For Researchers

Food for thought: new insights into how chemotherapy causes cachexia

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Nobody fully understands why people go off food in response to infection, early pregnancy and some chemotherapies for cancer. A flurry of research published in recent years has narrowed down the search for the culprit mechanism, and Cancer Research UK-funded researchers have just found another piece of the puzzle...

Cachexia, sometimes described as a metabolic mutiny, is a condition where lean muscle wastes away, leading to extreme weight loss and weakness. It can crop up in a variety of diseases including infection, the genetic disease Cockayne Syndrome and during cancer chemotherapy.

Cachexia can't be treated by simply eating more or taking supplements. It can leave cancer patients with a miserable quality of life and can impact treatment response and survival.

Professor Ketan Patel. Attribution: The Royal Society

"Chemotherapy-induced sickness and food aversion is a very big clinical problem," says Cancer Research UK-funded scientist Professor Ketan Patel, recently appointed Director of the MRC Weatherall Institute of Molecular Medicine at the University of Oxford. With his recent publication in Nature, Patel and his team have laid out for the first time the steps linking the genetic defect in Cockayne Syndrome with the onset of cachexia and, importantly for the cancer research community, they have showed parallel responses in mice fed the chemotherapy drug cisplatin.

A receptor is found

What we know about cachexia took a great leap forward in 2017 when scientists discovered the receptor for the hormone GDF15 (growth differentiation factor 15). This hormone had been identified back in 1997 but its function was still a bit of a mystery, even though blood levels appeared linked to various things such as aging, environmental toxin exposure, cancer and chemotherapy.

That key breakthrough came when four near-simultaneous *Nature* publications[1-4] from different pharmaceutical companies identified exactly what GDF15 binds to. The newly discovered receptor was identified as GDNF family receptor α-like (GFRAL) and was detected in the area postrema – a part of the brainstem known for handling various functions connected to food such as appetite and aversion to toxicity. The impact this had on the field was swift – the discovery immediately identified the GDF15/GFRAL signalling axis as a druggable target for food aversion issues such as anorexia and cachexia.

"The whole field exploded," says Patel, who unearthed something of particular interest in one of the seminal papers. "Buried in one of the supplementary figures was an experiment where they fed the mice cisplatin," he says. The figure showed that when the GDF15/GFRAL axis was blocked, the cisplatin-fed mice did not lose weight. This stood-out as vital for Patel, with direct implications for his research into how DNA repair fails in Cockayne Syndrome.

Clues from Cockayne

In Cockayne Syndrome, gene mutations break a DNA repair system that usually clears damaged DNA before it can block transcription. The broken repair system in Cockayne Syndrome sees the transcriptional apparatus get stuck on the DNA, leaving cells in a permanent state of transcriptional stress. "People who lack this repair system have a very unusual phenotype," says Patel. "From about 10 years of life on, their bodies spectacularly change. They're very small, they prematurely age and their kidneys fail. And they're also extremely cachectic."

Having previously shown how alcohol can overwhelm the body's defences to damage DNA and cause cancer and how endogenous formaldehyde can sidestep DNA repair systems to cause cancer and kidney disease, Patel had become a senior figure in the DNA repair field. By a stroke of serendipitous timing, Patel was working on Cockayne Syndrome as the 2017 papers identifying the GDF15/GFRAL axis were published. The hidden gem in the supplementary figure showing GDF15 mediating cachexia in cisplatin-fed mice helped Patel to link the consequences of Cockayne Syndrome, formaldehyde and cisplatin – with DNA damage and kidney disease at the heart of the overlap.

If GDF15 mediated cachexia in response to cisplatin, could it also be involved in the cachexia seen in Cockayne Syndrome? The clues all pointed towards an answer residing in the kidney.

To the kidney

"Quite by chance, we were trying to figure out the mystery of why the DNA repair system implicated in Cockayne Syndrome was very important in the kidney," says Patel. To do this, his team created a mouse model with a Cockayne Syndrome phenotype by knocking out the disease-causing *CSB* gene, along with the gene for alcohol dehydrogenase 5 (ADH5), which detoxifies aldehydes before they can damage DNA. "If you combine these two defects in mice, they get neurodegeneration, they're severely wasted, and their kidneys fail," explains Patel. "To find out which cells were involved in kidney failure we use single cell RNA sequencing, which allows you to profile the expression life of a single cell in a complex tissue. That told us a particular cell type from the proximal tubule of the kidney is impacted," he says.

> "I'm very excited about this work, because it's one of the few pieces of research that I've done in my career where I can see an obvious application"

A closer look at these cells found that GDF15 expression was upregulated, with raised levels of the protein also seen in the mouse's blood. Bingo. The team had just shown that accumulation of DNA damage stressed kidney cells into secreting GDF15, a well-known cachectic hormone.

In a bonus discovery, the team also found that the kidney cells also had upregulated p53. This is a transcription factor for GDF15, as well as being a well-known mediator of the DNA damage response. "This is the first proper genetic mechanism to explain cachexia," says Patel.

Joining the dots back to chemotherapy...

Having begun to elucidate the mechanism driving cachexia in Cockayne Syndrome, the last step was to join the dots with chemotherapy induced cachexia. The team fed cisplatin to mice lacking a DNA repair system. "Exactly the same response happens," says Patel, "the same kidney cells get induced, they secrete this hormone and cause a food aversion response." Further experiments confirmed p53 to be an essential part of the response.

Now that the team had figured out the pathways, it was time to see if they could disrupt them to block, or even reverse, cachexia. They went back to their Cockayne Syndrome mouse model and treated it with a monoclonal antibody to GDF15. The mice rapidly gained weight, a strong indication that GDF15 blockade could help reverse the cachexia caused by Cockayne Syndrome and indeed cancer chemotherapy. "I'm very excited about this work, because it's one of the few pieces of research that I've done in my career where I can see an obvious application," enthuses Patel. And biotech interest is strong, with several companies developing and evaluating drugs that disrupt the GDF15/GFRAL axis. "I think there will almost certainly be a generic drug to block this response," says Patel.

Next steps

With drugs in development, it may seem like the story is nicely wrapped up. Not so, says Patel. "It's the first genetic handle to this phenomenon of progressive weight loss, but it's not the whole explanation of how cancer cachexia arises."

It's clear there is lots of work left to do – which is why Cancer Research UK and the NIC have designated understanding and reversing cachexia as one of the Cancer Grand Challenges. For Patel, the next step is to zoom right in on exactly how DNA damage upregulates GDF15 expression in kidney cells. "We want to further explain that connection, what type of signal is sent when you damage DNA that tells the kidney cells to secrete this hormone," he says.

The team also have their sights set on widening their horizons. "We are keen to know whether this axis contributes to general cachectic syndromes that you see associated with chronic infection and cancer," says Patel.

But there is another, altogether more fundamental, question which Patel likes to ponder – why does cachexia occur at all? "It probably exists to put us off food that's toxic to us," he says, citing the case of early pregnancy when GDF15 levels are elevated and expectant mothers are feeling particularly queasy at the sight or smell of certain foods.

Whatever the evolutionary reason for cachexia, it causes misery for many people undergoing cancer chemotherapy. As Patel says, addressing cachexia won't cure cancer. But blocking it, say by interfering with the GDF15/GFRAL axis, could alleviate the side effects of chemotherapy and help patients stay on treatment, ultimately improving their outcomes.

"This would be a massive improvement," concludes Patel.

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