Review Article

J Babol Univ Med Sci
Vol 17, Issu 2; Feb 2015. P:71-80

An Overview of the Evolution of Pathogenicity in Human Pathogenic Fungi

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Received: Nov 29th 2013, Revised:Mar 7th 2014, Accepted:May 1st 2014

ABSTRACT

BACKGROUND AND OBJECTIVE: The number of fungal species on earth is estimated at about 1.5 million species, among which about 400 species belong to animal and human pathogens. Human pathogenic fungal species are mainly isolated from plant hosts. Studies on multi-host fungi have shown that with changes in physiological pathogenicity, these fungi are able to change their host according to the circumstances they are in. Horizontal gene transfer may play an important role in the evolution of fungal virulence in human hosts.

METHODS: In this retrospective study, Pubmed, Medline, Scopus, Google Scholar, Elsevier, Irandoc, Iranmedex, Magiran, SID, and MEDLIB databases were searched thoroughly. MeSH keywords in our search included the evolution of virulence, pathogenic fungi, human pathogenic fungi, pathogenic plant fungi, horizontal gene transfer, and limited host plants. The related articles, published during 1992-2010, were extracted and retrospectively studied.

FINDINGS: Molecular studies on multi-host fungi confirm the hypothesis of pathogenic fungal evolution from plant hosts to human hosts. The present study evaluated the recent findings on the origin of human pathogenic fungi and host changes from plant to human hosts.

CONCLUSION: By comparing the content and structure of genomes and genes in pathogenic fungi, with different host ranges, penetration methods, and pathogenicity, we will have a better understanding of pathogenic genes and the processes involved in the evolution of the disease.

KEY WORDS: Evolution of Pathogenicity, Pathogenic Fungi, Human Pathogenic Fungi, Plant Pathogenic Fungi, Horizontal Gene Transfer, Host Plant.

Please cite this article as follows:

Arzanlou M, Samadi R, Afsarian MH, Badali H. An Overview of the Evolution of Pathogenicity in Human Pathogenic Fungi. J Babol Univ Med Sci. 2015;17(2): 71-80.

Introduction

Among 1.5 million fungal species that have been reported so far (1), about 400 species belong to animal pathogens. Some of these fungi have been identified as pathogenic agents in humans. However, unlike plants

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[DOR: 20.1001.1.15614107.1393.17.2.10.5]

[DOI: 10.22088/jbums.17.2.71]

in which fungi are considered as major pathogenic agents, viral and bacterial diseases are more important than fungal diseases in animals (2). Fungal agents sometimes cause severe and fatal injuries in animals; in fact, invasive fungi are a major cause of death in many patients with compromised immune systems. These injuries and diseases include brain abscess, pneumonia, candidiasis, coccidioidomycosis, cryptococcosis, skin diseases such as tinea nigra and chromoblastomycosis, and eye infections such as keratitis (3-6).

Agents contributing to these diseases have unique characteristics that enable them to survive in the human body. Candida, the most common agent of candidiasis, which survives as commensals in the human intestine, is able to survive in humans and infect the body due to characteristics such as varying cell morphology, frequent replacement of colony phenotype, genetic variations, and reactions with various bacteria in the body (7).

Moreover, major human fungal pathogens can be found as species in the soil. Cryptococcus neoformans is a terricolous fungus that is able to produce melanin and polysaccharide capsule, express locus, secrete phospholipase, and use a variety of carbon sources to infect the human body and cause cryptococcal disease, given its ability to withstand a wide temperature range (from room temperature to physiological temperature in mammals) (8-10).

Coccidioides immitis, the agent of coccidioidomycosis in humans, is a dimorphic fungus that survives as a saprophytic mold in soil. This fungus can infect humans as systemic pathogens by morphological changes at 37 °C. The transfer of fungi to humans has been reported not only in soil as an inanimate environment but also from living organisms such as plants. In fact, plants are the most important source of the inflammation of the cornea or keratitis in humans (11).

In a more comprehensive look, common elements of human and plant pathogens are observed in all fungal and sub-fungal branches. In ascomycota order, aspergillus flavus is able to infect animals, insects, and plants, especially corn, peanuts, cotton, and hazel tree; this species, like several other species, can produce carcinogenic and highly toxic aflatoxins in humans and livestock (6, 12).

