Unlocking the role of glucose metabolism in lung cancer

Cancer cells have high glucose demands to support continuous cell proliferation and tumour growth. When it comes to the molecular mechanisms behind the glucose metabolism of cancer cells, very little is known. Dr Erik Norberg, Associate Professor of Metabolism at Karolinska Institute, Sweden, and his group have extensively studied the metabolic regulation in cancer cells, with a special focus on lung cancer cells. Their pioneer work revealed the importance of glycolytic enzymes that take part in the metabolic cycle, leading the way toward new diagnosis and treatment strategies.

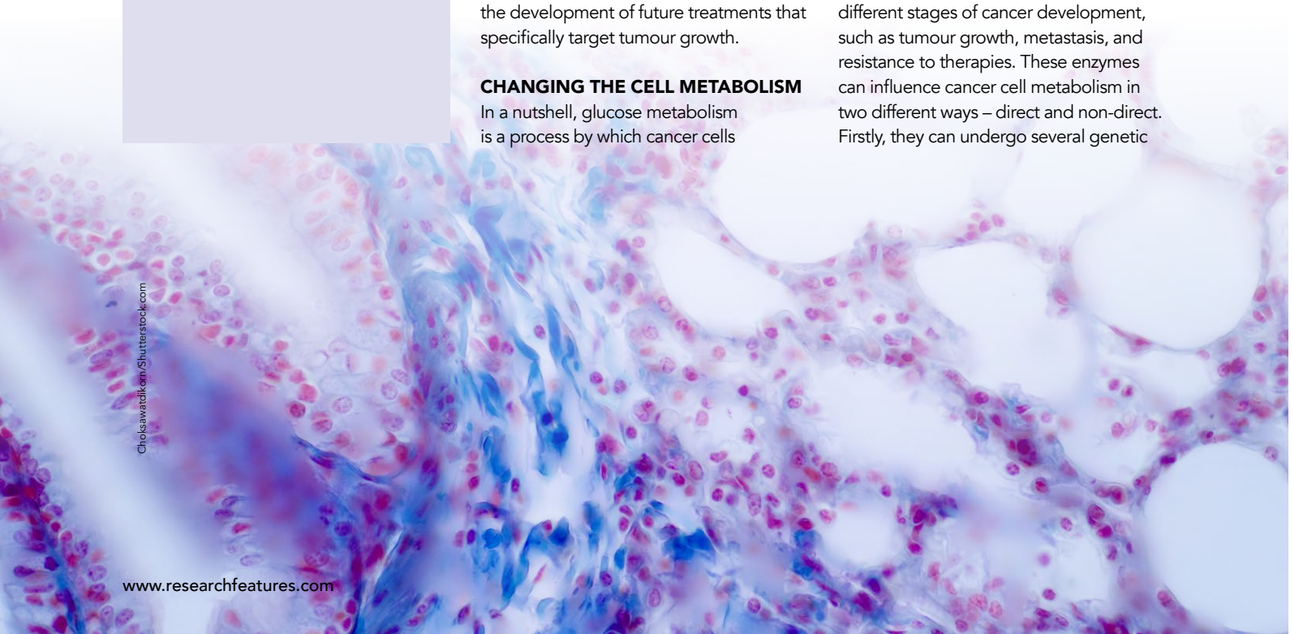
Healthy cells and cancer cells have many different characteristics. Among the most important features is the cell metabolism, which plays a vital role in tumour growth and, ultimately, in the disease outcome. As cancer cells multiply in an uncontrollable manner, they are in constant need of energy. Glucose – the most common monosaccharide – is the main source of energy, and cancer cells often require up to one hundred times more glucose compared to healthy cells. Cancer cells therefore need to reprogramme their metabolic processes to serve these unique demands.

Dr Erik Norberg and his group at Karolinska Institute, Sweden, believe that by deciphering the molecular mechanisms behind the glucose metabolism of cancer cells, one could not only shed light on how tumour cells grow but also help in the development of future treatments that specifically target tumour growth.

CHANGING THE CELL METABOLISM

In a nutshell, glucose metabolism is a process by which cancer cells produce the energy and building blocks required to grow, multiply, and spread throughout the organs and the body. Compared to healthy cells, cancer cells require more energy and building blocks, so they undergo a specific molecular reprogramming in their metabolic processes including four ways: a) by stopping the expression of tumour suppressor genes, b) activating oncogenic signalling, c) by changing the tumour microenvironment, such as nutrient availability and interactions with connective tissue cells (called stroma cells) present in organs, and d) by changes involving enzymes (proteins that act as biological catalysts) which take part in all metabolic processes in a cell – the so-called metabolic enzymes.

