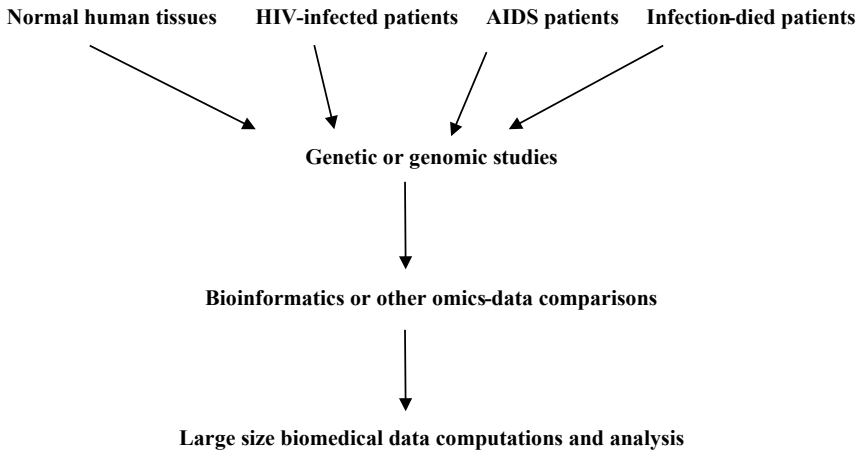

Figure 1: Outlook of genomic study and comparisons of HIV infectivity, pathogenesis and human mortality.

Conclusion

Up to now, it has been achieved some useful therapeutic agents and clinical strategies. Along with other HIV-induced pathogenesis and drug targets, a chain of more fruitful achievements may be achieved in future and further save the life of millions worldwide.

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