TUMOUR BIOLOGY

Fungi accelerate pancreatic cancer

The impact of fungi on human health is under-studied and underappreciated. One genus of fungus, *Malassezia*, has now been linked to the progression of pancreatic cancer. SEE LETTER P.264

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The communities of microorganisms that occupy specific regions of the body are often altered in cancer[1], and these microbiomes — particularly their bacterial components — are a current focus of cancer research. One example is pancreatic ductal adenocarcinoma (PDA), for which changes in the bacterial community occupying the pancreas have been documented[2]. This lethal disease often goes undetected until it has reached advanced stages, and the prognosis is usually very poor[3]. Aykut *et al.*[4] reveal on page 264 that the fungal component of the pancreatic microbiome (known as the mycobiome) is also altered in PDA. In fact, an abundance of a specific fungal genus actually promotes the disease.

The mycobiome is a historically under-recognized player in human health and disease, but its role in both is essential. Harmless organisms called commensals, including fungi, inhabit mucosal surfaces such as the linings of the gut, nose and mouth, and can activate inflammatory processes as part of the immune system's response to injury or infection. In some cases, changes in the biodiversity of fungal communities are linked to aggravated inflammatory-disease outcomes. For example, intestinal overgrowth of *Candida albicans* — a fungus that causes oral thrush in babies — has been associated with severe forms of intestinal ulcers[5] and with mould-induced asthma[6]. Moreover, it is becoming apparent that there is a relationship between the gut mycobiome and human cancers, including colorectal and oesophageal cancer[7].

Aykut *et al.* used DNA sequencing to search for fungus-specific genomic markers in the cancerous pancreas. This revealed increased pancreatic fungal colonization, both in humans who have PDA and in experimental mouse models of PDA, compared with the pancreas of healthy counterparts. What is the source of these fungi? The authors introduced a fluorescently tagged fungal strain into the guts of mice, and the fungus could be detected in the pancreas as early as 30 minutes later. It is known that there is a direct link between the gut and the pancreatic duct, and microbial translocation into the pancreas has been seen for other organisms[8], but not previously for fungi.

> ***"The mycobiome is a historically under-recognized player in human health and disease."***

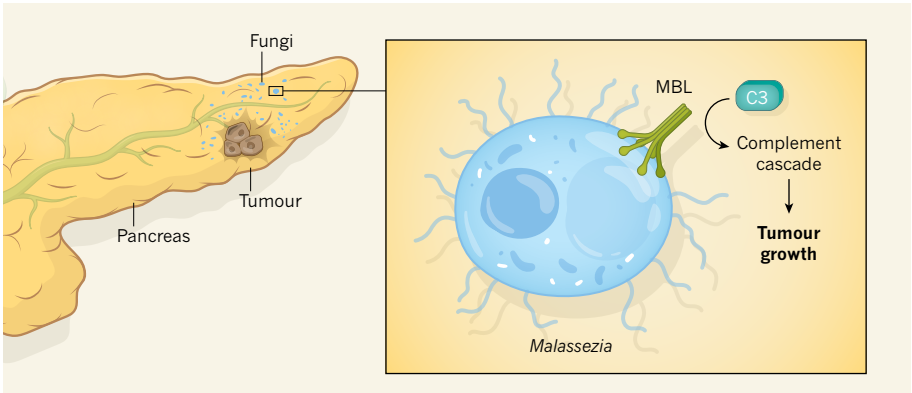

Figure 1 | Fungi called *Malassezia* promote pancreatic ductal adenocarcinoma. Aykut *et al.*[4] report that the community of fungi that inhabits the pancreas is altered when mice or humans have the cancer pancreatic ductal adenocarcinoma (PDA), with species of the genus *Malassezia* becoming particularly abundant. The extracellular protein mannose binding lectin (MBL) recognizes an unidentified carbohydrate structure expressed by *Malassezia* and activates the protein C3, triggering an inflammatory immune response called the complement cascade. Complement activation has many effects, including stimulation of cell growth, survival and migration — factors that fuel tumour growth.

The researchers then investigated the link between pancreatic tumour development and fungi using mice engineered to express a cancer-causing protein in the pancreas. These mice develop a slowly progressive PDA that recapitulates the human disease. The mycobiome of the pancreas was notably different from that of the gut in the mutant mice, although the mechanisms underlying this difference are unclear. One genus of yeast, *Malassezia*, was much more prevalent in pancreatic tumours than in either the guts of these animals or the pancreas of healthy animals. Importantly, *Malassezia* was also prevalent in human PDA samples.

Malassezia species have been best studied in skin conditions such as dandruff and atopic dermatitis. Indeed, they are the most abundant fungal species in mammalian skin, accounting for more than 80–90% of the skin's commensal mycobiome[9]. Because we are constantly exposed to *Malassezia*, healthy individuals can have immune responses to the genus, which in some cases lead to disease. For instance, inflammation caused by overgrowth of *Malassezia* can worsen gastric ulcers[10].

This information hinted that the abundance of *Malassezia* in PDA tumours could be medically relevant. Indeed, Aykut *et al.* found that antifungal drugs halted PDA progression in mice, and improved the ability of chemotherapy to shrink the tumour. Subsequent repopulation of the antifungal-treated animals with a *Malassezia* species accelerated PDA growth again.

