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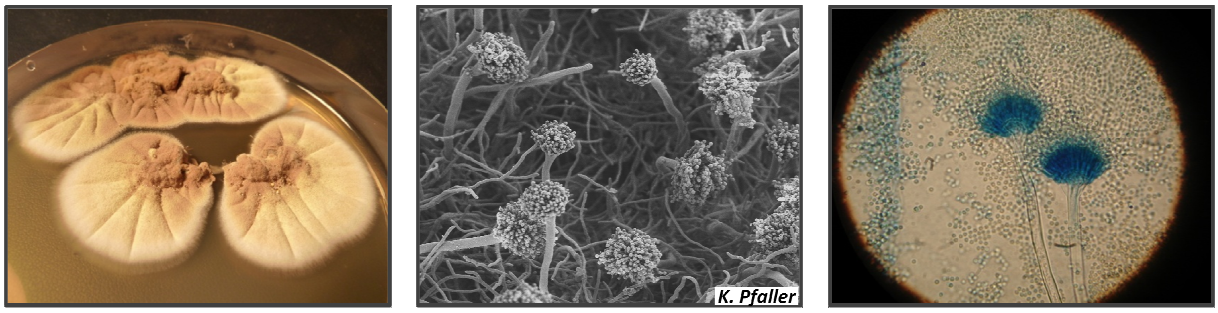
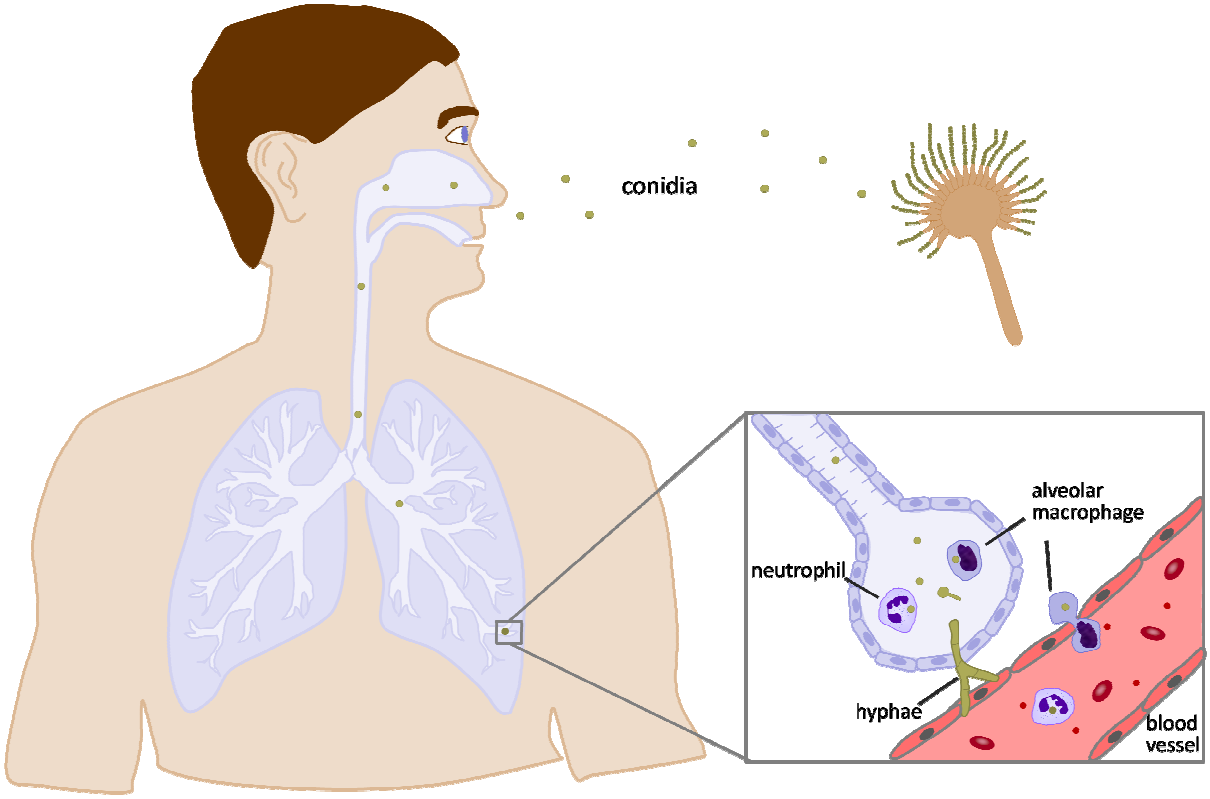
Innate immunity in fungal infections

