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2.1 INTRODUCTION

Viruses possess the ability to change the machinery of the living host body for the benefit of the continuity of the survival and are thus categorized as living organisms (parasites). The virus categorized as invasive is capable of infection and showing pathogenicity (Mcfadden, 2006). The host cells possess the ability to evolve and carry out various network of defensive measures against the pathogens but some microbial pathogens have the ability to neutralize the defensive measures of the host cells, rendering them useless (Mcfadden, 2006). It is a challenging and puzzling job to identifying the complex host responses that occur when a viral infection is encountered by the living host. It requires finding and categorizing the various host factors which could be involved actively in the cycle of virus infection. Moreover, there is also a need to categorize the identified host responses into a qualitative and a quantitative category through viral pathogenesis (Zheng et al., 2012).
2.2 THE HISTORY OF IDENTIFICATION OF VIRUSES AT A MOLECULAR LEVEL AND METAGENOMICS

There are multiple existing techniques to identify viruses. Some of the traditional techniques used to discover many of the well-known viruses consist of electron microscopy, inoculation studies, cell culture, and serology (Storch, 2007). These techniques have a lot of limitations such as the fact that viruses, because of being so small in size, cannot be cultured in a laboratory but rather have to be characterized by utilizing molecular methods. However, there have been numerous technological advances in the field of virology. This advancement in technology has set the precedent for metagenomics, a study of a collection of microbial populations called the microbiome. It is a culture-independent study which analyzes the content of the nucleotide sequence in the sample (Petrosino et al., 2009). The study of the viral microbiome, also known as the virome, is conducted on different samples of biological and environmental applications on humans, animals, water, soil, and plants (Breitbart et al., 2003; Zhang et al., 2006; Finkbeiner et al., 2008; Schoenfeld et al., 2008; Fierer et al., 2007).

Metagenomics sequencing makes it possible to find the functional potential hidden in the microbiome code. Moreover, metagenomics analyses are being utilized in discovering novel enzymatic functions as well as microorganisms and the genes which could possibly be utilized in bioremediation (Russell et al., 2011; Lovley, 2003) for better know-how of the host–pathogen interactions and also for creating novel therapeutic strategies which could be used for human diseases. However, metagenomics has some limitations in the variation of DNA according to the site of the body and the type of sample; for example, the sputum samples or samples of lung tissue in cystic fibrosis contain a large quantity of human DNA which is released by the neutrophils when the body shows an immune response. It can even amount to a total of 99% of the DNA (Breitenstein et al., 1993).

2.3 ADVANCEMENTS IN TECHNIQUES TO STUDY VIRUS–HOST INTERACTIONS

In the present years, virology is undergoing rapid advancement as a result of “high-throughput genome sequencing and proteome screening technologies.” Progress in proteome screening technologies and proteomics based on mass spectrometry have largely encouraged research inquiry into viral proteomes and also response of the host related to viral infections (Zheng et al., 2011). Mass spectrometry is one of the most core and emergent part of the most important discoveries made in the field of virology. The virus–host cell has formed a complex evolutionary relation because of their dynamic interactions that work to either sponsoring virus replication or help the host to carry out its defense against the pathogens invading the host cell and the body. The viral cell promotes multiple proteome changes which makes the understanding of the virus at a molecular level, a difficult task requiring both breadth and an in-depth analysis of the infection. Mass spectrometry is the solution to bridge the gap between experimental dichotomies. Its use in unbiased
system analysis and hypothesis-run studies has fastened the pace of discoveries in the area of virus pathogenicity and defense of the host (Greco et al., 2014).

Mass spectrometry–based techniques are being used to investigate the hosts of viruses and the viruses themselves. Following are the mass spectrometry–based techniques and their applications in virology:

1. Tandem affinity purification (TAP)–based mass spectrometry: This technique takes its role in explaining protein–protein interactions. It is used to study the proteins and the proteome and its structure which is very important when studying the evolution of viral proteins when viruses replicate within the host cell (Jorba et al., 2008). It uses a dual epitope tag for continued immunoaffinity isolations and it has been used in cells infected by viruses. This technique was used to isolate the vaccinia virus called A56 as well as K2 proteins. This was done by using a streptavidin and a calmodulin-attaching TAP system. The virus and the proteins were separated as they localized on to the surface of the cell and were then needed for interaction with the entry fused complex (Moss, 2007).