Ustilago maydis of basidiomycota order, as the agent of corn smut, causes skin injuries in humans (13). Also, schizophyllum camionero genus is considered as the agent for wood rot, which also has the ability to grow on human nails and toes. Rhizopus oryzae, which belongs to zygomycota, is the main agent of rice rot and the most common cause of mucormycosis in humans. Of yeast-like fungi (black yeasts), belonging to the order Chaetothyriales, cladophialophora, fonsecaea, and exophiala can be mentioned as agents living as saprophytes on decaying leaves and trees and leading to fungal diseases (from the relaxed type to lethal encephalitis) in humans and animals under ideal conditions (14-16). Finally, oomycota, belonging to the sub-fungal order pythium insidiosum, is a major cause of the rotting of seeds and roots and damping; this agent can cause pythiosis in humans (17,18). Although it is stated that most fungal infections result from opportunistic fungal parasites, having two series of different plant and human hosts can indicate the possible existence of a relationship between these agents in terms of nutritional evolution.

Methods

In the present retrospective study, databases including PubMed, Medline, Scopus, Google Scholar, Elsevier, Irandoc, Iranmedex, Magiran, SID, and Medlib were thoroughly searched. MeSH keywords in our search included the evolution of pathogenicity, pathogenic fungi, human pathogenic fungi, plant pathogenic fungi, horizontal gene transfer, and limited host plants. The articles published during 1992-2010 were extracted and retrospectively studied.

The infection of two hosts from two series: Pixiediaphora is an example indicating that the proximity between the diffuse host of "insects" and the main host of "fungus" leads to the parasitism of the diffuse host. Studies have shown that this genus can be the ancestral form of other laboulbeniales as obligatory insect parasites. Opposite of this mode has been observed in the cordyceps of order hypocreales.

Presence of a fungal parasite species among the members of this genus, which are mainly considered as parasitoids, indicate a situation that the terrestrial life of the host of ‘cicada larvae’ enables the possibility of nutritional evolution towards parasitizing

[DOR: 20.1001.1.15614107.1393.17.2.10.5]
[DOI: 10.22088/jbums.17.2.71]

cleistothecium of elaphomyces fungus (19). It should be mentioned that this genus belongs to the clavicipitaceae family.

In comprehensive evolutional studies, the clavicipitaceae family is divided into three clusters with evident inter-host mutations in each. Cluster A is unique to members that show inter-series mutations from animal to plant hosts in such a way that phylogenetic analyses indicate a close relationship between the common ancestor of the symbiotic fungi of plant species and insect fungal pathogens. This relation is confirmed based on the characteristics of symbiotic fungi including the biochemical potential of forming biologically active compounds against animals specifically insects (a feature inherited from animal pathogens), inability of most species to attack plant cells, non-responsiveness of tepic host to symbiotic fungus, and production of secondary metabolites.

However, phylogenetic studies indicate that the possible ancestors of animal pathogens come from necatoriasis by plant pathogens in an unknown way. In fact, plant symbionts show a nutritional return from animal to plant nutrition due to supplying the major carbon needs by plant hosts (20). Chaetomium globosum, as a root endophyte, is another example of plant symbiotic fungus whose aerobic spores can cause diseases such as pneumonia and brain infections in those with weakened immune systems (21, 22).

Chromoblastomycosis is a syndrome that can be caused by members of the order chaetothyriales. This order along with the sister group verrucosa is evolved from its rock-inhabiting ancestor, pyrnolal . Members of these three orders are known as close relatives and phylogenetic data have also confirmed the results (23). Studies have shown that the evolutionary path of verrucosa members from rock-inhabiting ancestors has moved towards lichen fungi (independent of other lichen members), given the unique characteristics of these fungi. Due to factors such as hyphal melanization, withstanding high temperatures, and meristem growth, members of chaetothyriales order also have gained the ability to live in abnormal environments and have evolved into two groups of plant and human pathogens (24).

The herpotrichiellaceae family of this order can infect humans and animals. Unlike the two other orders, members of the order chaetothyriales are mainly found in an asexual state in cladophialophora genus. Cladophialophoras include a wide host range of foliar pathogens such as cladophialophora hostae and cladophialophora protea, cactus endophyte such as cladophialophora yegresii, and human pathogenic species such as cladophialophora carrionii and cladophialophora bantiana.