Fungi are ubiquitously present in the environment, where they grow as saprophytes on dead organic matter. The different fungal species vary considerably in their taxonomic, ecological, and pathogenic characteristics. The genus Aspergillus with its numerous species and the mucormycetes (formerly called zygomycetes) are of particular medical relevance.



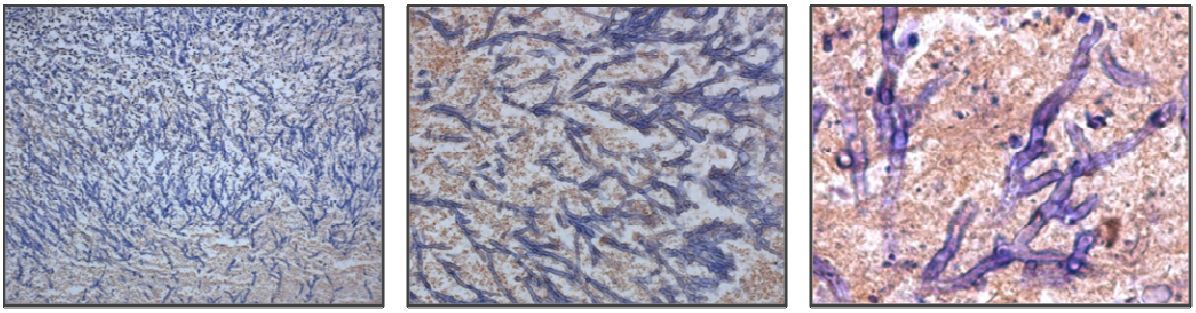
Aspergillus terreus: fungal growth on Sabouraud plates (left); hyphae and conidiophores in scanning electron microscopy (middle); lactophenol blue staining of conidiophores and conidia in light microscopy.

The principal dispersal vectors of Aspergillus and mucormycetes are the asexual conidia. Human exposure is inevitable; conidia are inhaled daily and, depending from outer circumstances, the exposure to the fungus can be considerable. In immunocompetent individuals, the inhaled conidia are eradicated by neutrophils and macrophages in the respiratory tract. When immunity is compromised, however, the conidia are able to germinate and cause pulmonary diseases; the growing hyphae can also penetrate the tissue barrier, invade the blood vessels, and disseminate throughout the body.