2. Co-immunoprecipitation–based mass spectrometry: This technique is used to identify the components that bind to a target protein. Co-immunoprecipitation is performed either in a single-step process or as a component of tandem purification. To obtain the target from the solution, an antibody which targets a known member of the complex is attached to a bead and then incubated with lysate. This antibody which is used for co-immunoprecipitation recognizes the protein of our interest or tagged protein which has been made by genetically fusing a tag with our protein of concern.

An alternate way of performing co-immunoprecipitation is by using a molecular tag and binding it with our protein of interest which is expressed from a transgene and then purified by using an antibody against the added tag. This tag can then further on be used for a tandem purification or a multi- or single-step purification (Schaffer et al., 2010). The technique was used to define the protein localization in Caenorhabditis elegans. In this experimental design, several tags were constructed and used in C. elegans. The reason behind this was that the functional effect of adding a single tag is not usually known and, therefore, different tags are attached at the C or the N terminus. The functionality of the tagged protein can be determined if it is able to extract the phenotype of a null mutant. Moreover, it is common to use green fluorescent protein–tagged proteins to govern protein localization in C. elegans and this can also be conducted as a single-step process of purification (Zhang et al., 2007).

3. HLA peptidome scanning chip–based mass spectrometry approach: This technique is used to look for peptides associated with disease as well as mutant or differently expressed proteins in a host cell after a viral infection. An example of the use of this technique is in the defense mechanisms employed by the cytotoxic T lymphocytes within the human body against the intracellular pathogens that attack the body. HLA class 1 associated immunopeptides by mass spectrometry has become a very important tool to increase our understanding of the T-cell responses against the pathogens, for example, HIV-1 (Ternette et al., 2015).
There are several other approaches that are being used to discover the pathogen and they include hybridization and PCR-based methods. The effectiveness of the methods mentioned earlier which are based on PCR and hybridization is established when the virus which interests us is first purified from the host cell and other nucleic acid contaminants. These amplified products are then identified by sequence. In the present day, the advances in sequencing have led us to the era of second-generation sequencing in which huge chunks of data can be sequenced in one go (Petrosino et al., 2009). Sections 2.3.1–2.3.5 provide a description of the current hybridization and PCR techniques for detection of viruses affecting animals.

2.3.1 Hybridization

2.3.1.1 Microarray Techniques

Microarrays are made up of probes of oligonucleotides which are of high density; in other words, these are portions of DNA immobilized on a solid surface. The sequences made up of complementary strands present in a test sample are tagged with fluorescent nucleotides which then hybridize with a probe present on a microarray. This hybridization can then be observed and followed by quantification using an observation method based on fluorescence to establish the result. This way the relative abundance or profusion of the sequences of the nucleic acid in a sample is found (Clewley, 2004).

There are two types of techniques of microarray which are utilized for the identification of the virus. The first utilizes short oligonucleotide probes and the other utilizes long oligonucleotide probes. The technique utilizing short oligonucleotide probes has been used to detect the human herpes virus (Foldes-Papp et al., 2004). Applications of microarray have been utilized in discovering viruses in animals, for example, beluga whale was found to have the coronavirus (Mihindukulasuriya et al., 2008).

The technology used in microarray is considered as a very important tool in viral screening as it is used in screening for a huge amount of pathogens concurrently.

2.3.1.2 Subtractive Hybridization

The principle of subtractive hybridization is the removal of the sequences of nucleic acid which are common in the two related samples, leaving behind the different sequences. This differentiates between the sequences in two related samples. There are two sources of nucleic acid called the “tester and the driver”; the tester consists of the pathogenic sequence (Ambrose and Clewley, 2006). Restriction enzymes are used to digest the DNA present in the tester and the driver. It should be noted that only the DNA fragments of tester sample are ligated with adapters.

