Chapter 9
Improving Animal Immunity to Prevent Fungal Infections with Folk Remedies and Advanced Medicine

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Abbreviations

ABPA	Allergic bronchopulmonary aspergillosis
ALS	Agglutinin-like sequence
CTL	Cytotoxic T lymphocytes
EC	Epithelial cells
IPA	invasive pulmonary aspergillosis
MHC	Major histocompatibility complex
NET	Neutrophil extracellular traps
NK	Natural killer
PAMP	Pathogen-associated molecular patterns
PBMC	Peripheral blood mononuclear cells
PRR	Pattern recognition receptors
TLR	Toll-like receptors

9.1 Introduction

Humans have historically taken great care of their animals, whether livestock or domestic—sometimes reaching a degree of sanctification. The pharaohs embalmed animals, believing they will accompany them in their next lifetime or return to life after death. Others believed animals to have the souls of their ancestors, who had returned to the worldly life as animals.

When animals reproduce, their offspring may have characteristics that are favored by humans and their local environment. Throughout history, human have

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chosen the most substantial and suitable animals for their environments. Calm-tempered animals were raised domestically, while aggressive ones were used for protection or in military actions. Humans have discovered that hereditary traits, and even sensory and moral qualities, are transmitted through heredity. An example of that is the Arabian horse, which is treated with great respect that has contributed to strains that are physically strong with the ability to withstand infections.

9.2 Nature Preserves Genes

When humans select animals based on their future characteristic, it is a simulation of what takes place naturally. Carnivores select old and weak animals to feed. Only strong males and females remain and reproduce. These natural or human-directed selections are one of many factors that help with resistance against pathogens and diseases, including fungal infections.

Fungal diseases were found to have three principal causes. The first reason is the exposure of a healthy animal to unfavorable conditions that lead to an infection. Such a case can be easily treated. Secondly, an animal's health may deteriorate to make them susceptible to a fungal infection. Health degeneration could be due to poor living conditions, bad food, genetic disease, or a particular infection. In this case, the treatment is complicated and the defect in the animal's body must be corrected, if possible; then, the fungal infection can be controlled. Third, conversely, healthy animal in a healthy environment may become susceptible to fungal infection, which indicates a hidden agent, such as a toxin in food. A fungal infection is an early warning sign for the presence of such toxins. The animal may have consumed food or crops containing materials that are harmful to the liver. After a time, this deteriorates the liver's function and leads to poor health of the animal, causing fungal infection.

By observing these fungal infections and searching for the real reason(s) for transforming the animal from resistant to suitable, many diseases (including fungal infections) can be controlled. Those who are not able to distinguish between the various causative agents of fungal infections may not be able to control them. Prolonged medical treatment also contributes to an animal's health deterioration. Fungal infections are based on both the animal's health and the environment where it resides. Most farmers can distinguish between the three general causes of fungal infections.

9.3 Why Fungi Are Different

Fungi include yeasts, rusts, smuts, mildews, molds, mushrooms, and toadstools. Fungi are eukaryotes that lack chlorophyll; they contain a nucleus, vacuoles, and mitochondria. They are approximately 80,000 recognized species in the kingdom.

Fungi are among the most widely distributed organisms on Earth and are of environmental and medical importance. Many fungi are free living in soil or water; others form parasitic or symbiotic relationships with plants or animals. The fungi can be distinguished from all other living organisms, including animals, by their principal modes of vegetative growth and nutrient uptake.

Fungi grow from the tips of filaments (hyphae) that make up the bodies of the organisms (mycelia). They digest organic matter externally before absorbing it into their mycelia. Fungi are everywhere in large numbers in the soil and the air; in lakes, rivers, and seas; on and in plants and animals; in food and clothing; and in the human body. With bacteria, fungi break down organic matter and release carbon, oxygen, nitrogen, and phosphorus into the soil and the atmosphere. Based on their structure and life cycle, they can be classified into five groups: Ascomycetes, Basidiomycetes, Zygomycetes, Oomycetes, and Deuteromycetes. The last group's hypha is septate, and thus there is no sexual spore (Hedayati et al. 2007). Fungal infections include ringworm, athlete's foot, and other dermatomycoses.

9.3.1 Fungal Cell Wall

The fungal cell wall generally consists mainly of chitin, which is a polysaccharide composed of long chains of N′-acetyl glucosamine (Duan et al. 2020; Huang and Huang 2019; Junior et al. 2019; Pathaw et al. 2020; Xie et al. 2012). The fungal cell wall contains other polysaccharides, the most significant of which is β-glucan; this is the site of action of the antifungal drug caspofungin (2001; Agarwal et al. 2006; Al-Baqsami et al. 2020; Alam et al. 2012; Alonso et al. 2009; Bohme et al. 2009; Bortolus et al. 2019), a long polymer of D-glucose (not peptidoglycan as in bacteria) (Jawhara 2020). Fungi are insensitive to antibiotics, such as penicillin, which inhibit peptidoglycan synthesis. The fungal cell membrane contains ergosterol (Ahmad et al. 2018; Alcazar-Fuoli et al. 2006; Andrade-Pavon et al. 2019; Cai et al. 2016; Chaudhari et al. 2018; Datry et al. 2001; do Nascimento et al. 2018), in contrast to the human cell membrane, which contains transports cholesterol.

Each fungal species has unique glycan (Jawhara 2020), polymers, and proteins, interconnected to each other in the cell wall. Cell wall proteins are highly glycosylated and have negatively charged phosphate groups in their carbohydrate side chains, which impress the electrostatic charge. The selective action of amphotericin B (Abrahamsen et al. 1992; Adams et al. 2008; Albengres et al. 1998; Alcazar-Fuoli et al. 2006; Perumal et al. 2007; Sar et al. 2006) and azole drugs (Abraham and Vas 1990; Abrahamsen et al. 1992; Al-Marzouqi et al. 2009; Arthur et al. 2004), such as fluconazole (Al-Marzouqi et al. 2009; Alcazar-Fuoli et al. 2006) and ketoconazole (Korting and Schollmann 2009; Moran et al. 1997; Saini et al. 2005; Shindo 1990; von Paleske et al. 1987), on fungi is based on this difference in membrane sterols (Lemos et al. 2020; Shing et al. 2020; St Georgiev 2000).

9.3.2 Fungal Toxins and Allergic Responses

The best-known mycotoxicosis occurs after eating Amanita mushrooms. These fungi produce five toxins, two of which (amanitin and phalloidin) are among the most potent hepatotoxins. The toxicity of amanitin is based on its ability to inhibit cellular RNA polymerase, which prevents mRNA synthesis. Another mycotoxicosis, ergotism, is caused by the mold *Oaviceps purpura*, which infects grains and produces alkaloids (e.g., ergotamine and lysergic acid diethylamide [LSD]) that cause pronounced vascular and neurologic effects. Other ingested toxins, aflatoxins, are coumarin derivatives. *A. flavus is* a common species of the Deuteromycetes group. *A. flavus is* also characterized by its ability to produce mycotoxins, a large and diverse group of fungal exotoxins. It commonly grows on improperly stored food, such as grain. The toxins produced by *A. flavus* are known as aflatoxins. Aflatoxins are highly toxic and induce tumors in some animals, especially in birds that feed on contaminated grain. They cause liver damage and tumors in animals and hepatic carcinoma in humans (Hedayati et al. 2007). Aflatoxins are ingested with spoiled grains and peanuts and are metabolized by the liver to the epoxide, a potent carcinogen. Aflatoxin Bl induces a mutation in the p^{53} tumor suppressor gene, leading to a loss of p^{53} protein and a consequent loss of development control in the hepatocyte.

