The first step towards finding new and better treatments for liver cancer is to understand how the cancer works”

Cancer cells march to their own tune

In many cancers, normal cellular metabolism is replaced by a new set of molecular interactions. According to **Professor Thorsten Cramer** of the University of Aachen, Germany, understanding these metabolic changes could be the first step to developing new and more successful treatments for some of the most intractable forms of cancer. Thorsten Cramer and his research team are investigating these novel advances in one of the most common cancer types – liver cancer.

For patients diagnosed with liver cancer, the current prognosis is rather bleak. The fifth most common cancer worldwide, its incidence continues to rise as a result of obesity and the growing rates of infectious liver diseases, such as viral hepatitis. Liver cancer can currently only be cured by surgically removing the tumour, but sadly it is often detected too late for surgery, and is frequently resistant to standard drugs by that time. Even the best available chemotherapy treatment prolongs life, on average, for a meagre three months.

KNOW YOUR ENEMY

Thorsten Cramer believes that the first step towards finding new and better treatments for liver cancer, is to understand how the cancer works, right down to the genetic and molecular level. One of the key features of cancer cells is their altered metabolism – the chemical reactions that take place inside the cell – compared to healthy cells of the same type. Fundamentally, these changes are caused by modifications to gene activity, with some genes increasing dramatically in the amount of protein produced from them, and others being switched off entirely.

These changes may send the cell’s metabolism off in radically new and different directions. For example, the German biochemist, Otto Warburg, discovered almost a century ago that liver tumours both take up and break down large amounts of glucose – far more than their non-tumourous neighbours. Since then, this feature has been found to be so consistent that it is sometimes used as a marker for detecting the presence of cancer.

Thorsten Cramer, with collaborators from institutes across Germany and Europe, is now investigating the role of glucose in much greater detail using both human cancer cell lines and mouse models. He and his research team have already shown experimentally that the first step in the chemical breakdown of glucose, glycolysis, is strongly activated in liver cancers in both human patients and mouse model systems.

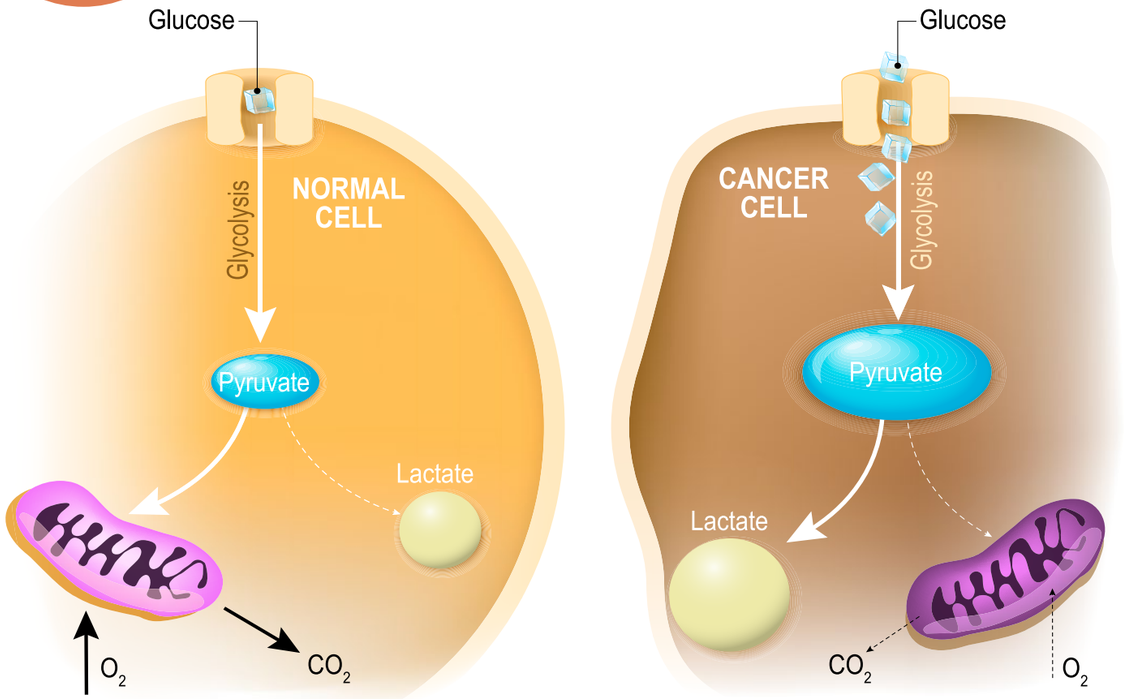
A LOW-CARBOHYDRATE THERAPY FOR CANCER?