Cladophialophora carrionii is the main agent of chromoblastomycosis or feohifomicosis from the relaxed state to fatal encephalitis in humans (25, 26). Endophytic cladophialophora yegresii has been proposed as the sister of cladophialophora carrionii (24). Therefore, the striking phylogenetic distance and high phenotypic similarities of these two species, presence of cladophialophora yegresii as cactus endophytes, adjacent to the residues of cactuses infected by cladophialophora carrionii, tracing cladophialophora carrionii in the area of spines rich in tannin remains of cactus, its less adjustment for growing in healthy cactuses and rural workers who live in the vicinity of the plant being affected by a disease with cladophialophora carrionii factor propose a hypothesis for the evolution of pathogenic fungi associated with plant hosts to human hosts. The plant remains spines, herein, as a transmission path for fungal factor from plant host to human host are considered as two different ecological environments. One of the major factors for the adaptation of the members of this order to human hosts is the ability to grow and survive in monoaromatic alkylbenzene, as the sole carbon source; i.e., the members of this order are enabled to survive in different ecological environments such as soil contaminated by a chemical compounds of foreign origin, natural environments such as grain, wood, and plants, stagnant surfaces, and living tissues of mammals. It is proposed that alkylbenzene absorption is an amplifying factor for virulence. However, major ecological similarities such as high temperature, osmotic pressure, and oxygenic activity have had a significant impact on the adaptation to such environments and the nutritional evolution of this fungus to human hosts (23-27).

Although the tendency of the fungus to exist in plant residues and transfer from these residues to human hosts can indicate the reduced tendency of the fungus to survive in plant hosts (and the nutritional

[DOR: 20.1001.1.15614107.1393.17.2.10.5]
[DOI: 10.22088/jbums.17.2.71]

change to human hosts), some researchers believe that plants only play a role in the dispersion of fungi, considering the transmission of the disease from the remains (25).

In this regard, the theory of the nutritional evolution of plant host to human host was confirmed by the isolation of fonsecaea pedrosoi, another agent of chromoblastomycosis in humans for indicating the closeness of the cuticles of the thorns of the plant mimosa pudica as a primary source of contamination by Coods et al. (28). Cultivation of two specimens obtained from the patient's wound and thorns of the plant showed morphologically similar fungal colonies (28). However, the meristematic growth of the fungus in plant thorns and the dominance of berry-like cells of these fungi, compatible with abnormal environments compared to the hyphae in humans, undermine the evolution theory. This means that humans cannot be considered as the natural preservatives of such fungi. However, the morphological change can be considered as an evolutionary strategy to adapt to a new host (25). Penicillium genus, one of the most common agents of decay in nature and among plant and human pathogenic agents, is an example for verifying the evolution theory. Penicillium marneffei species is one of the agents of respiratory, skin, and liver infections in humans, which shows an evolutionary adaptation to parasitizing the human host due to changes from the hyphae form to a yeast form in the human body (similar to coccidioides immitis), tolerability of a wide temperature range (similar to cryptococcus neoformans), and having cell division (similar to schizosaccharomyces) (4,9,10,17,18,29).

The remarkable point is that despite the fact that many of the fungi associated with plant hosts are able to adapt themselves to cause a disease in humans, in a common human and plant pathogenic agent, very low concentrations of fungal spores can generally infect the plant host. Since infecting the animal host requires the presence of high concentrations of the fungal agent, perhaps they can not be considered as the ancestral hosts in the fungus, and the nutritional evolution under abnormal conditions has led them to parasitize the animal host; in fact, during this evolution, adaptive changes might have occurred.

Several strains of aspergillus flavus, isolated from animals and insects, are capable of causing a disease in corn. It is stated that creating differences in food pathways may affect the virulence of the strains on different hosts in a way that cysteine and methionine auxotrophs decrease the conidia formation in vitro on plant hosts, while they are complementary factors for disease cycle in insect hosts (30).

The physiology of pathogenic factors in plant and animal hosts: The adhesion and connection of fungal agents to the host is the initiation of pathogenic cycle on different hosts. The derive for level identification such as chitin in the animal pathogen of cordyceps bassiana (3) and fatty alkaloids on avocado (concerning colletotrichum gloeosporioides pathogens) are among the factors contributing to the attachment to the host.

Generally, factors affecting the attachment to the host play a significant role in the germination of fungal spores in the next stage of infection. In general, the germination of plant and animal fungal pathogens is similar and requires a set of specific conditions such as humidity, morphological and metabolic changes, and special compounds. One such component is hydrophobin, proteins rich in cysteine, covering the surface of fungal spores. This compound has the same structure of animal and plant pathogenic fungi; however, it shows different performances in two different hosts.

In plant pathogens such as madurella grisea, hydrophobin is involved in germination, conidia formation, appressorium formation, and pathogenesis, while in animal pathogens such as aspergillus fumigates, it protects the conidia against macrophages and dehydration in the area during internal invasion.

