trained and validated using data collected from plots with sparse tree cover.

Tucker *et al*. have made their data freely available online in a 'viewer' app (see go.nature.com/3ys6nhu). This tool maps the positions of individual trees, details the amount of carbon stored in the wood, foliage and roots of each tree, and provides aggregate carbon stocks for hectare-sized squares of the map (Fig. 1). It could be used, for example, by farmers to provide up-to-date data on carbon sequestered by trees on their land, and thereby to work out credits due to them in carbon-trading schemes.

The authors make it clear that their analysis is a first step and that further updates will be needed. They would like to track the data over time to determine the effects of factors that alter ecological conditions (such as droughts and temperature anomalies), restoration projects, and the implementation of policies and regulations that affect tree growth and provision of ecosystem services, including carbon accumulation. More-accurate estimates of carbon stocks could be made by combining data from small-scale field surveys, ecosystem models, and low-, moderate- and high-resolution satellite images, and by taking into account the ecological conditions in which trees grow.

Nevertheless, the current data already form a basis for future dryland management. This will require locally customized programmes to train key players such as farmers, scientists and managers of restoration projects — because, although it is easy to measure trees, working out the next steps to promote carbon storage in the environment is not. For example, dryland trees are often pollarded (their branches are pruned to encourage dense young growth, for use as fuel or fodder), and might not produce biomass in the way that is described by general equations.

Tucker and colleagues' study is a big step forward for efforts to generate accurate data on dryland carbon stocks, and establishes a framework of scientific tools for this purpose. Encouragingly, it should be possible to improve these tools over time to provide even greater accuracy. Continuous monitoring would also be beneficial in the future, but, for maximum effectiveness, would require the establishment of 'permanent' plots (areas that undergo minimum disturbance from roaming livestock, bush fires and urbanization, for example), to enable the biomass-estimation equations to be fine-tuned to account for changes in growth rates. Establishing such plots can be challenging.

The study also raises awareness of the need for continuous monitoring of dryland trees, to inform dryland restoration projects and thereby help countries to achieve their international commitments for combating climate change and land degradation. We hope that the authors will maintain momentum to keep improving their framework, to support global and African restoration initiatives such as the UN Decade on Ecosystem Restoration, the Great Green Wall and AFR100.

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Cancer

A gut reaction can tune tumour fate

Le Li & Florencia McAllister

The discovery that molecules produced by gut microorganisms can affect immune cells, and thus the success of chemotherapy for pancreatic cancer, points the way towards the use of nutritional interventions to improve outcomes. **See p.168**

Chemotherapy is the most common treatment for pancreatic cancer that has spread to other sites in the body (metastasized). However, such treatment fails if the tumour becomes resistant to this therapy. Although new therapeutic regimens are emerging that use combinations of treatments, outcomes remain poor. If dietary interventions were to be identified that could reduce the emergence of chemotherapy resistance, and these interventions were shown to work in clinical trials, they might offer a readily available therapeutic approach. On page 168, Tintelnot *et al*.[1] present data from studies in humans and mice suggesting that certain gut microorganisms produce molecules that restore the response of tumours to chemotherapy.

Previous studies[2,3] indicate that gut-dwelling microorganisms (termed the microbiota) and tumour-associated microbes affect tumour formation, the immune response to cancer and resistance to cancer treatment. However, the mechanisms that underlie the response to chemotherapy have not been established. Microbes produce molecules from dietary components that can manipulate the immune system and ultimately affect the response to cancer therapy[4]. Understanding the mechanisms involved could lead to the use of dietary interventions to restore sensitivity to treatment.

Tintelnot and colleagues report that the gut microbiota of people with a cancer called metastatic pancreatic ductal adenocarcinoma, who were responding to chemotherapy, differed from that of individuals whose cancer was non-responsive. The authors also found that, in a mouse model of metastatic pancreatic cancer, animals that lacked their own microbiota, and that received microbiota in faecal transplants from people whose cancer responded to chemotherapy, had smaller tumours after chemotherapy than did mice given microbiota from human non-responders.

The bacteria in a tumour can determine whether treatment is successful and the clinical prognosis[5]. Moreover, gut microbes can leave the intestine, move to tumour sites and affect a cancer — either directly, or indirectly through molecules derived from microbial metabolism[6]. These metabolites can also act as chemical messengers between the gut microbiota and remote organs.

Tintelnot *et al*. tracked such molecules in people with metastatic pancreatic cancer using an analytical technique called metabolomics. They found that levels of the molecule indole-3-acetic acid (3-IAA) were higher than normal in the bloodstream of people who had responded to chemotherapy. A high level of

3-IAA in blood samples indicated a favourable clinical outcome in two groups of people assessed. The authors also found that 3-IAA levels were increased in blood samples from mouse guts that had been colonized with the microbiota of people who responded to chemotherapy.

To identify the bacterial species involved, the authors examined microbes associated with 3-IAA generation and found two such strains, *Bacteroides fragilis* and *Bacteroides thetaiotaomicron*. Could supplementation with 3-IAA mimic the effect of colonization with faecal transplants from responders and thereby increase therapeutic responses? The authors tested this experimentally in animal models, and found that oral administration of 3-IAA was indeed beneficial therapeutically across tumours from various tissues of origin, indicating that 3-IAA can act as an indicator of sensitivity to chemotherapy.

The production of 3-IAA involves the amino acid tryptophan and is mediated by bacterial species in the gut[7]. Could a tryptophan-rich diet also result in an anticancer effect? The authors showed that such a diet has a striking antitumour effect in mice given chemotherapy. The effect seems to be specific to 3-IAA because other tryptophan-derived metabolites, such as indole-3-propionic acid and hippuric acid, had no effect.

