Journal of Advances and Scholarly Researches in Allied Education
Vol. 16, Issue No. 9, June-2019, ISSN 2230-7540

Review on Mycobacterium Tuberculosis

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Abstract – Mycobacterium Tuberculosis (M. tuberculosis) is the bacterium causes the diseases called tuberculosis. It is one of the most serious global health issues across the world. M. tuberculosis' molecular typing is applied in different types of epidemiological conditions. It is also used in different modes of clinical management. In modern medical science, M. tuberculosis is typed through different techniques. Selecting the best technique according to the existing laboratory conditions and location-specific geographical features are important for M. tuberculosis typing. Restriction Fragment Length Polymorphism (RFLP) examination is considered as the best standard for molecular epidemiologic examination of tuberculosis. This process of investigation is based on IS6110 standard. A few species of the Mycobacterium Tuberculosis Complex (MTBC), especially Mycobacterium tuberculosis that is responsible for tuberculosis disease in human (commonly called TB) are the first reason of death connected to a distinct pathogen globally. In the last fifteen years, medical studies have improved a lot that has helped to understand MTBC more closely and traced its long co-evolution with the human race. It is capable of remaining latent in the human body. Humans are in fact its extraordinary asymptomatic career. Almost, one-third of the entire human population is the latent career of this bacterium. It is found to be highly resistant to antibiotics that are a proof of its evolutionary success.

Keywords: Tuberculosis, Mycobacterium Tuberculosis

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1. INTRODUCTION

One of the most common global health challenges that threats a large volume of the global population is tuberculosis. It is one of the easily communicable diseases that can acquire a deadly dimension. Tuberculosis also referred to as TB is caused by the infectious Mycobacterium tuberculosis. This contagious ailment affects generally the human lungs and also other body parts such as nails and hair. This is a disease that causes the death of nearly 1.3 million people every year. Research and survey reports summarize that nearly one-third of the global population is affected by this deadly disease. It is said that the rate of this disease is increasing at a rate of 1% on an annual basis [1].

The process of a direct analysis of the genomic polymorphism through molecular typing is used for understanding the population dynamics, evolutionary history, and common bacteria dissemination process has been improved. The process of M. tuberculosis molecular typing is put to use for epidemiologic purposes such as investigating the outbreak dynamisms, communities and their healthcare settings, to understand the proportion of epidemiologic links through the process of conventional contact tracing. This helps in understanding improper diagnosis out of laboratory cross-contamination. It will help you understand about reactivation or reinfection of the bacteria, the process of transmission of the diseases to the other subpopulations and the relation between genotypes and drug resistance.

Genotyping of M. tuberculosis for the purpose of molecular epidemiology has been done since the early 1990s. a recent strain distribution done on the global basis for M. tuberculosis linkages shows that the strain of Beijng was found to be the most prevalent in the region of East Asia and is found in more than 50% of all the cases. These genotypes are found to be present in the regions of North Asia, Central Asia, and also Southeast Asia. A small portion of the strain was also found in the regions of Western Asia, southern Asia, Australia, Africa, Central Austral, Australasia, Northern Europe, North America and also South America area. The method of genotyping helps the medical practitioners know all about the epidemiological details of the disease and also better and improved methods of managing the disease [2]. The process of strain classification comes to help while understanding the role of the genetic factors and

other elements of drug resistance, failure of treatment and also the problem of the transmission index of the disease. The method of molecular typing is being used in a number of places to understand the aspects of epidemiological trends, cross-contamination of cultures and also drug resistance aspects.

For the genetic fingerprinting of M. tuberculosis, the gold standard is insertion sequence IS6110-based restriction fragment length polymorphism (RFLP) analysis. However, similar discriminatory power and greater convenience has been demonstrated with other methods such as spacer oligonucleotide typing (spoligotyping), which detects 43 spacer sequences interspersed with direct repeats (DRs) in the genomic region uniquely present in members of M. tuberculosis complex; mycobacterial interspersed repetitive units-variable number tandem repeats (MIRU-VNTR) that uses polymerase chain reaction (PCR) amplification and gel electrophoresis to determine the number and size of tandem repetitive DNA sequence in 12 independent loci in the M. tuberculosis genome; repetitive-sequence-based PCR (rep-PCR), which is a fast and unified method for high-throughput genotypic fingerprinting of multiple Mycobacterium species; and whole genome sequencing (WGS), a recent method with high discriminatory power.