Ras is another protein that regulates the spore germination and pathogenic development in plant hosts. In the plant pathogen, this combination is coded by Cdc42 gene, similar to candida trifoli. The presence of Cdc42 gene in animal pathogens such as candida albicans has been demonstrated. This gene is involved in the formation of germ tubes and the invasive hyphal growth of the pathogen in such a way that its absence reduces the infection in mice "as the experimental model of man" (31-33). However, germination will be effective in infection if it manages to penetrate into the host tissues.

Penetration significantly varies between animal and plant pathogens. While penetration through the

[DOR: 20.1001.1.15614107.1393.17.2.10.5]
[DOI: 10.22088/jbums.17.2.71]

receptor, by the help of host macrophages, can be only seen in animal pathogens, direct penetration is specific to animal pathogens. Direct penetration is divided into mechanical and chemical types. Mechanical penetration in the plant host is done by producing appressorium. Appressorium production is associated with a protein called tetraspanin that is necessary in the penetration of plant pathogens such as botrytis cinerea and magnaporthe grisea into the host tissue, given its role in the production of penetration nails.

Although mechanical penetration into animal pathogens is not seen as a result of appressorium production, tetraspanin is involved in a variety of animal fungal infections in the differentiation and loosening of host tissue cells (34-36). Melanin is another cell-wall-associated compound, which plays an important role in penetration into host cells through melanizing the appressorium penetration nail into plant fungal pathogens like pyricularia oryzae, colletotrichum lagenarium, and hyphae in gaeumannomyces graminis (10, 37).

Although the influence of melanin on human pathogenic fungi has not been proven, the composition of the cell walls of human pathogenic fungi that contain dark hyphae has been demonstrated. Melanin in human pathogens acts as a pathogenic factor in the overthrow of the host immune system and plays its role via its protective effect against oxidative burst through the host immune response, resistance to enzyme digestion, host microbial peptides, and binding to hydrolytic enzymes (11,38,39). Chemical penetration is another form of direct penetration in plant fungal pathogens by hydrolytic enzymes such as cutinase, pectinase and cellulase. Another hydrolytic enzyme is asparatyl proteinase, which has been observed in plant pathogens such as sclerotinia sclerotiorum, and botrytis cinerea; however, the role of this enzyme is still unclear. Sparatyl proteinase also becomes synthesized in human and animal pathogenic ascomycetes. The enzyme in candida albicans contributes to tissue adhesion, loosening, and host molecule damage during nutrition. Toxins are among other effective compositions in infections.

These compositions are effective in colonizing the host tissue and causing the death of the host as they provide the pathogen with food. Toxins are divided into specific and non-specific types. Plant pathogens are able to produce both specific and non-specific toxins, while the production of specific toxins by animal pathogens has not been confirmed (40). Temperature plays a key role in triggering germination and infection in the host, especially animal pathogens. For instance, in penicillium marneffei, fungi are capable of causing infection only by the conversion of mycelium form at 25 °C to yeast form at 37°C (41). Morphological change is an important virulence mechanism against the host immune response and infection development. Candida albicans is capable of causing infection only by converting from yeast to mycelia form, which is related to fungal beta-glucans not being recognized by the host receptor in hyphae. These dimorphic changes do not generally occur in plant pathogens (42, 43).

Amplification is the final step of pathogenicity, occurring for pathogen amplification and survival. Unlike plant pathogens, the success rate of animal fungal pathogens is very low, and they generally lack a sexual state. However, recent reports of aspergillus fumigatus, responsible for aspergillosis in immunocompromised individuals, indicate pheromones and mating-type genes in this fungus as common plant and animal pathogens (44,45). This could indicate the loss of some of the fungal pathogenic features during the evolution of plant fungal pathogens to human fungal pathogens.

Horizontal gene transfer during evolution: Horizontal gene transfer causes increased pathogenic capacity, massive increase in the host range, and even changes in the type of host by affecting the population structure via mating, synthesis of small molecules, and transfer of pathogenic factors. Horizontal gene transfer in eukaryotic genomes, especially fungi, is not as significant as bacterial genome. Horizontal gene transfer in fungi has been reported at intra-series and intra-genus levels; however, there is little evidence about the role of this phenomenon in the evolution of human fungal pathogens. This could be due to the relatively small amount of fungal genomes available for analysis, the ancestral nature, and difficult identification of this phenomenon.

