of the Centaurus cluster (Fig. 1c).

The distinguishing feature of the XRISM satellite is its Resolve instrument, an X-ray spectrometer equipped with detectors offering an unprecedented energy resolution. Remarkably, this instrument can discern differences of just a few parts per thousand in the energy of incoming X-ray photons. Thanks to this exceptional energy resolution, Audard *et al.* were able to perform a careful analysis of the widths of emission lines from various metals, and so deduce the velocity of the plasma containing these metals in a central region roughly 60,000 parsecs across.

Their key finding is that a total plasma mass of approximately 10 billion solar masses is moving coherently in this region at a velocity of about 200 km s^{-1} relative to the central galaxy. In seeking to uncover the physical origins of this motion, Audard *et al.* also determine that the gas near the central galaxy exhibits only a low variation in its velocity. This suggests that the energy released by the AGN hosted in the central galaxy has a limited impact on driving the observed plasma motion.

The outstanding quality of the data and the meticulous analysis presented in this work unequivocally demonstrate that high-resolution X-ray spectroscopy can provide transformative insights into the physics of intracluster plasma. It brings closer a full understanding of the interplay between processes on scales of a few parsecs on which AGNs release energy, and processes on cosmological scales of millions of parsecs.

The XRISM satellite's remarkable energy resolution comes, however, with a compromise: reduced angular resolution in its imaging. At the distance of the Centaurus cluster, XRISM cannot resolve features in the plasma's distribution smaller than approximately 15,000 parsecs across. This coarse-grained perspective prevents researchers from drawing firm conclusions about the details of the plasma velocities and, therefore, what ultimately causes them.

By contrast, two older X-ray telescopes, ESA's XMM-Newton and, especially, NASA's Chandra X-ray Observatory, both launched in 1999, can produce much higher-resolution images of the intra-cluster plasma. However, this comes at the cost of much poorer energy resolution, making it impossible to conduct meaningful studies of plasma velocities.

The situation is expected to improve in the second half of the 2030s with the launch of ESA's NewAthena (New Advanced Telescope for High-Energy Astrophysics) mission. NewAthena will offer energy resolution that is superior even to that of XRISM, coupled with much greater X-ray photon collection capabilities, all while maintaining imaging quality that is at least comparable to that of XMM-Newton. NewAthena should finally uncover the mechanisms driving the powerful AGNs at the centres of galaxy clusters, simultaneously shedding light on the evolution of the Universe's most massive galaxies and the hot plasma that surrounds them.

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The author declares no competing interests.

Medical research

A way to disperse clusters of circulating tumour cells

Daniel J. Smit & Klaus Pantel

A drug that limits the clustering of malignant breast-cancer cells that are moving through the bloodstream to distant organs might open avenues to block the lethal spread of a tumour.

Malignant tumours such as breast, lung or prostate cancer can spread from the initial site of tumour growth to other parts of the body through the bloodstream. Such cells are called circulating tumour cells (CTCs), and the spreading process, called metastasis, is the leading cause of cancer-related death. Writing in *Nature Medicine*, Kurzeder *et al.*[1] present an approach to target CTCs.

CTCs can travel through the bloodstream either individually or as clusters, and ultrasensitive technologies can detect them among millions of blood cells. CTC clusters occur more frequently in people who have reached an advanced stage of the disease than in those at earlier stages (before metastasis results in cancer growth at a distant site), and having CTC clusters indicates an increased metastatic potential, compared with just having individual CTCs[2]. Thus, any intervention that can prevent cluster formation or break up existing CTC clusters might open a fresh therapeutic avenue. Kurzeder and colleagues provide proof-of-concept data demonstrating that CTC clusters can be separated in people who have breast cancer.

Previous preclinical animal studies[3] have paved the way for this work by showing that

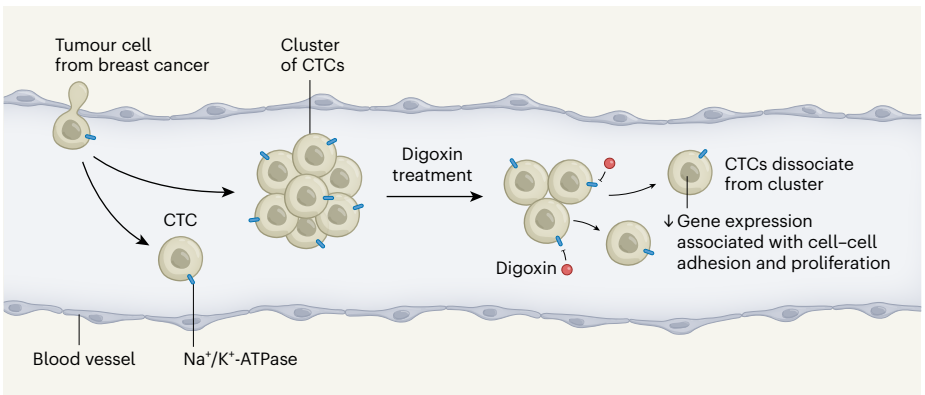

Figure 1 | A way to dissociate cells from clusters of circulating tumour cells. Breast-cancer cells can detach from the initial site of tumour growth and move into blood vessels. These tumour cells in the circulation are called circulating tumour cells (CTCs) and are thought to have a key role in the spread (metastasis) of a tumour to distant organs, which is associated with lethality. CTCs can move through the bloodstream as individual cells or as clusters of cells. CTC clusters are a sign of a high potential for tumour spread by metastasis[2]. Kurzeder *et al.*[1] report clinical data indicating that the number of cells in CTC clusters can be reduced by treatment with the drug digoxin, which inhibits the Na^+/K^+-ATPase ion pump. The Na^+/K^+-ATPase actively exports sodium ions out of the cell in exchange for potassium ions (not shown), affecting the electrical charge of the cell and also contributing to cellular signalling[4,5]. On digoxin treatment, the dissociated CTCs had gene-expression changes that included lower expression of genes involved in cell division and adhesion between cells.