There are other molecular approaches that are used for making a study of the microbial diversity, however, the IS 6110 – restriction fragment length polymorphism and also the method of variable number tandem repeat are the most prominent methods [3]. Apart from using a study of the molecular diversity this method also helps in the study of the outbreak of the ailment in a certain region. It also helps in understanding the nature of the transmission of the disease [4].

The IS 6110 RFLP is also known as the gold standard method used for molecular typing and is also used popularly for strain differentiation for Mycobacterium tuberculosis [5]. A sizable number of M. tuberculosis clinical isolates from India are reported to be without or with low copies of IS 6110 elements (Radhakrishnan et al, 2001), thus suggesting the limited use of this method in sub-speciation of M. tuberculosis isolates in South Asia [6].

The process of IS6110 RFLP typing of Mycobacterium tuberculosis has been used to understand the transmission of the problem and is one of the most popular forms of molecular typing processes. M. tuberculosis isolates from epidemiologically linked patients generally show identical IS6110 RFLP patterns, thus comprising transmission clusters. Consequently, the finding that a substantial proportion of tuberculosis cases in industrialized countries are clustered by DNA fingerprinting is interpreted as a reflection of a high rate of recent transmission. Nevertheless, the IS6110 RFLP always does not give correct readings that will initiate at correct epidemiological relation between different patients. Again since in a number of cases tuberculosis can occur out of general reasons, the link can be understood only after uniting the genotyping of M. tuberculosis isolates with the epidemiologic investigation. However the IS 6110 RFLP is a lengthy and time taking process which hinders early detection and prevention of the ailment.

Te mycobacterial interspersed repetitive typing method offers a great solution for the problems faced by the methods of IS 6110 RFLP. The MIRU-VNTR is a process that is much faster than the earlier method of IS 6110 – RFLP. Hence the process of MIRU-VNTR has been a better-preferred process of testing as compared to the older one. It gives us faster and more accurate results.

2. ETIOLOGY OF THE TUBERCULOSIS

The Mycobacterium tuberculosis is a rod-shaped bacillus that causes the ailment of tuberculosis. The bacilli are generally the size of 2-4 micrometers and 0.2 – 0.5 uM in width. The small size of the air droplets enabled the bacilli to get caught in the air droplets which are formed during sneezing and coughing by the patients of this disease. The bacilli remain in the aerosols that remain loaded with the bacilli when gets inhaled by a healthy person in the immediate proximity of the patient to get affected by the disease [7]. Often the bacteria remain within the body of the patient till it gets favorable conditions for growth such as immunity deficit or malnutrition.

The exact location of the infection decides whether the tuberculosis is a pulmonary one or an extra pulmonary one. The former is the most common form of the ailment and occurs mainly in the human lungs. Some of the common symptoms of this disease are coughing with blood, chest pain and the existence of pain for more than three weeks. In the case of the latter form of tuberculosis, the symptoms can be different and often gets decided by the nature of the place that is has affected [8]. Some of the common sites include the pleura in tuberculosis pleurisy, the central nervous system in meningitis, and lymphatic system in scrofula of the neck, a genitourinary system in urogenital tuberculosis, and bones and joints in Pott's disease of the spine. Extra pulmonary TB occurs more commonly in immune suppressed persons and young children [9].

3. MEMBERS OF MYCOBACTERIUM TUBERCULOSIS COMPLEX

In a research that was done currently it was found that the causative organisms of tuberculosis that was found to be developed in the East of Africa

about forty thousand years ago were from a collection of ancestral tubercle bacilli which together can be called as Mycobacterium Para tuberculosis [10]. In the beginning, it was found that bacilli used to cause infection in humans but approximately 10,000 to 20,000 years later it was divided into some other lineage that causes disease among animals [11]. These thoroughly associate causative organisms of the tuberculosis were together called as Mycobacterium tuberculosis complex. It includes Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium canettii, M.microti, Mycobacterium capraeand Mycobacterium pinnipedi.