Hypersensitive responses to fungal spores, particularly those of Aspergillus, manifest mainly an asthmatic reaction (rapid bronchoconstriction mediated by immunoglobulin E), eosinophilia.

9.4 Fungal Therapy

The drugs used to treat bacterial diseases have no effect on fungal diseases. The most effective antifungal drugs, amphotericin B and the various azoles, exploit ergosterol in fungal cell membranes that is not found in bacterial or human cell membranes. Amphotericin B (Fungizone) disrupts fungal cell membranes at the site of ergosterol. The selective toxicity of amphotericin B and the azole group of drugs is in contrast to the cholesterol found in human cell membranes and the absence of sterols in bacterial cell membranes. Azole drugs, such as itraconazole, fluconazole, and ketoconazole, inhibit the synthesis of ergosterol. The selective toxicity of echinocandins, such as caspofungin, is based on a cell wall in fungi and inhibits the synthesis of β-glucan, which is found in fungal cell walls but not in bacterial cell walls. Human and animal cells do not possess a cell wall. Echinocandins inhibit the synthesis of D-glucan, which is a constituent of the fungal cell wall.

9.5 Fungal Entry to Host

Fungi have hydrophobic cell surfaces, which is important for adherence to biomaterials. Similarly, the development of the fungus into the host implies continuous biosynthesis and remodeling of their cell wall (Mora-Montes 2020). Pathogenic fungi are able to invade the host at different morphologies. Several medically important fungi are thermally dimorphic. They form unique structures at different temperatures. They exist as molds in the environment at ambient temperatures and as yeasts (or other structures) in human tissues at body temperature (Casaroto et al. 2019; Childers et al. 2019). Most fungi are obligate aerobes, few are facultative anaerobes, and none are obligate anaerobes. All fungi require an organic source of carbon, hence their frequent association with decaying matter.

9.5.1 Fungi Infiltration to the Epithelial Surfaces

Fungi have a flexible genetic element that helps them to adapt the different fluctuating parameters (Childers et al. 2020; Dominguez-Andres et al. 2019). The conversion from a saprophytic lifestyle to pathogens of humans or animals activate different genes and sensors. The various immune cells are the major antagonists to the survival of fungal pathogens. Ambient temperature is suddenly replaced with the restrictively high temperature of the human body. Ambient pH is replaced with acidic mucosal surfaces or neutral blood and tissues. Familiar sources of carbon and metal ions are missing in an environment where essential nutrients are sequestered from microbes to support host survival. Carbon dioxide and oxygen concentrations are reversed in host tissues, leaving fungi to cope with hypoxia and high levels of carbon dioxide (Tronchin et al. 2008).

In that respect, there are different rates of fungal entry into the bodies of animals and humans. Accidental skin infiltration (i.e., the host's passive barriers are breached traumatically) through clinically implanted medical devices, such as central venous catheters, offer an entry point for microbial seepage through a gap in the epithelial surface. Formation of an overlying biofilm may shield the embedded *Candida spp*. from therapeutic levels of antifungal medications (Nobile and Mitchell 2007). Epithelial cells have two general types, keratinized and nonkeratinized, and their vulnerability to fungal invasion differs. Only dermatophytes can break down the intact, dry, keratinized epidermis: other fungal pathogens rely on their content to penetrate epithelia that is rich in keratin, or that occlusion or maceration have weakened. For fungi that normally live in the gastrointestinal tract, the process of persorption may cause the gratuitous uptake of infective propagules into the bloodstream. *Aspergillus spp*., *Cryptococcus neoformans*, Zygomycetes such as Mucor and *Rhizopus spp*., and the dimorphic fungi *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, and *Paracoccidioides brasiliensis*

all normally gain access to the host through inhalation and all can potentially invade beyond the respiratory tract (Mendes-Giannini et al. 2000; Tronchin et al. 2008).

9.5.2 Fungal Attachment

A successful pathogen is one that can survive and evade detection by the host's innate immune defense (Kirkland and Fierer 2020). Fungal pathogens have adopted tactics that avoid host defense and later cause disease in at-risk patients. The anatomy and composition of the skin and mucous membranes provide a strong defense line to any microbial invasion. Fungal pathogens display a broad range of adhesions that are expressed at their surface. When introduced into the host, they can then adhere to a large variety of cell types and interact with many ligands present in various host sites, such as biological fluids, extracellular matrixes, or basement membranes. Attachment of conidia to the epithelial cells or to the underlying basement membrane was thought to play a crucial part in establishing the fungus and starting the disease in a receptive host. *Aspergillus fumigatus* has virulence factors, such as proteolytic enzymes, phospholipases, catalases, superoxide dismutases, and non-ribosomal peptide synthases involved in the synthesis of hydroxamate siderophores necessary for iron uptake. The interaction with plasma or extracellular matrix proteins was extensively investigated, but non-specific interactions also seem to contribute to adherence (Bouchara et al. 1999; Latge and Calderone 2002). *Candida spp*. expresses adhesions that are attachment factors, surface proteins. They are covalently linked to the β-glucan of the cell wall. Adhesions include the agglutinin-like sequence (ALS) protein and hyphal wall protein-1 (HWP1). They play a role in biofilm formation by helping cell-to-surface and cell-to-cell adherence (Nobile et al. 2006a; Nobile et al. 2006b).

9.6 The Efficacy of the Immune System

Traditional medicine does not directly discuss the immunity, but it describes an alternative term. Thus, there is an understanding of the differences between immunologically based good health and poor health. In Egypt, animal with health issues but without apparent symptoms of a known illness were called *ghasha,* which can be translated to "compromised." The Egyptians correlated that to an issue with the animal's liver.

9.6.1 Folk Practices

9.6.1.1 Reactivating Animal Health

In Egypt, animals that showed the behavior of *ghasha* were treated by two particular methods: shocking the animal with a heated iron in a particular area or inserting cotton tissue under the animal's skin using a heated needle to burn pores into the skin, after which the skin is pulled and the tissue is passed from one pore to the other. Inserting this cotton tissue caused pus to be secreted in large amounts. After some weeks, the tissue was removed and usually there was positive progress in the animal's health. The process has been used by farmers in Egypt since ancient times (Fig. 9.1).