Next, Aykut and colleagues asked how *Malassezia* promotes PDA growth. Gene-expression analysis revealed that poor survival outcome in human PDA was associated with expression of a molecule called mannose binding lectin (MBL).

MBL is a soluble protein produced in the liver that binds carbohydrates on the surface of microorganisms and then activates a protein system called the complement cascade in the blood. The complement cascade serves a variety of immune functions, including activating immune cells to ingest and kill fungi and other pathogens. The cascade has also been linked to tumour development, because its pro-inflammatory pathways stimulate the growth, survival and motility of cells — including cancer cells. In a final set of experiments, Aykut *et al.* found that PDA progression was delayed in mice lacking MBL or a key component of the complement cascade called C3, even if *Malassezia* was present in the pancreas. Thus, *Malassezia* augments PDA progression by promoting pancreatic inflammation through the complement cascade (Fig. 1).

Aykut and colleagues' results reveal a previously unappreciated role for fungi in PDA progression. A valuable next step will be to determine whether this role somehow involves interactions with the bacterial species known to promote PDA progression[3]. Fungi and bacteria coexist in the gut and other mucosal

sites, and it is likely that alterations in one community will affect the other. In some scenarios, disease-specific coexistence of bacteria and fungi has been noted — for instance, bacteria of the genus *Pseudomonas* are often isolated from the lungs of people with cystic fibrosis, which are often infected with fungi called *Aspergillus*[10]. Understanding these microbial networks will further enhance our understanding of disease progression and inform therapeutic interventions.

Another unresolved question is how MBL and the complement system integrate with the rest of the immune system during PDA progression. For example, how do MBL and the complement cascade interact with the signalling pathways triggered by an immune-cell receptor protein called dectin-1? This protein recognizes the fungal cell wall and activates protective antifungal immune pathways, often in collaboration with other receptors, including those that recognize the complement cascade. In addition, dectin-1 can directly recognize proteins on tumour cells and modulate the activity of tumour-killing immune cells[11]. But dectin-1 can also associate with tumour-recognizing receptors, which can promote PDA progression[12]. Thus, it is clear that we need a much better understanding of the complex interplay between the components of the immune system that target fungi and those that target tumours.

This study highlights a role for fungi in the development of cancer. Excitingly, the work points to the possibility of new therapeutic approaches. Perhaps altering microbial communities by directly targeting specific populations could help ameliorate PDA. Alternatively, therapies targeting immune components such as MBL that control fungal infections could provide a route to combat this lethal cancer. ■

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SEISMOLOGY

Predicting if the worst earthquake has passed

When a big earthquake occurs, it is hard to tell if it will be followed by a larger quake or by only smaller ones. A method has been developed that aims to distinguish between these scenarios while events are still unfolding. SEE ARTICLE P.193

EMILY E. BRODSKY

After every major earthquake, seismologists warn the public that the danger has not yet passed: aftershocks will continue to shake the ground. These aftershocks usually get smaller over time, but, occasionally, an aftershock will be larger than the original event. Standard earthquake statistics suggest that the latter situation should occur about 5–10% of the time[1,2], but is there any way of knowing which aftershock sequences will behave in this anomalous way? More simply, after a big earthquake, is it possible to determine whether an even larger one is coming? On page 193, Gulia and Wiemer[3] propose an answer to this question. They suggest that, by continuously measuring the relative numbers of large and small earthquakes, comparatively safe aftershock sequences can be distinguished from those that will get bigger.

The magnitude distribution of earthquakes generally follows a relationship known as the Gutenberg–Richter law[4]. Roughly speaking, in most places on Earth, for every earthquake of magnitude 4 or larger, there will be 10 quakes of magnitude 3 or larger and 100 quakes of magnitude 2 or larger. The exact ratio of big to small earthquakes in a particular time or place is described by a parameter called the *b* value. If this value is low, there will be comparatively fewer small quakes for every big one. And if it is high, there will be more small quakes for every big one.

In previous work, Gulia and Wiemer, together with co-workers, found that the

50 Years Ago

It was recently announced that the United States will cooperate with India in setting up a satellite system for bringing educational TV into 5,000 Indian villages … Under the agreement with India, the sixth of NASA's series of Applications Technology Satellites will receive TV programmes transmitted from a ground station at Ahmedabad and relay them to small village receivers. The programmes will be under Indian control and are expected to be directed at family planning, education in agriculture and to make a much-needed contribution to Indian unity. Direct broadcasting to village receivers is made possible by an increase in the power which can be provided on Geostationary satellites, and by a highly directional aerial, which in turn means that the receivers on the ground can be modest and inexpensive.
From *Nature* 11 October 1969

100 Years Ago

Mr. V. Stefansson describes his successful method of Arctic exploration in an interesting article entitled "Living Off the Country" in the May issue of the *Geographical Review* … Mr. Stefansson's well-known adoption of [local] habits and diet have enabled him to travel … far into the unknown for long periods without any anxiety. He contends that from experience he has found that a diet of flesh or fish is quite sufficient to sustain a person in good physical and mental condition, and that salt is not necessary for health … So convinced is Mr. Stefansson of the abundance of food in the Arctic lands and seas he knows that he asserts that any man conversant with the ways of wild animals and the hunting and living methods of the [local people] can load on one dog-team all the equipment he needs for a journey of several years.
From *Nature* 9 October 1919