Next the two populations of DNA are first mixed, then they are further denatured into segments, and in the end they are annealed to form four molecules which are “tester/tester,” the “hybrids of tester,” “driver,” and the “driver/driver.” Through this method, the virus is then sufficiently enriched and the sample of tester is then sequenced to identify the pathogen.
2.3.2 Methods Based on PCR

2.3.2.1 Degenerate PCR

It utilizes primers which are specifically designed and manufactured to anneal to the “highly conserved sequence regions,” which are mutual in related viruses. When the primers are designed, they include some degeneracy that allows them to attach to all or the commonly recognized variants on the conserved sequences because these regions are usually not entirely conserved. Degenerate primers are utilized in the detection of viruses which include novel viruses from existent viral homologous families. An example of the use of the primers is in rabbits; they were used to detect an alphaherpesvirus that was linked with their deaths (Jin et al., 2008).

2.3.2.2 Random PCR

Random PCR is used to conduct microarray analysis by amplification and labeling of the probes using fluorescent dyes. It is also associated with identifying novel viruses. Random PCR utilizes two different PCR reactions and two different primers. A singular primer is utilized in initial PCR and has a distinct 5’ sequence with a degenerate hexamer at 3’ end. After this, the next PCR reaction is done with another different specific primer which is complementary to the 5’ region of the initial primer which allows for the amplification of the first products created in the initial reaction. Random PCR is used for finding RNA and DNA viruses and is used for identification of unknown viruses. Examples of a virus which is found through random PCR include a circular DNA virus which was found in the feces of wild chimpanzees (Blinkova et al., 2010) and a seal picornavirus (Kapoor et al., 2008).

2.3.3 Metatranscriptomics Analysis

A general metatranscriptomic experiment includes seclusion of the complete RNA from the microbiome followed with the enrichment of RNA which depends on the type of RNA which has to be sequenced, for example, mRNA, lincRNA, and microRNA. The RNA is then further fragmented into small pieces and then cDNA is synthesized by using reverse transcriptase and random oligo dT primers. The next step includes the repair of the 5’ and 3’ ends or just the 5’ or the 3’ end of the cDNA followed by ligation with adapters. After this, the library is cleaned up, amplification and quantification is carried out, and lastly, the library is sequenced (Liu and Graber, 2006; Ozsolak and Milos, 2011; Ozsolak et al., 2009; Hickman et al., 2013).

However, large-scale use of metatranscriptomics has its limitations in the following: storage and collection of the RNA samples, problems with obtaining sufficient amounts of high-quality RNA from human microbiome samples, the enrichment of mRNA by removal of rRNA, short life of the mRNA, limited transcriptome database, contaminations in the host RNA, and lastly, the poly-A RNA collection kits which are required to store the mRNA population is not usable in prokaryotes (Bikel et al., 2015).
2.3.3.1 Metagenomics Joined With Metatranscriptomic Analyses

Metatranscriptomics is becoming a practical tool to analyze the regulation and dynamics of transcriptionally active microbes. By using metagenomics in combination with metatranscriptomics has enabled us to observe gut microbiome and the results show that it has unique groups of active microorganism in different individuals (Benitez-Paez et al., 2014; Franzosa et al., 2014). The potential of this combination of metagenomics and metatranscriptomics can be observed by looking into the Franzosa study (Franzosa et al., 2014) which states that a fraction of almost 59% of the microbial transcripts are differentially regulated relative to their genomic abundances. Furthermore, it depicted the quantity of gene families, with many that were less abundant at the metagenomics level turning out to be quite active at the level of metatranscriptomics and vice versa (Franzosa et al., 2014). It can be concluded that performing one of the two techniques alone could lead to underestimations or overestimations of the functional relevance of the genes which are encoded in the metagenomes. The author also adds that the functional diversity at the level of transcription displays a subject-specific metagenome regulation pattern which is measured by the function of the top 10 gene families in the specific analyzed individual (Franzosa et al., 2014).

2.3.4 Viral Screening for Development of Therapeutics

The large portion of the antiviral therapeutics which are available in the market involves inhabitation of a viral protein which shows catalytic ability. Viruses encode necessary enzymes which are unique from cellular genes which may make them easier to be targeted with specific therapeutics. Scientists can utilize this property by applying high-throughput small molecular screening technologies or enzyme assays which are target based to determine specific drugs which could inhibit the viral proteins. It is easier to apply this technique on viruses that have a limited coding ability as it is easier to identify if a specific compound is targeting the viral protein or not. This technique is still in research and has recently been employed by utilizing a small molecule library called REDD1 and tested on influenza virus and vesicular stomatitis virus (VSV) infection and by using the Niemann-Pick C1 as a cellular receptor for the Ebola virus (Chen et al., 2010).

