8.4: Fungal Pathogenicity

Skills to Develop

- Name at least three fungal virulence factors that promote fungal colonization.
- Name at least two fungal virulence factors that damage the host.

As with the bacteria, fungal virulence factors can be divided into two categories: virulence factors that promote fungal colonization of the host; and virulence factors that damage the host.

Virulence Factors that Promote Fungal Colonization

Virulence factors that promote fungal colonization of the host include the ability to:

1. adhere to host cells and resist physical removal;
2. invade host cells;
3. compete for nutrients;
4. resist innate immune defenses such as phagocytosis and complement; and
5. evade adaptive immune defenses.

Examples of virulence factors that promote fungal colonization include:

1. A compromised immune system is the primary predisposing factor for serious fungal infections. A person highly immunosuppressed, such as a person taking immunosuppressive drugs to suppress transplant rejection, or a person with advancing HIV infection, or a person with other immunosuppressive disorders, becomes very susceptible to infections by fungi generally considered not very harmful to a healthy person with normal defenses.
2. As with bacteria, the ability to adhere to host cells with cell wall adhesins seems to play a role in fungal virulence.

3. Some fungi produce capsules allowing them to resist phagocytic engulfment, such as the yeast *Cryptococcus neoformans* and the yeast form of *Histoplasma capsulatum* (Figure 1).

4. *Candida albicans* stimulates the production of a cytokine called GM-CSF and this cytokine can suppress the production of complement by monocytes and macrophages. This may decrease the production of the opsonin C3b as well as the complement proteins that enhance chemotaxis of phagocytes.

5. *C. albicans* also appears to be able to acquire iron from red blood cells.

6. *C. albicans* produces acid proteases and phospholipases that aid in the penetration and damage of host cell membranes.

7. Some fungi are more resistant to phagocytic destruction, e.g., *Candida albicans*, *Histoplasma capsulatum*, and *Coccidioides immitis*.

8. There is evidence that when the yeast form of *Candida* enters the blood it activates genes allowing it to switch from its budding form to its hyphal form. In addition, when engulfed by macrophages, it starts producing the tubular germ tubes which penetrate the membrane of the macrophage thus causing its death.

   A movie of *Candida* killing a macrophage from within from the Theriot Lab Website at Stanford University Medical School: *Candida albicans* killing macrophages from inside out.

9. Factors such as body temperature, osmotic stress, oxidative stress, and certain human hormones activate a dimorphism-regulating histidine kinase enzyme in dimorphic molds, such as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*, causing them to switch from their avirulent mold form to their virulent yeast form. It also triggers the yeast *Candida albicans* to switch from its yeast form to its more virulent hyphal form.

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**Virulence Factors that Damage the Host**

Like bacteria, fungal PAMPs binding to PRRs can trigger excessive cytokine production leading to a harmful inflammatory response that damages tissues and organs. As fungi grow in the body, they can secrete enzymes to digest cells. These include proteases, phospholipases, and elastases. In response to both the fungus and to cell injury, cytokines are released. As seen earlier under Bacterial Pathogenesis, this leads to an inflammatory response and extracellular killing by phagocytes that leads to further destruction of host tissues.

Many molds secrete mycotoxins, especially when growing on grains, nuts and beans. These toxins may cause a variety of effects in humans and animals if ingested including loss of muscle coordination, weight loss, and tremors. Some mycotoxins are mutagenic and carcinogenic. Aflatoxins, produced by certain *Aspergillus* species, are especially carcinogenic. A mold called *Stachybotrys chartarum* is a mycotoxin producer that has been implicated as a potential serious problem in homes and buildings as one of the causes of "sick building syndrome." Mycotoxin symptoms in humans include dermatitis, inflammation of mucous membranes, cough, fever, headache, and fatigue.
Summary

Many of the same factors that enable bacteria to colonize the body also enable fungi to colonize. Many of the same factors that enable bacteria to harm the body also enable fungi to cause harm.

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