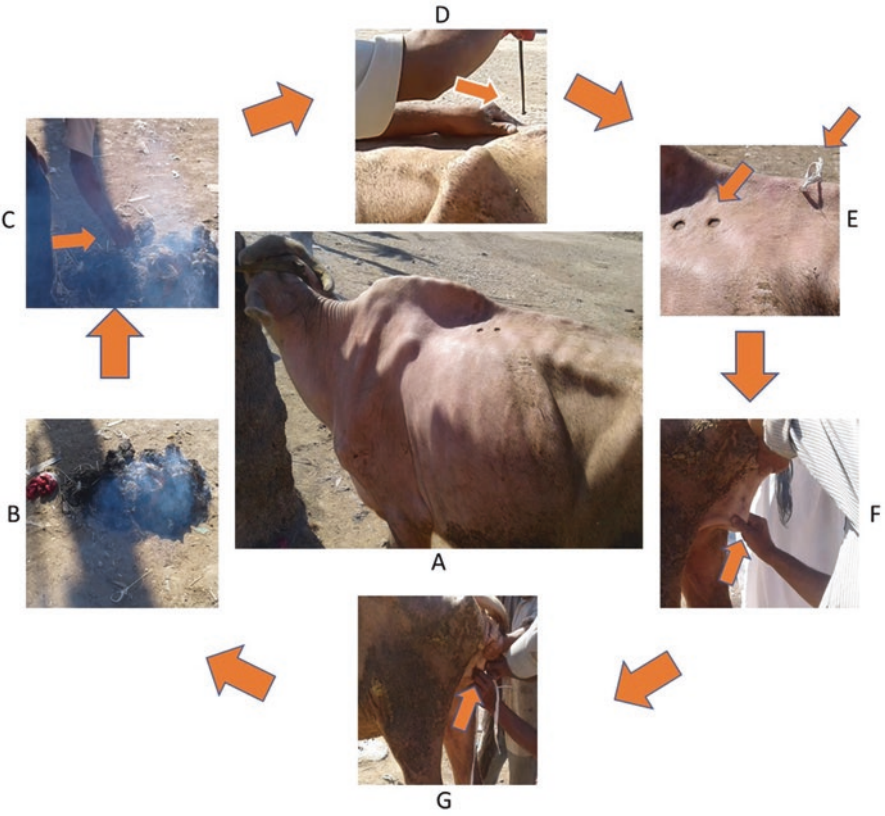

Fig. 9.1 Egyptian methods widely used by farmers to treat compromised animals and restart the immune system: (**a**) compromised buffalo, (**b**) fire ashes, (**c**) iron needle during its heating, (**d**) treating the animal with the heated iron needle, (**e**) two neighboring pores are formed to pass cotton tissue between, (**f**) another location prepared for the same process

9.6.2 Infection, Susceptibility, or Both

Microbes play key roles in the equilibrium of the land ecosystem. Many of them are hydrocarbon-degrading microbes. Hydrocarbons are the main origin of foods and energy. The microbes consider the body only as a movable mass of hydrocarbons, but these masses are protected physically and immunologically from a microbial attack. However, when there is a weakness in the immune system, microbes of different types start to attack humans and animals directly. They do their work spontaneously, only under the control of the surrounding biological, chemical, and physical factors. Opportunistic pathogens are nothing but microbes with extra degradation power—unable to harm when the body is healthy, but they can take advantage when the immune system is compromised (Du et al. 2020).

9.6.2.1 Turning the Opportunistic Pathogens into Lazy Microbes

Opportunistic infection is any infection caused by a microorganism that rarely causes disease in humans; it occurs in individuals with abnormally operating immune systems. Opportunistic pathogens may exist peacefully with us, but then suddenly attack us when the body has a weakness that invites them to perform.

9.6.2.2 Put Sugar Between Your Toes

Humans have long understood methods for keeping opportunistic pathogens calm. For example, in a simple Egyptian practice, individuals with bad foot odor were advised to put sugar between their toes just before sleep. *Candida albicans* and other pathogens prefer sugar to humans and would thus stop attacking human tissue. While they are happy with the sugar (and any useful natural beneficial microflora would be happy too), the tissue has time to rebuild itself and protect the body from the pathogens. Again, just water and our natural flora (i.e., normal hygiene practices) will be enough. This case is presented to highlight approaches aside from typical antimicrobial treatment that help in the recovery from fungal diseases. These simple treatments can be attempted before moving on to the more complicated ones.

9.6.2.3 The Fungal Smart Invasion

Opportunistic pathogens are early biological indicators that the immune system has a problem (Amara 2011). They should attract attention, including from scientists. Virulent fungal infections should be treated with a fast and serious response. However, slow infections should not be ignored. Ignored treatment due to unapparent illness might cause an acute infection. Any fungal infection should be considered as

a problematic disease because some infections grow by a rate compatible with the reduction in our immune capacity—a type of smart invasion. The quality of our immunity usually declines at a slow rate, normally due to certain health problem in our bodies. In contrast, a fungal infection for an immunocompetent individual shows a fast rate of symptoms but without real defense (Tronchin et al. 2008). Our understanding of the immune system/fungal relationship will help in the control, prevention, and treatment of fungal infections. Immune response at the mucosal sites is essential and preferred for the clearance of the infection and long-term protection.

9.6.3 Interactions Between Fungal Pathogens and the Immune System

1. All fungi and other microbes, even those who are friendly to us, are foreigners to our body. They could exist as microflora in superficial colonization forms. Even so, they will be attacked by the immune system if they are introduced to the body tissue or blood.
2. Fungi are exceptional microbes that could trick the immune system and invade our tissue. They are capable of slow, smart invasion and can trick both our observations and our immune system. Late treatment is usually difficult because fungi deeply invade the tissues (Tronchin et al. 2008).
3. Microflora can inhibit the development of pathogenic microbes, including fungi, by filling in any suitable place for settlement and by producing inhibitors for the pathogenic microbes. Continuous exposure to chemical factors such as detergent, alcohols, disinfectants, or perfumes can be a cause. Superficial exposure to antimicrobial agents is helpful for the pathogens. Particularly those microbes that remark such hydrocarbons antimicrobial agents as food, so they survive and become dominant while our microflora did not. Our microflora is a part of our body's defense (immune) mechanism. Thus, it is important to rebuild the microflora after losing it.
4. The body is a connected system. Deterioration (by physical, chemical, or biological factors) in any part of it will affect the other parts and make it susceptible to microbial infections.
5. Few fungal species are considered to be microflora, but the numbers are huge in the surrounding environment. They are ready to attack when they have a chance.
6. Creatures are created resistant to fungal infections. For some microbes, the various creatures are just a food either contain an antimicrobial agent or not.
7. Most fungi are hydrocarbon-degrading organisms, so most disinfectants are just food for them.
8. Opportunistic pathogens are mostly part of our microflora; however, if our immune system becomes weak (by whatever means), they attack us.

9. Pathogenic fungi are characterized by the number of virulence factors they experience.
10. Treatment of a fungus infection can be tricky. The treatment components might affect the body or cause more virulent mutants. Fungal treatment is immunologically based. The best antifungal agents either improve the immune system or maintain it as it is (Tronchin et al. 2008).
11. Microbes can weaken the immune system.
12. Microbes of different sizes cause different immune responses.
13. Dead fungi can activate the immune system and cause natural immunization upon their entry to our body. Some fungal infections/or dead fungi can protect against others, whereas weakened or attenuated fungi can facilitate the control of virulent ones. Scientists should use immunological tactics that have demonstrated success with bacteria and viruses because the immune system can be directed smartly or aggressively to offer full protection. Our understanding of case-by-case microbial and fungal treatments will aid in their control (Hussain and Amara 2006).
14. Some folk remedies and natural products have proven efficacy and should not be overlooked. Some cannot be explained scientifically right now, but future research should provide answers.