inhibitors of the sodium and potassium transporter protein, called the Na^+/K^+-ATPase, suppress CTC clusters and block metastasis. A drug called digoxin, which inhibits the Na^+/K^+-ATPase, is approved for the treatment of cardiac diseases, and digoxin became the focus for further clinical testing. The Na^+/K^+-ATPase has a key role in generating the ion (electrochemical) gradients across the cell membrane that provide the electrical charge of the cell when it is at rest (the resting potential) or when it is active. This transporter exports three sodium ions out of the cell for every two potassium ions imported[4]. Moreover, the Na^+/K^+-ATPase can act in several signalling pathways and affect the regulation of other ions as well as cellular properties[4,5], making it an interesting and versatile target for anticancer therapy.

In this pilot study of people who have breast cancer with metastasis, Kurzeder and colleagues treated nine individuals daily with a dose of digoxin, which resulted in an average reduction of 2.2 cells per CTC cluster (before treatment, the average number of cells in a cluster was around four). This response to digoxin was associated with lowered expression of genes involved in cell–cell adhesion and cell division (Fig. 1). The treatment was safe, with no treatment-related adverse events reported.

This proof-of-concept study might prompt follow-up studies testing digoxin or other inhibitors of the Na^+/K^+-ATPase. More people will need to be tested to draw firmer conclusions about whether this might provide a cancer treatment option. These studies should also include a control group and assess clinical outcomes such as progression-free survival (survival time without any worsening of disease) or overall survival (survival rates after treatment). Metastatic breast cancer shows high variability in clinical outcomes between individuals. Therefore, an observation based on nine people with cancer is hypothesis-generating rather than fully conclusive.

Although the cluster reduction was statistically significant, it was rather moderate in terms of the number of cells lost per cluster, raising doubts about whether a partial and moderate CTC-cluster dissolution could change the course of disease for people with advanced cancer who already have cancer growths at distant sites (metastases). This cluster dissolution would limit the number of new metastases but not the growth and progression of existing metastases that might drive the clinical disease outcome. Furthermore, digoxin treatment would not affect the clustering of CTCs with blood cells such as neutrophils that also support metastatic progression[6]. Finally, it should be noted that single CTCs predict an unfavourable clinical outcome in breast cancer and some other tumours, as demonstrated in clinical studies on large groups of individuals[7,8], even if the metastatic potential of single CTCs might be lower than that of CTC clusters.

In future clinical studies of the effects of digoxin on CTCs, an earlier intervention in people with less-advanced disease might be better at preventing the formation of metastases. Reports have indicated[9] that blood analyses for CTCs (or circulating cell-free fragments of tumour DNA) can detect cancer cells that remain in the body after treatment (termed minimal residual disease). If CTCs are detected, people have a higher chance of developing a metastasis. However, a challenge is that CTC clusters have rarely been detected in the typical 10-millilitre blood samples obtained from people at an early stage of cancer who don't have detectable metastases. One way to overcome this bottleneck might be to analyse larger volumes of blood, which can lead to improved CTC capture rates[10].

For clinical implementation, it will be crucial to harmonize and standardize the published protocols for detection of CTC clusters. International consortia such as the European Liquid Biopsy Society (www.elbs.eu; based in Hamburg, Germany), which K.P. chairs, are engaged in this important task.

Kurzeder and colleagues' work has highlighted the potential of CTC analyses and manipulation for developing anti-metastatic therapies. Viable CTCs can give rise to distant metastases, and an in-depth analysis of these cells might provide insights into the ability of CTCs to form metastases in people who have cancer.

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The authors declare no competing interests.
This article was published online on 28 January 2025.

Cell biology

Signs of damage that drive protein degradation

Alfred Freeberg & Michael Rapé

Many environmental toxins damage proteins, which then must be removed to avoid dangerous protein aggregation and disease. How cells dispose of chemically modified proteins has been unclear, but a discovery offers some clues. **See p.519**

All organisms are constantly exposed to a barrage of environmental insults that can compromise the integrity of cells and tissues. To preserve cellular function, dedicated signalling pathways can detect and alleviate challenges to proteins and the genome. These protective networks are called stress responses, and they often use a modification termed ubiquitylation to mark a damaged protein for degradation. On page 519, Muhar *et al.*[1] provide insights about how the stress-response machinery can eliminate chemically damaged proteins to ensure continued cell function and survival.

The reaction at the heart of stress responses, ubiquitylation, is best known for its ability to drive protein destruction using degradation machinery called the proteasome[2]. In this manner, ubiquitylation controls cell proliferation, inflammatory signalling, as well as the timely execution of cell-death programmes. In human cells, the substrate specificity of ubiquitylation depends on approximately 600 enzymes known as E3 ligases, which often select targets by detecting short stretches of amino acids referred to as degrons[3]. For example, the E3 ligase APC/C binds to D- or KEN-box degrons in proteins that regulate cell division to establish a sequence of protein-degradation events that orchestrates the complex process of producing identical daughter cells[4]. The recognition of E3-ligase substrates can be modulated by other modifications of the target protein, such as the addition of a phosphate group, which couples ubiquitylation to a variety of preceding signalling events.

When encountering cellular stress, E3 ligases must deal with proteins that have