Their first approach was to reduce the intake of dietary carbohydrate (which the body breaks down into glucose) in their mouse subjects. As predicted, reducing the amount of carbohydrate in the diet, from fifty to fifteen percent, caused dramatic reductions in tumour formation and improvements in treatment response in mice – even in mice with tumours that were resistant to the main chemotherapy agents used against liver cancer.

However, on further analysis, the team found that despite this reduced carbohydrate intake, levels of glucose remained normal in both the blood and the tumour. This suggests that the body is able to produce glucose from sources other than carbohydrates when necessary, but did not explain how the low-carbohydrate diet worked on liver tumours. Clearly the impact was not as simple as reducing glucose availability to cut off the energy supply for tumour growth.

AN ‘OMICS APPROACH’

Thorsten Cramer and his team’s second approach was to make use of new ‘omics’ technologies to explore the activation of



signal transduction pathways (all the proteins activated by external stimulation of a given cell or tissue) of liver tumours under both normal and low-carbohydrate diets. Here, they made an intriguing discovery. One particular pathway, phosphoinositide 3-kinase (PI3K), was activated at much lower levels in tumours under a low-carbohydrate regime than those of mice fed a normal diet. PI3K was already known to stimulate the growth of cancer cells, and the pathway controlled by PI3K has also been found to be activated in several types of cancer, including liver cancer.

Thorsten Cramer's team hypothesised that PI3K is a tumour-promoting factor, active in healthy liver cells, hyperactivated in cancerous ones, and suppressed by a low-carbohydrate diet – which results in a slowed tumour growth and more successful treatment.

But what processes or mechanisms link a reduced-carbohydrate diet with suppression of PI3K? There are two main possibilities: firstly, the link could be mediated by changes in hormone levels throughout the body. After all, carbohydrate consumption is fundamentally linked to levels of the hormone insulin, which is also known to be a stimulant for tumour growth, in part via activation of PI3K.

Secondly, local changes to the cellular environment within the tumour could be the key. The rapid proliferation of cells inside a tumour often results in a shortage of oxygen – a key chemical requirement for continued tumour growth. This, in turn, may stimulate metabolic reprogramming within the tumour to compensate.

Finding the answers to these questions is one of the focuses of Thorsten Cramer's most recent research project, funded by the German Research Foundation (Deutsche Forschungsgemeinschaft). The aim is to determine three main things: firstly, whether restricting carbohydrate intake consistently slows liver cancer progression both *in vitro* and *in vivo;* secondly, whether it is a safe method of treatment; and thirdly, whether it can be combined with chemotherapy to give patients with inoperable liver cancer a better chance of survival for a prolonged period.

Thorsten Cramer and his collaborators hope to take advantage of the growing field of 'systems biology' to get to grips with the big picture of the molecular linkages and connections between cells in the body and tumour, using sophisticated biological and mathematical methods to observe and map the location of these reactions, even in real time.

Once the mechanisms behind tumour formation and its activation by PI3K are understood, the team can go on to develop potential therapies based on their findings. This, after all, is their overarching goal. As Professor Cramer says: "Our basic motivation of course is to improve clinical patient care."