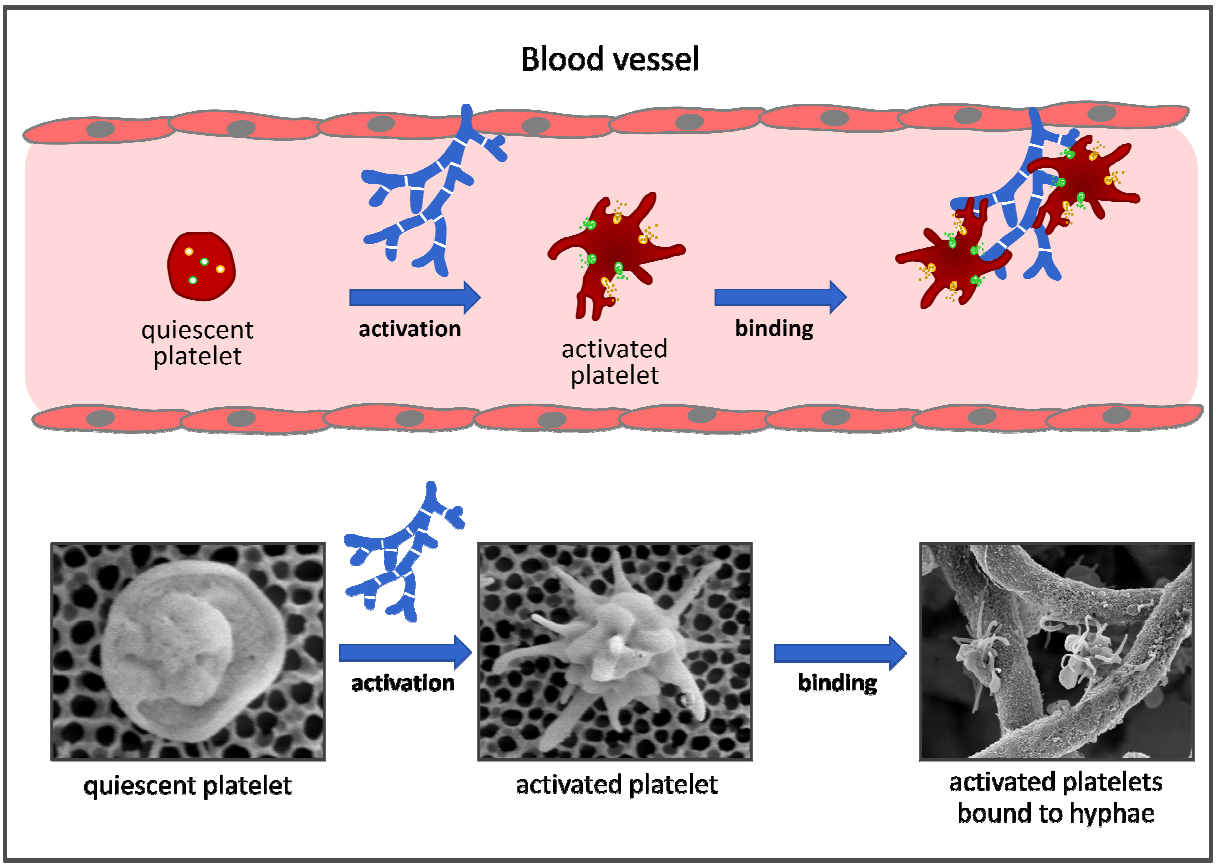
All individuals constantly get in contact with fungi by inhalation of the conidia. In immunocompetent individuals the inhaled conidia are eliminated by neutrophils and macrophages that are present in the airway tract. In immunosuppressed patients, however, conidia can germinate, invade the blood vessels and disseminate throughout the body.

The incidence of invasive fungal infections has been increasing over the last decades. The whole spectrum of immunosuppressed patients can be affected, including patients with haematological malignancies, recipients of haematological stem cell and solid organ transplants, AIDS patients, and patients treated with immunosuppressive regimens due to autoimmune diseases. Beside the lung, the brain is the most affected site of the body, but fungi can be detected in all other organs.



