In terms of potential applications, it is not yet clear whether higher-order topological modes localized to corners or hinges have practical advantages over their conventional counterparts. For instance, higher-order topological insulators rely on the existence of crystal symmetries that typically limit the robustness of the edge modes. Moreover, it has been shown that protected modes can also be localized to points or lines of dimensionality lower than ($d-1$) in ordinary topological insulators that have material defects[11–14].

Finally, one can speculate about such systems beyond third order — in other words, beyond the octupole moment. However, these are difficult to realize because of the unfortunate lack of spatial dimensions in our everyday world. Possible ways of overcoming this difficulty include resorting to 'synthetic' dimensions provided by internal degrees of freedom (such as the oscillation modes of a resonator), or artificially enhancing the connectivity of crystal lattices using long-range links[15].

The authors' experimental evidence for higher-order topological insulators illustrates the rapid transition from theoretical proposals to experimental realizations in current research on topological materials. We expect the next few years will be the time for such materials to prove their engineering worth. ■

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IMMUNOLOGY

Melanin triggers antifungal defences

Melanins are enigmatic pigments that have many roles, and the melanin in pathogenic fungi can aid host infection. Identification of a mammalian protein that recognizes melanin now reveals an antifungal defence pathway. SEE LETTER P.382

ARTURO CASADEVALL

Most organisms produce numerous varieties of the highly diverse dark pigments known as melanins, which are among the last remaining biological frontiers with the unknown. These polymer molecules can act in protective or harmful ways, in biological functions as diverse as providing protection against DNA-damaging ultraviolet radiation[1] to bolstering fungal cell-wall strength[2]. Melanins bolster microbial virulence[3], including that of many disease-causing fungi. The presence of melanin can trigger an immune response in the infected organism[4], but how this occurs was unknown. On page 382, Stappers *et al.*[5] report the identification of a protein that can recognize a type of melanin produced by the fungus *Aspergillus fumigatus*. Their finding illuminates the immune-system response to a fungal infection that can be lethal in people who have a suppressed immune system, such as those who have undergone transplantation surgery[6].

Melanin pigments are stable free radicals, and, in animals and fungi, they are produced in membrane-bound organelles known as melanosomes, which shield the cell cytoplasm from the potentially damaging free-radical reaction needed for melanin production. They are insoluble and resistant to degradation by acids. These striking characteristics probably explain why their structures are difficult to analyse and are not fully understood. Host immune cells can trigger potentially damaging cell-signalling pathways in fungi. But such attacks can be neutralized by fungal melanin, which also reduces susceptibility to antifungal drugs[3].

Human disease caused by fungi of the genus *Aspergillus* is called aspergillosis. If a

NATURE

50 Years Ago

Like many other museums of its type, the Museum of Comparative Zoology has teaching and curatorial responsibilities, expeditions are organized to build up collections, and staff travel to study collections in other museums. Research conducted in the museum covers a wide range of topics — evolution, behaviour, ecology, zoogeography, physiology and biochemistry and taxonomy. Almost all the research produces results of interest to the evolutionist. One interesting find during the year was the discovery of a fossil insect from Cretaceous amber from New Jersey. This is the oldest known ant and is apparently virtually a missing link between ants and wasps. The presence of worker characteristics in these insects is evidence of the existence of social Hymenoptera as far back as about 100 million years.
From *Nature* 16 March 1968

100 Years Ago

An announcement in the daily Press states that whale-meat furnished the principal article of food at a luncheon given in New York by the American Museum of Natural History to demonstrate the possibilities of whale-meat for home consumption, in order that the beef thus saved might be sent by America to relieve the scarcity prevailing among the Allies in Europe … Unfortunately, we can do little to assist in this saving, for the whales in our home-waters cannot be "fished", since neither ships nor men are available for the purpose … It is to be hoped, however, that the fullest possible use will be made of the carcasses of the various species of Cetacea stranded around our coasts. Of course, no great quantity of meat would thus be obtained, but locally it should form a very welcome addition to the scanty meat rations now of necessity prevailing.
From *Nature* 14 March 1918