9.6.4 Infection or Susceptibility, which one is more climed?

Before the invention of the microscope, humans had some knowledge about these diseases. Ancient texts describe the transmission of diseases between animal/human, animal/animal, and human/human. Orders were issued for people to entirely avoid the movement of both animals and humans from an epidemic location to some other area. The word "infection" was identified clearly in old Arabic books written nearly 1400 years ago—and may have been used earlier in oral communication.

Indeed, the concept of infection was known, but what about susceptibility? How do microbes become suddenly active? In an open, clean area with low biodiversity, such as the desert, the emergence of an infection should raise questions. Research concerning *Pseudomonas aeruginosa,* the most famous opportunistic bacteria, has provided some answers (Amara 2011; Hussain and Amara 2006). However, even in highly sanitized area, fatal diseases can emerge when bodies either lack immunity or have not developed gradual resistance. In these cases, diseases may become more fatal and more aggressive. In other words, what causes an infection for some people will not affect others. Hence, there is a need to reevaluate our understanding of the contagion.

The immune memory should be built smartly, as it needed to be ready for defense against moderate versions of the contagion (which were created to build better defense against the strong ones). For example, contact with cows can lead to a cowpox infection, which protects against smallpox, a fatal disease. In another example, hens were subjected to continous lights and feed and isolated in a sanitized

condition, and protected with antibiotics, they build, approximately no resistance to infections. A farm containing 5000 hens could lose more than 70% of its number if a particular disease is transmitted (personal communication). In contrast the old farming process seldom faces such loss.

To simplify the contrast between infection and susceptibility, consider twins living in the same home: tooth plaque could occur in one but not the other. Twins who are genetically identical, live in the same home, and eat together should be identical in their susceptibility to diseases; however, only one may plaques because that twin did not brush his teeth after consuming sugary food (personal observation).

9.6.5 Immunity Building

The immune system possesses a memory for an infective disease. Thus, a pathogen may not seriously affect an animal who has a second infection from the same disease. Mammals have cross-protection between infections independently of T and B cells, and more recently memory properties of NK (natural killer) cells and macrophages, which are prototypical cells of innate immunity (Drummond et al. 2014; Netea et al. 2011). Monocytes stimulated in vitro with β-glucans, a component of fungal cell walls, were demonstrated to protect animals deficient in an adaptive immune system against lethal systemic candidiasis infections; this protection was attributed to epigenetic reprogramming (Netea 2013).

9.7 Folk Remedies for Animal Immunizations

9.7.1 Save the Young Turkeys

Egyptians have traditionally used a unique practice to raise turkeys. Young turkeys usually died in the Egyptian environment if not fed after their hatching with a mix of egg, cheese, and *Allium porrum*, a traditional folk mixture. The reason for the deaths of young turkeys is not known to farmers, and I do not know the source of this recipe, which was used in the village of my father. Recently, a more simple protein than the egg white lysozyme was used to investigate the power of cell wall degrading enzymes in bacterial ghost formation (Amara 2015a; Amara 2016b; Amara 2018; Amara et al. 2013a, b). The powerful force of the lysozyme on different microbes indicates that it is a universal cell wall degrading enzyme, explaining why egg was one component of this concoction. *Allium porrum* is rich in antimicrobial agents, which increases the chance of survival. Cheese is rich in probiotics, which aids in the immunity and in the digestion of the young turkeys. Thus, this could be one of the earliest primitive immunization tools.

9.7.2 The immunized Hen

Re-infection results in a memory of the previous infection, allowing antibodies to defend against them both. A third infection could have some antigens similar to the previous two. However, a third infection could be lethal for a hen that was not infected earlier, which could explain the response differences to epidemic diseases globally. Natural selection plays a big role in protection, protecting conservancy of the inherited components. Nevertheless, natural selection will remove any weak or sick animals.

9.8 Innate Immunity

The skin and mucosal surfaces act as physical barriers between the environment and deep tissues. Most cell types described previously are found in abundance in barrier tissues and are important in surveillance, maintaining commensal relationships, and providing protection from invasion (Drummond et al. 2014; Garcia-Carnero et al. 2020).

9.8.1 A. Sites Contributing to the Innate Immune System

9.8.1.1 Skin

Human skin is readily colonized by fungi, predominantly *Malassezia spp.* (Findley et al. 2013). Skin-resident dendritic cells (DCs) are easily positioned to encounter cutaneous pathogens and are needed for the installation of adaptive immune reactions. Malassezia is a pathogenic yeast that is associated with exacerbation of various skin diseases, including atopic eczema and atopic dermatitis (AD), in which barrier function and immune regulation are compromised (Saunders et al. 2012). Malassezia-derived products were proven to influence host responses, including generating cross-reactive T cells that exacerbated AD, down-regulation of human DC maturation, and proinflammatory cytokine production (Vlachos et al. 2012). *C. albicans* infections of the skin were recently shown to be controlled by different DC subsets resident in the skin, LC and Langerin^{+} dermal DCs, which were each responsible for driving Th17 and Th1 adaptive immunity, respectively (Drummond et al. 2014; Igyarto et al. 2011).

9.8.1.2 Respiratory Tract

Aspiration is a common route of exposure to fungal spores that could cause invasive pulmonary aspergillosis (IPA) and other disease, as well as sensitization and exacerbation of allergic reaction and asthma. Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder to *A. fumigatus*, leading to serious asthma symptoms and affecting nearly 5 million people worldwide (Agarwal et al. 2013; Drummond et al. 2014).

9.8.1.3 Genital-Urinary Tract

The most common fungal pathogens colonizing the genital-urinary tract are *C. albicans* (Jaeger et al. 2013) and *Vulvovaginal candidiasis* (Jaeger et al. 2013). It is yet unclear why vaginal candidiasis occurs more frequently in some individuals. Animals deficient in IDO1, an enzyme promoting tolerant T-cell responses and producing tolerogenic kynurenines, were recorded to have increased susceptibility to *V. candidiasis*; treatment with kynurenines could ease disease (De Luca et al. 2013; Drummond et al. 2014).

9.8.2 Cell Barriers

9.8.2.1 Epithelial Cells

Epithelial cells (ECs) are the first point of contact with microbes. Although not characteristically considered immune cells, there are several examples of ECs contributing to the innate immune response, primarily through producing chemokines, such as interleukin (IL)-8. Corneal and bronchial ECs both produce inflammatory cytokines in response to *A. fumigatus* (Guo and Wu 2009). Mechanisms driving EC chemokine production were stimulated with antimicrobial peptides (Drummond et al. 2014; Wagener et al. 2013).

9.8.2.2 Immune Cells

Cells that are part of the innate immune system are characterized by inherited receptors with broad specificity and a rapid response time. Several cell populations contribute to antifungal responses. Predominant cell types used for antifungal defense include neutrophils, macrophages, DCs, NK cells, innate-like lymphocytes, and ECs.

9.8.2.3 Neutrophils

Neutrophils are highly phagocytic granulocytic polymorphonuclear cells. Neutrophils kill pathogens by producing reactive oxygen species, which kill phagocytosed microbes. Mice deficient in the neutrophil granule serine proteases elastase and/or cathepsin G are susceptible to fungal infections.