4. RESTRICTION SITE ANALYSIS OF GENOMIC DNA

The molecular typing of M. tuberculosis was initially tried on the basis of the Restriction Enzyme Analysis (REA) of the DNA of bacteria. With the help of various REA, the chromosomal DNA of the examined strains is assimilated and the resultant fragments are divided and envisaged by electrophoresis gel. The pattern of DNA fragments, for example, the inherited fingerprint that was obtained is characteristic for each strain. However, using the original process, the sensitivity of the technique is rather limited because of the technical problems in offering a high-resolution electrophoretic parting of fragments inside a broad variety of sizes. Also, a huge number of DNA particles will create a dependable analysis impossible. Hence, a new method is offered for additional correct separation of DNA molecules, for example, REA-PFGE (pulsed-field gel electrophoresis), that assures high resolution of the constraint patterns. More normally used methods, which are changes of the customary REA, engage DNA hybridization examination in the procedure of particular pattern detection. Precisely, after electrophoresis, the detached DNA fragments are denatured in situ and moved onto a membrane, which is then hatched with a radiolabeled probe (Southern blot) for the objective order. Hybridization signals are also envisaged on autoradiography. The Southern blot method was initially applied to the examination of Restriction Fragment Length Polymorphism (RFLP), which is henceforth a mixture of REA as well as hybridization technology. In the previous research studies, RFLP methodology was utilized which shows that strains of M. tuberculosis presented a significantly low degree of genetic variation. However, such understanding of the outcomes was essentially ambiguous since investigations used in that type of research studies targeted extremely preserved regions and were of low specificity. The resolution of the RFLP method augmented considerably when Insertion Sequences (IS) were recognized and used in investigation construction. Different repetitive orders that were found in the genomes of M. tuberculosis and NTM are a significant source of genetic polymorphism and offer a reliable marker that permits the determination of genetic relations at both species as well as strain levels.

5. MOLECULAR STRAIN TYPING OF MYCOBACTERIUM TUBERCULOSIS

Initially, explained Mycobacterium tuberculosis supplement order IS6110 and its implication as the normal method to genotyping of M. tuberculosis separates on the basis of RFLP analysis. It was demonstrated by numerous studies [12]. IS6110 is from the IS3 family of mobile elements and it is found to be 1,355 bp long. The IS6110 is only within the M. tuberculosis complex, and, the sequence is found to exist in numerous copies, though M. bovis usually covers only one copy. Overall, the copy number of IS6110 varies from 0 to 25, which actually depends on the frequency of transposition. It is conditioned mainly by the nature of the genomic area at which an exchange happens. Alterations in the copy number, as well as the locations within the genome, are accountable for the high degree of IS6110 polymorphism. Apart from that it also has predisposed this order to be beneficial as a particular molecular marker for genotyping M. tuberculosis stresses.

It was also found that the IS6110-RFLP process is extremely biased and reproducible, and its profiles are steady over some period of time. It permits us to differentiate epidemiologically associated separates from unconnected ones. The half-time of the modification of the IS6110-RFLP pattern is assessed in several studies. The rate at which IS6110-RFLP patterns transforms is important to know for the accurate explanation of molecular typing in the epidemiology of tuberculosis. A projected rate of variation may support the value of IS6110-RFLP typing for recognizing TB circumstances related to the current transmission or long term epidemiological research study. The half-time of the alteration of the IS6110-RFLP pattern is also assessed in several research studies. De Boer et al considered that the half time was 3.2 year. However, Warren et al considered the half time as 8.74 years and also exposed diverse rate of alteration in RFLP band pattern that totally depends on the phase of the disease.

The key benefits of the IS6110-RFLP process are its extraordinary inequitable power, reproducibility, as well as the steadiness of its pattern. The key restriction of the process is the low inequitable power in isolates offering five or lesser IS6110 copies. In many research studies, it was confirmed that the occurrence of clinically established epidemiologic links that are there in between the cases was lessened in groups designed by isolates with five or lesser IS6110 copies.