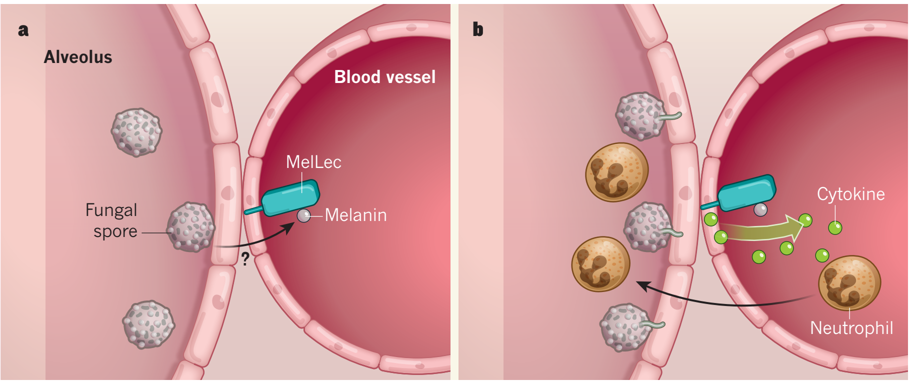

Figure 1 | A receptor that recognizes melanin and triggers antifungal defences. **a**, Infection by the fungus *Aspergillus fumigatus* can be lethal to certain people with weakened immune systems[6], and many aspects of the body's immune response to such infections are unknown. *A. fumigatus* spores contain melanin and can infect air-filled sacs in the lungs called alveoli. Using mice, Stappers *et al.*[5] investigated a protein family linked to antifungal defences[8] called C-lectins, and found evidence that one of these proteins, named MelLec by the authors, can bind a type of melanin pigment present in fungi. Melanin pigment can be sensed by MelLec in cells lining blood vessels, but how melanin reaches MelLec is unknown. **b**, As infection progresses, the germinating spores form cellular protrusions. Melanin recognition by MelLec triggers the synthesis of cytokine molecules that can attract immune cells called neutrophils. Neutrophils can then enter the alveolus and target the infection.

lung infection takes hold in someone who has inhaled *A. fumigatus* spores, it can result in an infection that spreads elsewhere in the body. When *A. fumigatus* infects the lungs, host cells can trigger a cellular-degradation pathway called autophagy that aids fungal destruction. However, fungal melanin can inhibit autophagy[7]. Moreover, melanin is linked to inflammation.

The ability of melanin to target host defences, and the molecule's role in fungal virulence, raises the question of whether mammalian cells can recognize melanin. Stappers and colleagues investigated this by studying members of the C-type lectin protein family, which has previously been identified[8] as being involved in antifungal defence. Using an *in vitro* biochemical approach, the authors tested whether any C-type lectins from mice can bind fungal spores from *A. fumigatus*. One of the proteins they tested could do so, and they named it MelLec.

The authors tested strains of *A. fumigatus* containing mutations that block steps in the melanin-synthesis pathway, and found that MelLec recognizes 1,8-dihydroxynaphthalene melanin. MelLec did not recognize other tested forms of melanin that are associated with fungal disease.

The authors found that mouse MelLec is expressed in the endothelial cells that line the surface of vessels forming the circulatory system. This suggests that it responds to infection after *A. fumigatus* has breached the lung defences in air-filled sacs called alveoli and moved farther into the body to reach the circulatory system (Fig. 1). In humans, MelLec is expressed in endothelial cells and in a type of immune cell known as a myeloid cell[9].

The authors genetically engineered mice that lacked MelLec. These mice seemed normal, but after treatment with molecules to induce immunosuppression and the injection of *A. fumigatus* spores into their bloodstream, they were more susceptible to infection than wild-type counterparts that had undergone the same treatment. Direct introduction of *A. fumigatus* into the lungs of mice lacking MelLec resulted in fewer immune cells called neutrophils entering the animals' lungs than was the case for wild-type mice, suggesting that melanin recognition by MelLec aids neutrophil recruitment to sites of infection. The authors found that the reduced neutrophil recruitment in mice lacking MelLec was linked to lower expression of neutrophil-attracting molecules called cytokines.

Although *A. fumigatus* is ubiquitous in the environment, not everyone with impaired immunity develops aspergillosis, suggesting that some individuals might be particularly vulnerable to the infection. To investigate this, Stappers and colleagues studied people who were in an immunosuppressed state following transplantation. Those who had a mutant version of MelLec in which a specific glycine amino-acid residue was replaced by alanine were more susceptible to infection by *A. fumigatus* than those who had the normal version of the protein. *In vitro* analysis of human cells revealed that this mutation is associated with decreased cytokine production in response to fungal exposure compared with cytokine production in cells containing the normal version of MelLec.

The identification of a MelLec mutation linked to susceptibility to fungal infection suggests an immediate clinical application in identifying patients at high risk of developing *Aspergillus* infections and who might benefit the most from antifungal treatments. Moreover, individuals with a functioning immune system can develop a hypersensitive reaction to *Aspergillus,* a condition known as allergic pulmonary aspergillosis, and other MelLec mutations might be responsible for this predisposition.

As with all good scientific studies, the answer to the question of whether the body can sense melanin raises many additional questions. For example, how does melanin pigment on spores in the alveoli reach MelLec on cells located more internally? Perhaps when spores germinate and form cellular protrusions, these damage alveolar integrity and enable the spores to reach blood vessels. Another possibility is that spores are ingested and transported by macrophage cells of the immune system[10].

Stapper and colleagues' work might mark the beginning of an era in which additional melanin-binding molecules are discovered. L-Dopa melanin and other types of melanin are pro-inflammatory[4], so it seems reasonable to speculate that they are recognized by as-yet-unknown host proteins. Furthermore, MelLec offers a target for drug development because drugs that enhance its activity might boost immune responses to *Aspergillus* infection.

Like the discovery of the Toll-like receptor proteins that sense microbial infection in the fruit fly *Drosophila melanogaster*, Stapper and colleagues' identification of this first known melanin receptor arose from fungal-infection studies in model animals. At a time when researchers are increasingly urged to focus on studies with immediate clinical relevance, it is important to remember that transformative work often begins with model systems. Given that fungi are major pathogens targeting invertebrates, perhaps MelLec homologues exist in animal models such as *D. melanogaster* and the worm *Caenorhabditis elegans*, opening the door to the use of these organisms for additional investigation of this phenomenon. These and other studies building on the work of Stapper and colleagues might further our understanding of host-defence mechanisms. ■

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