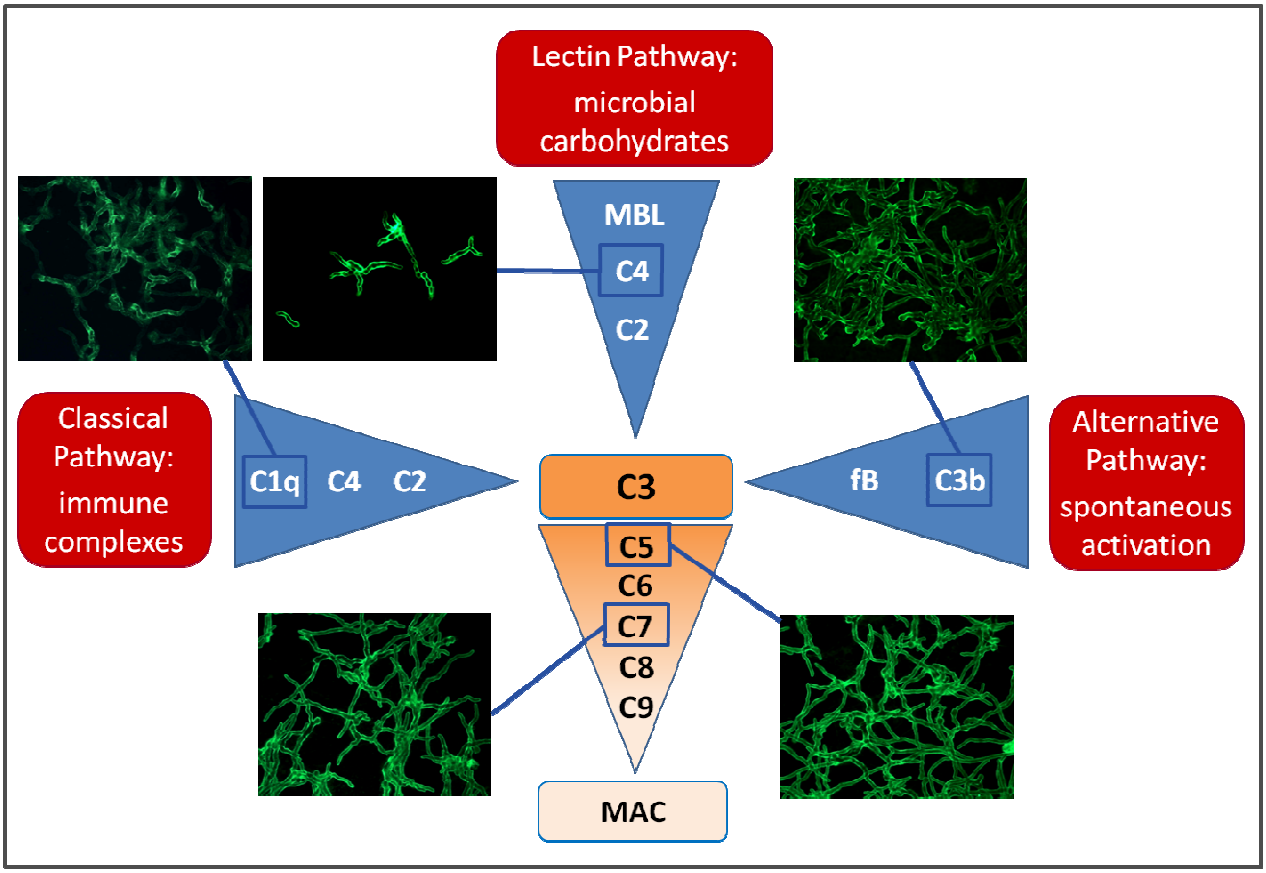
After dissemination, Aspergillus fumigatus has penetrated the blood-brain-barrier, grows in the brain tissue and induces widespread lesions.

Innate immunity is considered to be the most significant host defence against invasive fungal infections. Platelets - recently discovered to be part of the innate immunity - are activated after contact with the fungi, change their shape and release the content of their granules. Two immunological roles can be attributed to platelets in the course of invasive aspergillosis: the direct attack of the invading pathogen by antimicrobial peptides, and the interaction with and stimulation of innate and adaptive immune responses. However, platelets might also contribute to excessive inflammation and thrombosis in the course of invasive fungal infections. For these reasons we aim to gain deeper insight in the interaction between the fungal pathogen and platelets.



The fungus penetrates into the blood vessel where it can interact with the thrombocytes. The thrombocytes get activated, change their shape, release their granules and adhere to the fungal hyphae. Electron microscopic images: K.Pfaller

The complement system represents a crucial part of the soluble innate immune defence and comprises direct effects against invading pathogens as well as bridging functions to other parts of the immune network. Pattern recognition molecules of three different activation pathways can bind to fungal surface structures and thereby start a multifunctional cascade. Some complement proteins coat and label the pathogens for phagocytosis, a process called “opsonization”. Other complement factors directly target the pathogen by formation of the membrane attack complex (MAC) that aims to destruct the pathogen. Receptors for complement proteins are present on B-/T-lymphocytes and on phagocytes and trigger their activation. In addition, complement products act as anaphylatoxins that exert a broad spectrum of biological functions. To further investigate the interaction between fungi and the complement system is another focus of our research.



The complement system is activated after contact with the fungal surface via three different pathways. The complement (C) proteins are deposited on the fungus and form an activation cascade that ends in formation of the membrane attack complex MAC.

Our projects are:

- interaction of innate immunity (thrombocytes, complement) with the invading fungi
- mechanisms of the fungal pathogens to evade the innate immune attack by thrombocytes and complement
- development of therapeutic strategies to support an innate immunity-driven elimination of the fungi