For horizontal gene transfer in fungi, we can mention obtaining URA1 gene from saccharomyces cerevisiae of lactobacillus species, the transfer of genomic regions involved in secondary metabolism

[DOR: 20.1001.1.15614107.1393.17.2.10.5]
[DOI: 10.22088/jbums.17.2.71]

from magnaporthe grisea (plant pathogen) to aspergillus clavatus, and horizontal gene transfer in candida, fusarium, and aspergillus oryzae. Genome-wide analysis on three species of fusarium has shown complete chromosome transfer with the ability to cause infection in different fungal strains. Horizontal gene transfer has been reported in the species pathogenicity locus among the members of fusarium oxysporum lycopersici species. Studies on the multi-host fungus fusarium oxysporum show an evolution from the plant host to the human host.

Results

Since 1973, fusarium has been reported as one of the leading causes of poisoning and superficial or localized infections in a large number of people suffering from immunodeficiency. Most fusarium species, associated with human infection, belong to two compound groups of fusarium oxysporum and fusarium solani (46). These two species, along with fusarium verticillioides, have a dual ability to cause disease both in plants and humans (47).

Even though fusarium oxysporum is less pathogenic than fusarium solani, it exhibits the general pattern of opportunist fusarium species and is considered in the study of animal pathogenic fungi (47). This species accounts for most of soil's saprophytes and organic matters and is the main cause of vascular wilt, rotting in onion and storage organs, and root and plant death. This species is found in the rhizosphere of many plant species throughout the world and has several specialized forms which vary in terms of host range (17). The fusarium responsible for vascular wilt in tomato is the best example of human and plant pathogenic isolate, which is capable of killing mice suffering from immunodeficiency (2). The 4278 isolate of this species is able to survive and reproduce in immunocompromised mice, colonizing multiple organs and ultimately causing the death of the host. This ability is related to the fundamental characteristics, required for pathogenesis in mammals. The study of this fungus has revealed clear differences and similarities in its pathogenic mechanism in animal and plant hosts (46).

Studies conducted on the genome of various fungal groups have indicated differences in pathogenic patterns between animal and plant models. Fmk1 gene is required for infection in plants but does not play a significant role in animal hosts. In plant hosts, gene ChsV causes resistance to antifungal compounds due *to* chitin synthetase during pathogenesis, while in animal hosts, it causes gradual death in wild species and slow death in mutant individuals. The reason for this is that morphological changes in the microconidia of the pathogen are mutated in individuals.

PacC gene is also part of the intracellular signaling system in several filamentous fungi which respond to the PH range. This gene is activated by the proteolysis enzyme in the alkaline range, and while it is essential for virulence in mice, it has a negative effect on virulence in plant hosts. This difference in pathogenicity is related to the difference in PH range between the two hosts (46). Studies indicate that the pathogenic pattern of these fungi is different between rat and potato models; in case of animal hosts, it is similar to candida albicans and cryptococcus neoformans.

In candida albicans, fungi are responsible for human keratitis. The proteolytic activity of RiM101pi gene and the homologous translation factor of Pac.C strengthen the development of fungal hyphae and fungal invasion (47). Corneal infection or keratitis is probably the most common form of surface contamination. Inflammation of the cornea caused by fusarium is similar to other genera, although it is more severe and is associated with rapid corneal shedding.

Fusarium oxysporum f.sp. lycopersici, as one of the major causes of keratitis, is not easily capable of invading the cornea and requires wounded or dead tissues for penetration (48). The penetration of this pathogen into tomato's vascular wilt is either through the existing wound at the furcation site or directly from the root end (49). After the penetration of the PacC regulator gene into the eye, this gene begins to adapt to the environment, making filamentous growth and invading the eye tissue. Given the tendency to invade and block intraocular vessels, fusarium ocular diseases cause secondary infraction, hemorrhage, and narcosis. It is reported that the occlusion of the secondary renal artery by fusarium oxysporum can cause endocarditis in immunocompromised patients (48). However, in plants with vascular wilt, due to the transfer of microconidia and germination in face of blockage,

[DOR: 20.1001.1.15614107.1393.17.2.10.5]
[DOI: 10.22088/jbums.17.2.71]

vascular obstruction caused by mycelium, spore, engom, tilose, and vascular enmeshment (due to an increase in adjacent parenchyma cells) are among the major factors for the collapse and failure of raw sap transfer in plants (49).