9.8.2.4 Monocytes/Macrophages

Monocytes and macrophages are Phagocytes family members. Phagocytes are large white cells that can swallow and digest microbes and other foreign particles. Monocytes are bloodborne cells circulating in the blood that differentiate into macrophages in tissues, which they infiltrate following an inflammatory signal. Monocytes produce chemical signals named monokines that are involved in the immune responses (Brummer et al. 1999; Dotis et al. 2008; Roilides et al. 1994, 1999; Wildfeuer et al. 1990, 1992). On their migration to the tissue, they become macrophages specialized in the tissue where they exist. Such tissues include lungs, kidneys, brain, and liver. Once in tissues, monocytes are differentiated to become macrophages, which further develop into a distinct functional phenotype, which is influenced by the cytokine milieu. Proinflammatory cytokines, particularly interferon γ (IFN-γ), drive a classically activated (M1) phenotype. The anti-inflammatory cytokines (such as TGF-β) drive otherwise activated (M2) macrophages. Different homeostatic activities include host defense, wound healing, and immune regulation (Mosser and Edwards 2008). The macrophage phenotype can have a profound effect on antifungal immunity. The immunity to pathogens requires pattern recognition receptors (PRRs) to trigger intracellular signaling cascades that start and direct innate and adaptive immune reactions (Drummond et al. 2014).

9.8.2.5 DCs

DCs are important innate cells involved in initiating immune responses and generating adaptive immunity via antigen presentation. DCs have attracted specific attention in their potential as effective targets for novel therapeutic and vaccine strategies. Plasmacytoid dendritic cells (pDCs), typically considered as antiviral cells, may be a protective part of pulmonary fungal pathogens. Animals resistant to *P. brasiliensis* infection were shown to get a mixed lung DC population, including pDCs, which susceptible mice lacked (Drummond et al. 2014; Pina et al. 2013) .

9.8.2.6 NK Cells

NK cells are a type of white blood cells or lymphocytes. Like cytotoxic T lymphocytes (CTLs), NK cells have granules containing potent chemicals. NK cells are not able to recognize major histocompatibility complex (MHC) molecules or recognize cells having missing or low MHC class I molecules. They are able to attack different types of molecules (Camilli et al. 2018; Fernandez-Ruiz et al. 2015; Safdar 2010; Schmidt et al. 2013; Voigt et al. 2013; Zhang et al. 2018). NK cells in both mice and humans were described as having antifungal activity against a range of fungi such as *C. albicans*, *A. fumigatus* (Schmidt et al. 2013), *C. neoformans* (Islam et al. 2013), *Pneumocystis murina* (Kelly et al. 2013), and *P. brasiliensis* (Longhi et al. 2012). NK cells exert their effects through the direct killing of yeast using perforin, killing infected host cells, and secreting proinflammatory cytokines (Drummond et al. 2014; Schmidt et al. 2013)`.

9.9 Adaptive Immunity and Fungicidal Mechanisms of White Blood Cells

9.9.1 Sites Contributing to the Adaptive Immune System

9.9.1.1 Skin

The skin contains a network of DCs that can be divided into the epidermis-associated LCs and a collection of dermis-associated dermal DCs (Henri et al. 2010). On subcutaneous injection of *B. dermatitis* as a vaccine, DEC205^{+} skin-derived DCs migrated to the draining lymph nodes in a CCR7 dependent fashion, presented (or transferred) model antigen expressed by the yeast, and activated CD4+ T cells (Ersland et al. 2010). Dermal DCs were shown to specialize in antigen presentation and T-cell polarization functions in a cutaneous exposure model to *C. albicans* (Igyarto et al. 2011; Verma et al. 2014).

9.9.1.2 Lung

DCs in the lungs and airways are constantly exposed to inhaled spores and hyphal fragments. A network of DCs lines the airways, sampling inhaled antigens and shuttling into the mediastinal lymph nodes. CD103+ DCs can acquire soluble and apoptotic-cell-associated antigens from the respiratory tract and migrate to mediastinal lymph nodes under steady-state and inflammatory conditions. At the lymph node, CD103+ DCs cross-present antigens and activate CTLs (Desch et al. 2011). CD11b + DCs differ from monocyte-derived DCs and specialize in cytokine and chemokine production (Beaty et al. 2007), also presenting antigens to CD4+ T cells in the mediastinal lymph node after migration (del Rio et al. 2007). On lung

exposure to *A. fumigatus* conidia, CD103+ DCs failed to take up and transport conidia to the mediastinal lymph node, whereas CD11b + DCs did transport conidia (Hohl et al. 2009). Lung CD11b + DCs were reduced in CCR2$^{-/-}$ mice, relative to wild-type mice, following *A. fumigatus* exposure (Verma et al. 2014).

9.9.1.3 Intestine

DCs in the intestine are on the basolateral side of the epithelium, largely isolated from the gut microflora, and localized to the lamina propria (LP-DCs) and Peyer's patch (PP-DCs); both subsets in each region differentially regulate immune responses. *C. albicans*, a gut commensal, can cause systemic infection if the gut epithelial/DC barrier is breached or in the setting of broad-spectrum antibiotic use, leading to Candida overgrowth. Potent induction of Treg cells by LP-DCs in the mesenteric lymph node highlights the role of limiting inflammation in the gut to go up the epithelial barrier and prevent disseminated infection. Furthermore, heightened Th17 responses in the gut impair protective Th1 responses and worsen Candida infection (Bruno et al. 2020; Casaroto et al. 2019; Lang et al. 2019; Zelante et al. 2007). Although bone marrow–derived DCs produce IL-23 in response to Candida in vitro and IL-23, neutralization promoted fungal clearance in vivo (Verma et al. 2014).

9.9.2 Cell-Mediated Host Response to Fungal Aggression

After the success of the fungus in bypassing the first body parries and the various innate immune structures, it suits the role of the adaptive immunity to fight this foreigner. During the action of the natural immune system, the adaptive immunity works intensively to bring out its elements. It coordinates both systems, the innate and the adaptive immune response, to eliminate the fungal infection and to produce a memory for it. Different reactions are due to different anatomical positioning of the infections, as well as different fungus and surface marker expression. Each of the helper, regulatory, and effector T- and B-cells are responding and integrated against the fungi (Verma et al. 2014).

9.9.2.1 Characterization and Function of DC and Monocyte Subsets

When DCs encounter antigens at the boundary of immunological defense sites, such as the skin, the airways of the lung, and ordaining nodes of the lymphatic system, DCs amplify the innate immune response by secreting cytokines that recruit and activate other white blood cells. After ingestion, processing, and presentation of antigens, DCs start and shape adaptive responses by promoting naïve T-cell differentiation into effector or regulatory T cells. Since the discovery of DCs, many

subsets were identified based on anatomical location, function, and surface marker expression (Steinman et al. 1975; Steinman and Cohn 1973, 1974; Verma et al. 2014).

9.9.2.2 Plasmacytoid DCs

pDCs are characterized by interferon (IFN)-α production in response to nucleic acids sensed by endosomal TLRs. They are characterized by surface expression of sialic acid binding immunoglobulin-like lectin H (Siglec H). pDCs recognize *A. fumigatus* DNA via TLR9 (Ramirez-Ortiz et al. 2008) and inhibit Aspergillus growth in vitro. pDCs accumulated in the lungs in a murine model of *Aspergillus pulmonary* infection (Ramirez-Ortiz et al. 2011). Their elimination enhances progression of infection. pDCs recognize and combat fungi in vivo (Li et al. 2011). This pDC subset fails to produce IFN-α after stimulation with TLR ligands. Nevertheless, they secrete elevated levels of IL-6 and IL-23 and prime antigen-specific Th17 cells in vivo (Verma et al. 2014).