Metabolic enzymes are proteins that take part in important biological activities inside the cell. They have been linked to different stages of cancer development, such as tumour growth, metastasis, and resistance to therapies. These enzymes can influence cancer cell metabolism in two different ways – direct and non-direct. Firstly, they can undergo several genetic



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Norberg and his group analysed samples taken from biopsies of lung cancer patients.

mutations. In this case, the observed functional changes are in accordance with the type of mutation present in an oncogene. In a non-direct way, the function of the metabolic enzymes can be influenced via the presence of other enzymes including deubiquitinases (DUBs). DUB enzymes can interact with the metabolic enzymes and influence their action in the metabolism. Norberg's group attempted to study in which ways DUB enzymes influence metabolic enzymes and, ultimately, whether the DUB enzymes can have a direct effect on cancer metabolism.

Since JOSD2 controls the glucose metabolism, when JOSD2 is absent, the glucose metabolism would slow down and the cancer growth would stop.

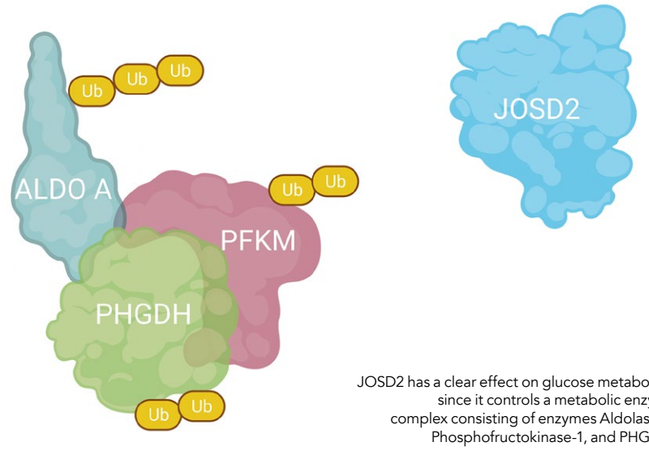
UNDERSTANDING THE ROLE OF DEUBIQUITINASES

As a primary cell function, DUBs are a group of enzymes that help regulate the degradation of proteins – including the degradation of metabolic enzymes. To do so, DUBs use a specific mechanism that is very well studied. Specifically, they act by cleaving off a very important part of the enzymes called ubiquitin, a small 76-amino acid protein regulating the synthesis and destruction of proteins and enzymes. In practice, Norberg's work revealed that DUBs work by cutting off the ubiquitin tag – an amino acid found on the ubiquitin molecule. This mechanism allows them to stabilise and make metabolic enzymes more abundant in cancer cells compared to normal cells. Moreover, DUBs play an important role in many cellular processes, including cell cycle regulation, cell growth, and proliferation, while they can also be suppressed in the case of a mutation. Apart from these characteristics, their role has never been studied in depth, and very little is known when it comes to their function, targets, and regulation.

In an attempt to decipher the role of DUBs, Norberg's group analysed samples taken from biopsies of lung cancer patients and studied specific molecules found in abundance in these samples. They discovered that high levels of a metabolic enzyme called Phosphoglycerate dehydrogenase (PHGDH) are linked with poor prognosis in an adenocarcinoma subset of patients. This is very valuable information as the Norberg lab was able to show that this protein can act as a prognostic factor by providing an indication to the clinician of the state and the possible outcome of the disease. Meanwhile, trying to explain the regulation of the enzyme, they discovered that a DUB enzyme called JOSD2 is involved in the degradation of PHGDH. Additionally, it was found that DUB has a functional role in regulating metabolic heterogenicity in tumour cells, meaning it influences the differences in metabolic regulations of tumours.