In addition to the dysfunction caused in the host by fungal organs, fungal pathogens produce toxin compounds to overcome the host. Fusaric acid is one of the toxins produced by *fusarium* oxysporum with fusarium oxysporum f.sp. lycopersici as the main producer. High accumulation of toxins in plants reduces the growth of roots and root hair and causes temporary hyperplasmy. This toxin is proposed as the cause of rotting in potato glands and wilt in pepper and corn (50).

Fusaric acid is toxic for animals and exhibits tumorigenesic activities in patients with head and neck squamous cell carcinoma. This toxin causes reduced activity of T and B lymphocytes and as a result, prevents normal cell death and weakens the protection against tumor development (50, 51). Studies on the epidemiology of this fungus show that the epidemiology of fungal keratitis depends on climate in a way that fusarium is the major cause of disease in South America, while candida and aspergillus are considered as the major causes of the disease in other parts of the world (48).

This is comparable with the vascular wilt of tomato with a common agent. Vascular wilt exposes the highest amount of damage to regions with high soil and weather temperature in most seasons. Therefore, in the United States, the severity of the disease is higher in the south and central states (49). Considering the hosting range of this fungus (soil, plants, and animals) and the presented evidence, soil can be considered as a means for the transfer of the fungal agent from plant to animal hosts. In this state, the fungal agent adapts to the host with a series of physiological changes. Fusarium solani is another cause of keratitis and has been extracted in large quantities from soil, plant remains, and immunocompromised patients. So far, 45 physiologic and biologic species of this fungus have been reported as parasites of agricultural products. According to the physiologic data, this species is divided into three clusters and the isolates of clusters 1 and 2 are unique to dead plants and soil. All human, animal, and hospital pathogens fall in the third cluster. Members of this cluster are easily detached from the soil and have a higher growth rate and more asexual propagules, compared to the members of cluster 2. These two characteristics contribute to the ability of fungal pathogens in adapting to animal hosts (46). The isolates of human pathogens fall into four main categories where the first and second groups are capable of infecting humans and plants. As an independent group, group 1 includes isolates such as the race 2 of fusarium solani f. sp., *as* a special form of cucurbitae A, which is introduced as a pathogenic agent in cucurbitaceae.

The previous literature refers to this species as fusarium solani species complex group 1. The members of this group are the first plant pathogenic isolates, differentiated from medical samples. Pathogenic tests of clinical isolates on pumpkin showed that these isolates are capable of causing disease in plant hosts. The significance of this issue is in the fact that fungal pathogens, capable of infecting both human and plant hosts, are very rare. In contrast with fungal diseases, which are generally present in immunocompromised patients, 93% of patients with keratitis are not immunocompromised.

Physiological studies confirm that pathogenicity, germination, growth, conidia production, and sexual compatibility are not affected by the host. Also, from the biologic point of view, the collected isolates from human sources show sexual compatibility with cucurbitaceae's mating type and produce oxysporum with germination capability. The only differentiating factor is the temperature of the host. Reduced germination, growth, and conidia production are witnessed at 37°C, unlike 25°C. In addition, microconidia changes from a sausage-like and oval form at 25° C to an oval and spherical form at 37 °C (the predominant form at this temperature).

In consistence with the pervious findings, the results of molecular studies, conducted on the nucleotide sequence of several genomic regions, indicated that medical FSSC1 isolates are indistinguishable from the pathogenic isolates of cucurbitaceae (51,52). Thus, it can be stated that human pathogenic isolates are generally plant pathogens, facultative saprophytes, and extremophiles, which are capable of surviving in human hosts by making changes in their physiology under certain

[DOR: 20.1001.1.15614107.1393.17.2.10.5]
[DOI: 10.22088/jbums.17.2.71]

conditions. Sources such as soil and hospital environment act as the transfer mediators of these pathogens from plants to humans.

Conclusion

Generally speaking, the results of this study confirm the evolutionary theory of human fungal pathogens from plant hosts. Findings related to the species of fusarium genus with the dual ability to cause virulence on both plant and human species are noteworthy. Considering the recent advances in molecular biology and molecular techniques for genome sequencing and by comparing the genomes of different fungal species, it is possible to conduct comprehensive and accurate studies on this subject matter. Comparative genomics are discussed as a powerful tool for the study of fungal pathogenesis and pathogenic evolution. Content comparison and genome/gene organization in pathogenic fungi, with different host ranges, penetration methods, and pathogenicity, can give us a deeper understanding of pathogenic genes and the processes involved in the evolution of pathogenesis.

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[DOR: 20.1001.1.15614107.1393.17.2.10.5]

[DOI: 10.22088/jbums.17.2.71]