9.9.2.3 Conventional DCs

Conventional DCs or resident DCs existing in the lymphoid tissue are comprised of two main subpopulations; $CD8^+$ and $CD4^+CD8^-$ resident DCs. The spleen contains a third minor population of so-called double-negative DCs, which lack CD4 and CD8 expression and appear to be mostly similar in function to $CD4^+$ $CD8^-$ DCs (Luber et al. 2010). DCs acquire and cross-present *Histoplasma capsulatum* antigens to CTL by ingestion of live or killed yeasts or uptake of Histoplasma-containing apoptotic macrophages (Lin et al. 2005). Fungal antigens can be acquired and presented by resident DCs; the resident DC subpopulation(s) involved in vivo remain undefined. DC acquisition of antigen required ferrying of yeast from the skin to the lymph node by migratory and monocyte-derived DCs. Resident DCs in the skin-draining lymph nodes acquired and displayed antigen and primed antigen-specific CD4+ T cells (Ersland et al. 2010; Verma et al. 2014).

9.9.2.4 Migratory DCs

Migratory DCs (or tissue DCs) are immature DCs located mainly in peripheral tissues, such as the skin, lung, and gut. Migratory DCs line the surfaces of the body exposed to the surroundings and thus encounter fungi and other pathogens and antigens. The skin, lung, and intestine DCs share similarities, but each site has functional differences that are important in antifungal immunity (Verma et al. 2014).

9.9.2.5 Monocytes, Monocyte-Derived DCs, and Inflammatory DCs

Monocytes are derived from a macrophage-DC progenitor and, in the absence of inflammation, are found in the bone marrow and circulating at low levels in the blood and spleen. Monocyte-derived DCs have an outsized role in antifungal immunity through the induction of Th1 cells. $CCR2^{-/-}$ mice show skewed Th2 responses and poorly controlled *H. capsulatum* infection compared to wild-type mice (Szymczak and Deepe Jr. 2009). Similar $CCR2^{-}$dependent phenotypes are found in experimental infection with *A. fumigatus* or *C. neoformans*; that is, priming Th1 cells in response to fungi requires CCR2+ monocyte-derived inflammatory DCs (Ersland et al. 2010). The tissue environment has a striking role in inflammatory DC function, as the defect in CD4 + T-cell priming by these DCs during infection with *A. fumigatus* is restricted to the lung in $CCR2^{-/-}$ mice and not to other lymphoid organs, such as the spleen (Hohl et al. 2009). Ly6C+ CCR2+ monocytes play a major role in delivering B. dermatitidis into skin-draining lymph nodes after subcutaneous vaccination; this shuttling function can be counterbalanced by other skin migratory DC subsets in $CCR2^{-/-}$ mice (Ersland et al. 2010; Verma et al. 2014).

9.10 Recognition, Signaling, and Other Forms of Interactions

The innate immune system is the body's first line of defense against the foreign pathogens and performs indispensable work. The ability of the pathogen to invade the human host relies on its capability to evade and circumvent host defense mechanisms. Triggering of the host defense depends on proper detection of the invading pathogen. The mechanism responsible for the recognition is regulated by host PRRs that recognize conserved pathogen-associated molecular patterns (PAMPs) expressed by microbes, but not by the host (Richardson and Smith 1981). By PRRs recognizing microbial ligands, the innate defense system is triggered. A direct antifungal response results in either a phagocytic process or secreting microbicidal compounds. Cytokine and chemokine production take off. Antigen uptake and the triggering of the adaptive immune system is induced. The role of recognizing fungal pathogens was ascribed to a major class of PRRs, the TLRs. TLRs are expressed in various immune and nonimmune cell types. In the TLR family, TLR2 and levels of antifungal medications provide a secure harbor for genetic variance to arise (Netea et al. 2006; Tada et al. 2002; Tronchin et al. 2008).

9.10.1 PRRs

The three major PAMPs that are unique to fungi and set them apart from the mammalian host are chitin, α- and β-glucans, and mannans. The induction of an immune response begins with the innate recognition of the pathogen by PRRs, which drive early protective mechanisms that are necessary for host defense. Toll-like receptors (TLRs) and CLRs are the key families involved in antifungal immunity, and animals and humans lacking signaling adaptors shared by several PRRs stand to indicate more severe phenotypes than the single PRR deficiencies (Gross et al. 2006; O'Neill et al. 2013). TLRs initiate intracellular signaling pathways using myeloid differentiation primary response protein 88 (MyD88) or TRIF adaptor proteins, which finally activate transcription factors NF-kB and the interferon regulatory factors (O'Neill et al. 2013). MyD88-deficient mice, which have defective TLR responses from multiple family members, have shown a role for TLRs in immunity to a range of pathogenic fungi, including *C. albicans* and *C. neoformans* (Biondo et al. 2005). TLR-dependent cellular responses that promote antifungal immunity include the production of type I interferons (IFNs) (Bourgeois et al. 2011). The innate recognition of these fungal PAMPs activates signaling cascades to induce the expression of MHC, costimulatory molecules, and cytokines by APC that influence the evolution of adaptive immunity, TLR and C-type lectins (CLR). TLR1–4, 6, 7, and 9 recognize a variety of fungal species through mostly undefined ligands (Bourgeois et al. 2011). TLRs involved in sensing fungal ligands are TLR2, TLR4, and TLR9 that recognize zymosan, phospholipomannan, O-linked mannans, glucoronoxylomannan, and fungal DNA. Mice lacking the signaling adaptor Myd88 are more susceptible to infection with *C. neoformans*, *C. albicans*, *A. fumigatus*, *B. dermatitidis*, and *Paracoccidioides brasiliensis* (Wuthrich et al. 2011), emphasizing important roles for TLR signaling in antifungal immunity, but also regarding the involvement of Myd88 in IL-1 signaling(Tronchin et al. 2008).

9.10.2 Regulatory T Cells

The appropriate regulation of responses generated against invading infectious agents is necessary to limit collateral damage to the host. In murine models of fungal infections, accelerated clearance of disease is achieved by altering the Treg cell activity. In candidiasis and paracoccidioido mycosis, signaling through the Toll-like receptor TLR2 and its downstream molecule MyD88 is necessary for prolonging survival of Treg cells (Loures et al. 2009). TLR2$^{-/-}$ mice express fewer Trig cells under homeostasis and disease states (Tronchin et al. 2008).

9.10.3 Dectin-1

Dectin-1 is the archetypical and best studied non-TLR PRR (antifungal CLR) shown to link innate and adaptive immunity and instruct differentiation of Th1 and Th17 cells (Rivera et al. 2011). Dectin-1 is the best-described PRR that recognizes exposed β-glucans in the cell walls of many pathogenic fungi, including *C. albicans*, *A. fumigatus*, and *Pneumocystis carinii*. Dectin-1 is expressed primarily by myeloid cells and drives complex intracellular signaling pathways (Drummond and Brown 2011; Tronchin et al. 2008).