As TB is an old human disease, it is crucial to study its history along with humans for explaining how this bacterium has grown and the present TB

epidemiology. In fact, the current data have confirmed that, opposing to what was initially thought TB has been producing a serious effect on humans from the time before the agriculture or animal/plant domestication was developed during the Neolithic transition. It is guessed that this bacterium has developed in humans approximately 70 000 years ago. Actually, Roberts et al (2009) has planned that TB could precede modern humans a 500 000-year-old fossil of Homo erectus was discovered in Turkey along with distinctive TB bone scratches. These studies propose that opposing the widespread hypothesis MTB does not have the origin of an animal, instead, a human origin was found. This hypothesis is reinforced by the reduced size of the genome of M. bovis (60000 bp smaller) and of additional MTBC animal species in comparison to that of the human species [13]. Thus MTB and animal species, such as M. bovis, can share a mutual ancestor, and the transmission might have happened from humans to the animals during animal/plant domestication at the time of the Neolithic period [14]. However, in the current analysis of Mycobacterium genomes which was taken from Peruvian skeletons of the pre-Columbian period, it was found that sea mammals might have played a part in the diffusion of TB beyond the ocean. The data which is available support the hypothesis of inclusion of MTBC into the American continent through the pinnipeds, followed by a human adaptation as well as the following spread in the region [15].

As per Gutierrez et al (2005), the mutual ancestor of all MTBC species might have created from M. Canettii as well as the group of smooth tubercle bacilli from the East of Africa. Based on the series of six housekeeping genes, estimated age of three million years for this type of common ancestor was assessed by authors whom they called Mycobacterium prototuberculosis. On the other hand, this dating is also disputed by Smith (2006). It should keep in mind that Africa is the only county that has all seven MTBC ancestries which are adapted to humans and hence the largest genetic variety in the world is found in Africa [16]. This condition completely reflects that of contemporary humans. Certainly, Homo sapiens that are found in Africa are taken to be the predecessor of contemporary humans and to comprise the largest genetic variety [17]. Lastly, MTBC adjusted to humans demonstrates a phylogeographical population construction with ancestries that are more precisely related to specific human populations [18].On these bases; the suggested situation is that human MTBC could have created from Africa and hence has been contaminating humans for several years. The relocations of contemporary humans out of Africa and the improved population density at the time of the Neolithic period could be at the beginning of its growth [19]. Actually, when four ancient ancestries have endured in Africa, the other ancestries could have left Africa and spread. It was found that the three modern ancestries have occupied Europe, India, and China, perhaps due to the unexpected population upsurge in these areas. Later, human relocations, trading as well as human colonization of countries and continents also found to be contributed to their dispersal for developing final endemic all over the world [20]. This situation was established by the discovery of the molecular signatures of the growth of current inhabitants in less than 200 years on the basis of the study of minisatellites. These authors detected that these signatures were more noticeable in the European and Asiatic inhabitants than that of the African inhabitants, which supported the 'out-of-and-back-to-Africa' situation as suggested by Hershberg et al (2008).

It is now found that MTBC has grown collectively with humans for a long period of time and that they have thus prejudiced mutually for their development. Epidemiological data, as well as the work done by Comas et al (2013) on the contrast of mitochondrial DNA from humans and also from MTBC ancestries, propose that the various ancestries which might have precisely modified to the diverse human populations. Certainly, specific human inherited variations are also related to diverse MTB ancestries, which clearly signify that the tight connections between humans as well as the MTBC. These data designate that, as for several other infectious diseases, the long co-evolution of MTBC with humans had a consequence on the biology as well as the epidemiology of TB found in human beings. It is found that TB has every feature of a high-population-density sickness and also of allow-population-density disease.

5. CONCLUSION

Tuberculosis (TB) is certainly a curable contagious disease which is mainly caused by Mycobacterium tuberculosis composite strains. Molecular typing using IS6110 is usually used as the normal technique in studies of the diffusion of tuberculosis, on the supposition that IS6110 RFLP-based clustering of cases is the outcome of current transmission. Presently, molecular typing is extensively used by various TB control programs since it provides an influential tool for displaying epidemiologic trends as well as diffusion dynamics of drug-resistant strains. It is essential not only for the evolution phase of moving to the innovative technology but also significant that over such a grouping, we will get substantial information but it depends on the hereditary characters as well as changes of each M. tuberculosis strain. However, as per Gagneux (2012), it is essential to note that the low rate of active TB comparative to several people with dormant TB proposes that MTB is not a 'potent' pathogen. However, it is found to be very competent in producing secondary contamination succeeding active TB. Gagneux (2012) imagined that infection which is caused by MTB and he

found it to be beneficial for some persons who have a very less chance of developing the active disease.

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