2.3.5 Therapy

2.3.5.1 Omics Approach for Elucidating Host and Virus Interaction

Viruses, by virtue of their structure, are dependent on their host for the cellular processes such as DNA replication, RNA capping and splicing, translation, and transport of messenger RNA to accomplish the replication of their genome for invading host machinery and survival (Cherry, 2009). During the process, the viral proteins interact with the host cell proteins to assist the process. Multiple sophisticated technologies have been used to understand the complete process of viral genome interaction with the host cell genome, using the host cell factors, but the complete identification had not been possible due to the absence of systematic methodologies. The recent progress in the development of novel techniques to study cellular factors involved in host–virus interaction has now made it
possible to develop a detailed understating (Watanabe et al., 2010). The development of RNA interference (RNAi) methods has brought the possibilities to study the loss-of-function screenings (Meliopoulos et al., 2012). Some of the recent advances in the high-throughput screening using virus as the examples are listed in Section 2.4.

2.4 APPLICATIONS

2.4.1 Cell-Based Screenings

The antiviral drugs work by inhibiting the viral proteins, therefore hampering the completion of the molecular mechanism needed to complete the viral genome replication. The viruses encode special enzymes which are distinct from the host cell enzymes. Screening for such enzymes helps developing the drugs that inhibit the viral replication cycle. Previously the screening of target proteins led to the development of libraries which were used by the pharmaceutical industry to develop the antiviral drug of interest, but the exact target protein of interest is still marked unknown in most of the disease. Therefore there is a room for improvement and exploration for the development of target-based biochemical assays. Cell-based assays are used to pinpoint the target compounds used against the viral proteins. Since viruses have limited coding capacities, the screening can provide straightforward evidence whether a specific compound hampers the viral replication process by targeting the viral proteins. Compounds can be targeted this way but the identification of the cellular pathway is not possible with the compound screening technique. New targets for some of the viruses have been discovered using this technique. Some examples have been shared in Table 2.1.

The method of developing therapeutic molecules using the small molecules or target molecule/compound screening has worked successfully for various diseases but the limitations of this method can be overcome by the use of reverse genetic screening methods which directly reveal the sequence of the target molecule (Mata et al., 2011; Côté et al., 2011; Filone et al., 2010).

2.4.2 Gain-of-Function Method

One of the basic techniques that are used in genetic screening is the gain-of-function method, the other being the loss-of-function approach. In the gain-of-function approach, the function of a specific gene can be probed with the help of the ectopic cDNA

| TABLE 2.1 Examples of Target Proteins in Viral Replication Cycle |
|---------------------------------------------------------------|
| Compound                  | Function                                      |
| Protein kinase Cε (PKCε) | A factor required to assist the infection by Rift Valley virus |
| REDD1                     | A factor that restricts the infection by VSV and the influenza virus |
| Niemann-Pick C1 (NPC1)    | Ebola virus cellular receptor                   |

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expression. Previously, the technique used the libraries of shotgun cloned cDNA. The MCG collection has enhanced the applicability of this technique.

2.4.3 Loss-of-Function Method

The RNAi methodology has been used for the development of the loss-of-function screening. The different RNAi tools such as the short hairpin RNAs, small interfering RNA, and the long double-stranded RNA are some of the commercially available tools used for this purpose.

2.4.4 Comparative Genome Profiling

The comparative genome profiling helps to find out the potential viruses in the same family or between different families that target the same enzymes, proteins, or cellular factors. The screening for the proteins gives only the modest target proteins by the RNAi screens because of a minimal overlap against the same virus (Stertz and Shaw, 2011). The comparison between the viruses of the same group has been made; for example, the comparative screening for coxsackievirus B and polio virus infection in polarized endothelial cells was performed and more than 70% host factor dependency overlap was observed (Coyne et al., 2011). Genome profiling study revealed a high level of dependency in the flaviviruses (Krishnan et al., 2008). A comparative genome profiling performed on the gene set of lymphocytic choriomeningitis virus, varicella zoster virus, and human parainfluenza virus type 3 revealed that all three viruses had 35% similarity of the validated genes (Panda et al., 2011).

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