9.10.4 Dectin-2

The Dectin-2 family is comprised of Dectin-2, Mincle, MCL, DCIR, DCAR, and BDCA-2. Aside from DCIR, all of the other receptors have short cytoplasmic tails that lack signaling motifs and associate with the FcR-γ chain, an adaptor containing an ITAM motif (Graham and Brown 2009). Members of the Dectin-2 family have a single carbohydrate recognition domain and lack intracellular tails with signaling motifs, although there are some members that are exceptions (e.g., DCIR) (Kerscher et al. 2013). Dectin-2 binds high mannose-containing structures; accordingly, α-mannose and amannose-rich glycoprotein were recently identified as ligands (Kerscher et al. 2013). Dectin-2 associates with FcRg to drive intracellular signaling pathways, of which the best characterized is the Syk-CARD9 pathway, shared with Dectin-1 (Drummond et al. 2011; Tronchin et al. 2008).

9.10.5 Mincle

Mincle is another member of the Dectin-2 family that, like Dectin-2, associates with FcRg and signals through Syk-CARD9. Using deficient mouse models, Mincle was shown to play protective roles during infections with *C. albicans* (Wells et al. 2008). Malassezia-derived glyceroglycolipid and mannitol-linked fatty acids were recently described to activate Mincle-dependent cytokine production (Ishikawa et al. 2013). Cytokine production appears to be the main protective mechanism downstream from Mincle, as phagocytosis is unaffected in the absence of this PRR (Tronchin et al. 2008; Wells et al. 2008).

9.10.6 Mannose Receptor (CD206)

The MR has a short cytoplasmic tail that lacks classical signaling motifs. Its located downstream signaling pathway is unknown (Willment and Brown 2008). The mannose receptor (MR) recognizes a broad range of pathogenic microbes including bacteria, parasites, viruses, and fungi through terminally mannosylated molecules. Several antifungal activities downstream from the MR were shown, including producing IL-17 from human peripheral blood mononuclear cells (PBMCs) stimulated with *C. albicans* mannans (van de Veerdonk et al. 2009) and phagocytosis of *C. albicans* yeast in DCs. They are also hypothesized to be involved with sampling of phagosomes because of the late-stage recruitment pattern (Heinsbroek et al. 2005; Tronchin et al. 2008).

9.10.7 Complement Receptor 3

Complement receptor 3 (CR3) is an integrin made up of CD11b and CD18. It is part of the evolutionary ancient complement system that targets and attacks foreign microbes using functionally diverse complement proteins released by a proteolytic cascade. CR3 is involved with leukocyte adhesion, phagocytosis, and chemotaxis using mechanisms that can either be dependent or independent of other components of the complement system (Tronchin et al. 2008).

9.10.8 DC-SIGN

DC-SIGN is a human CLR expressed on myeloid cells that binds fucose/mannose-containing glycans. There are eight murine homologs (named SIGNR), which were used to study the probable antifungal activities of DC-SIGN. In vitro assays have shown SIGNR1 recognizing *C. albicans,* leading to cytokine production and activation of the respiratory burst. However, some of these functions seemed to depend on Dectin-1 signaling, suggesting a collaborative effort (Lanoue et al. 2004; Takahara et al. 2011; Tronchin et al. 2008).

9.10.9 IL-17 Defenses

IL-17 is classically associated with $CD4^+$ Th17 cells. There was an increasing admiration of the importance of innate lymphoid sources of IL-17 (Cua and Tato 2010). These sources include NK T cells, γδ T cells, $CD4^2CD8\text{-}TCRb^+$ cells, and "natural" Th17 cells, which do not need activation by a specific antigen and are therefore

considered innate. However, these innate "type 17" cells bear several similarities to conventional Th17 cells in that they express CCR6, IL-7Rα, IL-23R, and the master transcription factor ROR-γt (Tronchin et al. 2008).

9.10.10 Th17 Immunity

Th17 cells are a subset of CD4+ T cells that are developmentally distinct from Th1 and Th2 cells and are distinguished by the expression of cytokines IL-17A, IL-17F, and IL-22. The specialization of this T-cell lineage requires various cytokines and transcription factors. TGF-b and IL-6 prime the initial differentiation of naïve CD4+ T cells to Th17 cells, and IL-23 is necessary for maintenance and enlargement of these cells (Zuniga et al. 2013).

9.10.11 Th1 Immunity

The Th1 immune response is instrumental in host defense against most fungal pathogens. Following exposure, APCs produce IL-12, which is necessary for Th1 lineage commitment. Genetic variations in the IL-12 signaling pathway are related to a predisposition to a broad diversity of fungal diseases, such as cryptococcosis, candidiasis, paracoccidioido mycosis, and coccidioido mycosis (Jirapongsananuruk et al. 2012). Th1 cells orchestrate antifungal immune responses through the release of proinflammatory cytokines IFN-γ, TNF-a, and GM-CSF.

9.10.12 Th2 Immunity

Th2 immunity has a detrimental influence on the host. This genetic effect is hypothesized to predispose individuals to *C. albicans* by suppressing the fungicidal activity of macrophages encountering *C. albicans* yeasts (Cenci et al. 1993). The mechanisms by which Th2 cytokines dampen host immunity are multifactoral. Both IL-4 and IL-13 drive alternative activation of macrophages that is associated with uncontrolled fungal growth. These alternatively activated phagocytes display amplified levels of arginase-1, an enzyme that potentially diminishes the amount of nitric oxide required for fungicidal activity (Davis et al. 2006).

9.10.13 Inflammasomes

Inflammasomes are a recently identified family of proteins originally characterized for their important part in causing inflammation. They contain a carboxy-terminal leucine-rich repeat, a central nucleotide oligomerization domain, and an amino-terminal effector domain used to categorize inflammasomes into one of three classes: pyrin-containing NOD-like receptors (NLRPs), CARD-containing NOD-like receptors (NLRCs), and a baculovirus inhibitor of apoptosis protein repeat (BIR) domain-containing class.

9.10.14 T- and B-Cell Immunity

It is acknowledged that activation of the adaptive arm of the immune system is necessary for resolution of a fungal infection in the host. The transition from innate to adaptive immunity is facilitated primarily by DCs, although macrophages contribute. These phagocytes process and present fungal antigens to naïve CD4+ T cells in class II MHC.

9.10.15 CD8+ T Cells

CD8 + T cells are vital for protection against viral pathogens and tumors; however, their relative contribution to host immunity against fungal infections is not as comprehensively understood as CD4+ T cells. In mice deficient in MHC Class II, CD8+ T cells suppress *H. capsulatum* infection by targeting macrophages laden with yeasts (Lin et al. 2005). The most likely mechanisms through which memory $CD8^+$ T cells coordinate solution of pathogen in these models is by the release of IFN-γ and IL-17, and cytotoxic effects on infected cells. Thus, vaccines that elicit a robust CD8+ T-cell response can potentially be utilized as an alternative scheme to prevent fatal mycoses in immune-deficient patients.