Low carbohydrate diets are not a recent fad – they have been safely used for almost a century, suggesting they could be applied in clinical practice. If so, this would be the first clinical treatment to be established based on undoing the metabolic reprogramming that cells undergo when they become cancerous. This would put them back in harmony with the body, where they had previously been marching to their own tune.

Reducing the amount of carbohydrates in the diet caused dramatic reductions in tumour formation and improvements in treatment response

Q&A

What factors cause healthy cells to become cancerous?
"Becoming cancerous" is a multi-step process that usually takes many years to become clinically relevant. A lot of different factors have been identified that either cause the initial genetic changes or fuel them on their way to fully established cancer, e.g., infections (e.g., chronic viral hepatitis), dietary factors (processed meat, alcohol), smoking and environmental factors (e.g., radiation, UV light, asbestos, toxins in food).

Why are liver cancers so often overlooked for so long?
Because there are no specific symptoms. Once symptoms have developed that are suspicious for liver cancer, e.g., weight loss, loss of appetite, stomach bleeding or chronic abdominal discomfort/pain, the tumour is usually already advanced and of greater size without the possibility for surgical intervention (which is still the only cure for liver cancer). Chronic liver disease such as inflamed fatty liver disease (NASH, non-alcoholic steatohepatitis) and liver cirrhosis are known to predispose for liver cancer. Unfortunately, the current means of surveillance are not ideal and a lot of cases are missed despite regular consultations.

What is the role of PI3K in liver cancer and how might it be involved in treatment?
PI3K has been found activated in different kinds of cancer, including liver cancer. PI3K is involved in a process called "signal transduction", which basically determines how a cell responds to stimulatory or inhibitory cues from the microenvironment. Activation of signalling pathways that control cell growth is a hallmark of cancer and these pathways are attractive targets for cancer-specific therapies. Unfortunately, the majority of drugs that inhibit growth-promoting signals lose anti-tumour efficacy over time (a phenomenon called therapy resistance). To combat resistance, a comprehensive understanding of the molecular mechanisms that control pathway activity is needed. The observation that PI3K is sensitive to dietary changes bears the potential to improve our understanding of these important cancer-promoting pathways.

What other metabolic 'switches' do you think could become targets for liver cancer treatment?
In our analysis of human and mouse liver cancer, enhanced glucose uptake and metabolism was clearly the predominating feature. However, we are now looking into other metabolic pathways and found interesting alterations in glutamine (an important amino acid) metabolism and mitochondrial activity. We are not the only ones studying metabolic switches of liver cancer and many talented and motivated groups are on the hunt for specific metabolic alterations in liver cancer. I am sure we will learn a lot of exciting new things within the next years.

What questions remain to be solved before your research moves to clinical application?
In Western countries, liver cancer usually develops in cirrhotic livers. Liver cirrhosis per se is a serious condition with a lot of challenges for clinical care. Patients with liver cirrhosis typically show frailty and malnutrition. It is well known that regular dietary counselling improves the prognosis of patients with liver cirrhosis. We need to balance our idea of carbohydrate restriction with the established dietary needs of the patients. In essence, we need to test how patients with liver cirrhosis tolerate a carbohydrate restriction. An interdisciplinary effort with clinical nutritionists is needed to serve the patient best.

Activation of signalling pathways that control cell growth is a hallmark of cancer and these pathways are attractive targets for cancer-specific therapies

Detail

RESEARCH OBJECTIVES
Thorsten Cramer's research focuses on liver cancer (hepatocellular carcinoma (HCC)). He and his team are investigating the pathogenesis of HCC to better understand how to develop potential life-changing therapeutics.

FUNDING

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BIO
Thorsten Cramer worked as a Postdoctoral Fellow at the University of California, San Diego between 2001 and 2003. He later established an independent research group at the Charité in Berlin before starting as an Assistant Professor for Molecular Tumour Biology at RWTH University Aachen in 2014.

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