Tintelnot and colleagues then investigated whether 3-IAA affects the response to chemotherapy through an immunological mechanism (Fig. 1). Immune-cell profiling revealed that the presence of 3-IAA was associated with a population of immune cells called neutrophils. These cells are known to be involved in the antitumour effects observed in people who respond to chemotherapy. Neutrophils can sense signals from the gut microbiota, and their importance in influencing tumour spread is well established[8].

The authors tested whether 3-IAA boosts the effect of chemotherapy by modulating neutrophils. They report that it induces the release of toxic products by neutrophils through an oxidation process mediated by the enzyme myeloperoxidase. Levels of these toxic products rose in tumour cells after treatment with 3-IAA. The authors found that 3-IAA induced the release of molecules called reactive oxygen species (ROS) in cancer cells, ultimately killing them. This effect was blocked when ROS activity was limited using a molecule called a free-radical scavenger. The finding suggests that ROS production is required for 3-IAA's effectiveness.

Next, the authors found that 3-IAA decreases the activity of a stress-related pathway (associated with a type of stress called oxidative stress) in cancer cells, and that this effect depends on the proteins GPX3 and GPX7. Deficiency of this pathway led to increased accumulation of ROS, boosting chemotherapy-induced tumour shrinkage.

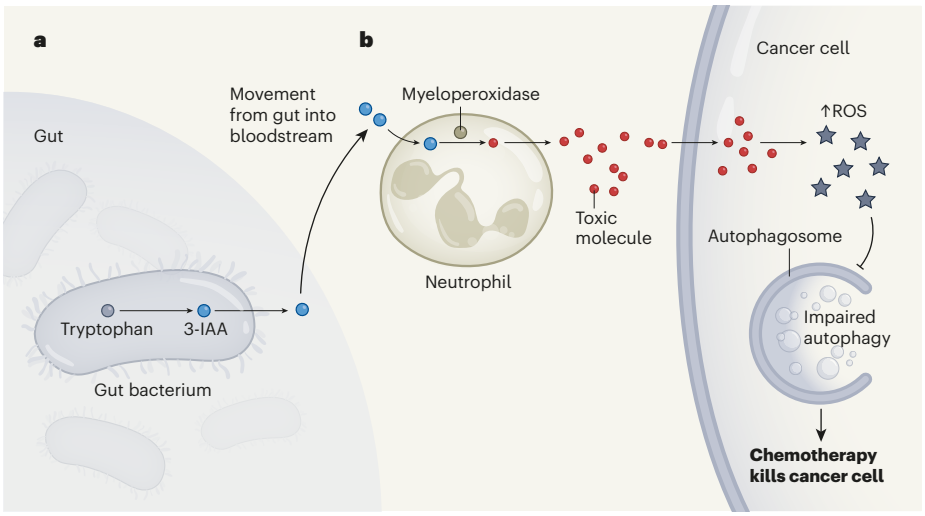

Figure 1 | A molecule produced by gut microbes boosts the success of chemotherapy. Tintelnot *et al.*[1] investigated factors that might affect whether people with a condition called metastatic pancreatic ductal adenocarcinoma respond to chemotherapy. The authors report results from clinical and animal studies indicating that microbial production of a molecule called indole-3-acetic acid (3-IAA) boosted the treatment's effectiveness. **a**, Some gut bacteria use the amino acid tryptophan to produce 3-IAA. **b**, 3-IAA leaves the gut, enters the bloodstream and is eventually taken up by immune cells called neutrophils, in which it undergoes an oxidation process mediated by the enzyme myeloperoxidase to generate toxic molecules. The production of these molecules is associated with an increase in compounds called reactive oxygen species (ROS) in cancer cells. This, in turn, inhibits a key cellular degradation process called autophagy, which is mediated by structures called autophagosomes. Interference with autophagy enables chemotherapy to kill cancer cells.

The molecule AhR is a candidate receptor[9] for 3-IAA. However, the authors found that 3-IAA-dependent chemotherapy sensitivity is independent of AhR.

The authors investigated the role of ROS-dependent molecular pathways in the killing of cancer cells, and found that 3-IAA reduces the concentration of substrates for a cell degradation and molecular recycling process called autophagy. This impairs autophagy and reduces cancer-cell proliferation. Autophagy promotes cancer-cell survival and growth[10]. Treatments to induce autophagy reversed the effectiveness of 3-IAA, whereas blockade of autophagy through pharmacological or genetic inhibition increased the chemotherapy susceptibility of cancer cells.

The interaction between microbial compounds arising from tryptophan metabolism and cancer therapies has been receiving growing attention. Tintelnot *et al.* present evidence that 3-IAA sensitizes cancer cells to chemotherapy by facilitating ROS-mediated cell death associated with impaired autophagy. Another study[9] of pancreatic cancer reported that gut microbiota-produced 3-IAA reduces the effectiveness of a form of cancer treatment called immunotherapy by activating AhR on the surface of immune cells called macrophages. Thus, more studies are needed to clarify the molecular basis of 3-IAA's role and the various cell types involved in cancer progression in the context of different forms of therapy.

An improved understanding of the interaction between gut microbes and associated metabolic pathways might indicate how the microbiota could be manipulated to aid cancer treatment. Although the tumour bacterial population is much smaller than the gut microbiota, the direct production of metabolites by tumour-dwelling microbes might be capable of altering cancer susceptibility and chemotherapeutic resistance, and deserves further investigation.

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