9.10.16 Humoral Immunity

The impact of immunoglobulins and the B cells secreting them was well scrutinized in *C. neoformans* (Szymczak et al. 2013) and *C. albicans* (Saville et al. 2008). The clinical importance of immunoglobulins in mycoses is evident from reports that patients with B-cell defects, including X-linked hyper-IgM (de Gorgolas et al. 2005), hypogamma globulinemia (Neto et al. 2000), and IgG2 deficiency (Marr et al. 2012), are susceptible to cryptococcosis. The mechanisms by which these

antibodies mediate protection in the host are broadly classified into direct and indirect mechanisms.

9.11 Fungal Ghosts

Evacuating microbes from their cytoplasmic content is a natural phenomenon. Pores could be introduced to the microbial cells as a result of different mechanisms (Amara 2016d; Dong et al. 2012; Laemmli 1970; Makino et al. 1999; Panthel et al. 2003), such as the evacuation of the gram-negative bacteria by the bacteriophage infections. The bacteriophage *E* lysis gene is used for evacuating the cells and turning them to ghosts by controlling its expression using a heat-sensitive promoter (Amara 2016d; Dong et al. 2012; Hensel et al. 2000; Panthel et al. 2003; Weibull 1956; Witte et al. 1992). Recently, the Sponge-Like protocol was introduced (Amara 2015b; Amara et al. 2013a, b, 2014b; Menisy et al. 2017a; Sheweita et al. 2019). Its main concept is using active chemical compounds that could introduce pores in the microbes and degrade the DNA at concentrations that did not change the surface antigens or the 3D structure (Amara et al. 2013a, b). This allows the evacuation of gram-negative and gram-positive bacteria, eukaryotes, and viruses (Amara 2015a, b, 2016a, c; Amara et al. 2013a, b, 2014a; El-Baky and Amara 2014; Hussain and Amra 2016; Menisy et al. 2017b; Park et al. 2016; Vinod et al. 2014, 2015; Wu et al. 2017). The Sponge-Like protocol was used to evacuate two types of fungi, *Aspergillus flavus* and *Aspergillus niger* (El-Baky et al., 2018a, b), and Oyster mushroom spores (Haddad et al. 2019).

These preliminary studies on fungal ghosts and their spores pave the way for many applications, including the immunological-related ones. A dead microbe with correct surface antigens can be used as a vaccine. In fact, I have spent a large part of my career researching DNA/plasmid isolations to provide a better understanding of microbial evacuations (Amara 2005, 2010, 2015c, 2016a, b, c, 2017a, b, c, 2018; El-Baky et al. 2018a, b).

9.12 Plants Involved in Folk Fungal Treatments

Traditional medicine has different usages for plants able to fight fungal infections. Plants that show antimicrobial activities for certain microbes have been used in treatment. Many attempts have been made to find new antifungal compounds from natural products from plants. Some plants used in traditional medicine show activities against some fungal infections, such as *Candida albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. guilliermondii*, *C. parapsilosis, C. pelliculosa*, *C. tropicalis*. *C. krusei*, *Microsporum gypseum*, *M. canis*, *Trichophyton mentagrophytes*, *T. violaceum*, *T. simii T. rubrum*, *T. mentagrophytes*, *T. simii*, *Trichosporon asahii*, *T. rubrum*, *Epidermophyton floccosum*, *Magnaporthe grisea*, *Porphyromonas gingivalis*, *Aspergillus niger, Scopulariopsis brevicaulis*, *Cryptococcus spp*., and *M. furfur,* as shown in Table 9.1.

Table 9.1 Examples of medicinal plants used to treat fungal infections in folk medicine

Plant name	Country/ Region	Fungal Infection	Reference
Rhus tripartitum (African sumac)	Tunisia	*Candida albicans*	(Abbassi and Hani 2011)
Dracaena cinnabari Balf. f. (Dracaenaceae) Dragon's blood (Dam Alakhwin)	Soqotra Island, Yemen	*Microsporum gypseum* and *Trichophyton mentagrophytes*	(Al-Fatimi 2018)
Capparis spinosa and *Juglans regia*	Palestine	*Microsporum canis*, *Trichophyton mentagrophytes,* and *Trichophyton violaceum*	(Ali-Shtayeh and Abu Ghdeib 1999)
Ononis spinosa L	Southeast Anatolia	*Candida albicans* standard strain (ATCC 95071), *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida guilliermondii*, *Candida parapsilosis*, *Candida pelliculosa*, *Trichosporon asahii*, *Trichophyton rubrum*	(Altuner et al. 2010)
Psidium guajava L		*Candida albicans, Candida tropicalis*, and *Candida krusei*	(Bezerra et al. 2018)
Astronium sp	South America	*Candida albicans*	(Bonifacio et al. 2019)
Larrea cuneifolia and *L divaricata* extracts	Argentina	*Candida albicans*	(Espino et al. 2019)
Toddalia asiatica (L.) Lam. (Rutaceae)	India	*Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton simii*, *Epidermophyton floccosum*, *Magnaporthe grisea,* and *Candida albicans*.	(Duraipandiyan and Ignacimuthu 2009)
Pulsatilla patens		Candida glabrata	(Laskai et al. 2018)
Isodon flavidus	Leigong Mountains Southwest of China	*Trichophyton rubrum Porphyromonas gingivalis* and *Candida albicans*	(Zhang et al. 2018)
Acalypha indica, *Cassia alata*, *Lawsonia inermis*, *Punica granatum*, *Thespesia populnea* and *Wrightia tinctoria*	Tamil Nadu, India	*Trichophyton rubrum*, *Epidermophyton floccosum*, *Aspergillus niger,* and *Scopulariopsis brevicaulis*. *Trichophyton mentagrophytes* and *Trichophyton simii*, *Aspergillus niger*, *Candida albicans* and *Cryptococcus sp*	(Ponnusamy et al. 2010)
Ononis spinosa L.		Candida strains	(Stojkovic et al. 2020)
Alpinae officinarum		Antifungal	(Zhou et al. 2007)

(continued)

Table 9.1 (continued)

Plant name	Country/ Region	Fungal Infection	Reference
Eucommia ulmoides Oliv. *Eucommiaceae Engler*		Antifungal.	(Huang et al. 2002)
Mahonia fortunei (Lindl.) *Fedde Berberidaceae*		Antifungal	(Li et al. 2007)
Pseudostellaria heterophylla (Miq.) Pax ex Pax et *Hoffm. Caryophyllaceae*		Antifungal	(Wang and Ng 2006)
Melaleuca alternifolia. Melaleuca alternifolia		*Malassezia furfur*	(Pooja et al. 2013)

9.13 Conclusion

The body has been created to resist any kind of infection. There are two main elements of the immune system: the innate and the adaptive. Other factors can strengthen or weaken the immune system. Humans have been able to distinguish diseases related to the immune system. Two general approaches have been used to regenerate it: heat shock and the insertion of foreign tissue (cotton) under an animal's skin. The immune system works collectively as one unit. Signals activate the effective agents that can control certain infections or illness. Despite the many natural and manmade tools for protection from infection, fungi still have the power to overcome most immune system tactics. Their power is associated with their size, nature of invasion (eukaryotic), mode of invasion, ability to trick the immune system, ability to differentiate, and capacity to colonize the tissues (Tronchin et al. 2008).

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Conflict of Interest The author declares that there are no conflicts concerning this study.

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