JOSD2 AS A POSITIVE REGULATOR

Trying to understand the role of DUBs even further, Norberg used a variety of different tools and techniques, such as proteomics (a tool helping in the analysis of the entire set of proteins found in a cell), isotopomer tracing (a method to study the rate of metabolic reactions in a cell), and classical biochemical analyses. He and his team also performed in vitro studies using several



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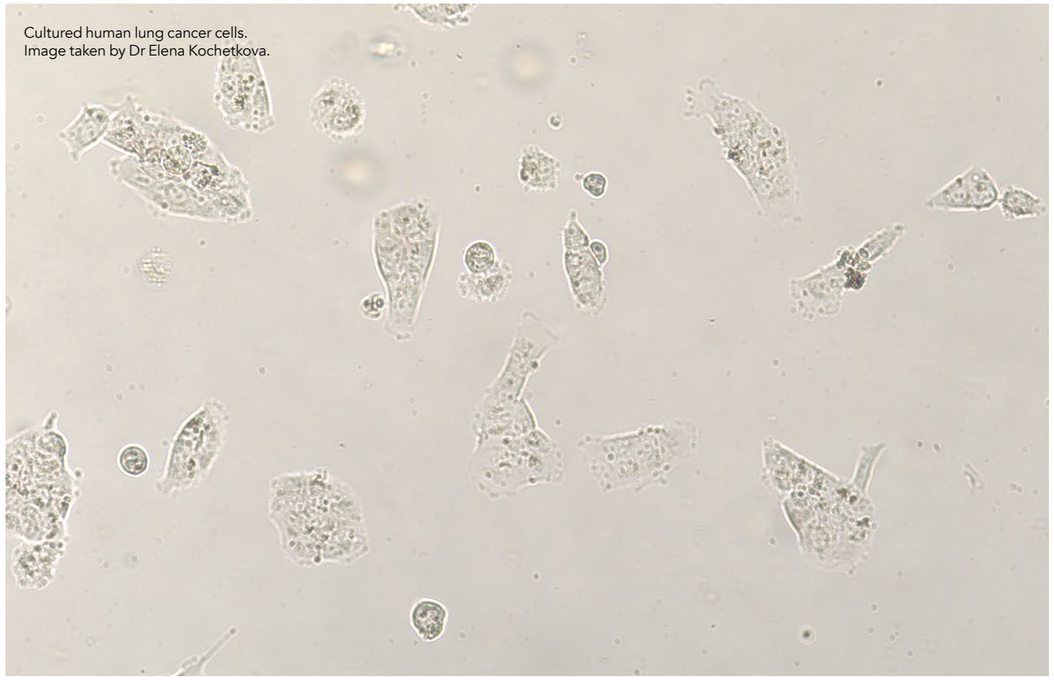
JOSD2 has a clear effect on glucose metabolism since it controls a metabolic enzyme complex consisting of enzymes Aldolase A, Phosphofructokinase-1, and PHGDH.



Cultured human lung cancer cells.
Image taken by Dr Elena Kochetkova.

cancer cell lines, including lung and ovarian cancer cell lines, and in vivo studies using tumour-bearing mice as animal models.

His group identified that JOSD2 is a positive regulator of cancer cell proliferation, meaning that its presence triggers cell growth. In particular, they found that JOSD2 has a clear effect on glucose metabolism since it directly controls a metabolic enzyme complex which consists of the enzymes Aldolase A, Phosphofructokinase-1, and PHGDH. Their results showed that JOSD2 can stimulate the enzyme complex to metabolise glucose to feed cancer cells with energy and building blocks required for their rapid growth. They also showed that lung cancer patients with high expression of JOSD2 had a worse prognosis.

STARVATION OF CANCER CELLS

These observations provided new insights into how the enzymes involved in cell metabolism work. The Norberg lab wanted to take this knowledge even further. After establishing how the function of a DUB enzyme can influence glucose metabolism, the researchers worked to find a way to make use of this valuable information in a new cancer treatment line. Norberg's idea was both elegant and smart: since JOSD2 controls the glucose metabolism, when JOSD2 is absent, the glucose metabolism would slow down, and the cancer growth would stop. Cancer cells with low glucose uptake or production would starve and ultimately degrade and die. As a proof of concept, the team performed cell experiments using NSCLC cells, a type of non-small-cell lung carcinoma which heavily relies on glucose metabolism. According to the results, JOSD2-deficient cancer cells have reduced glucose metabolism.

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The results of this study can be of great importance when it comes to cancer cells with high glucose demands, such as lung cancer cells. Moreover, in the clinic this could potentially be harnessed to be used as a novel cancer treatment that specifically targets cancerous cells while limiting any unwanted side effects. Specifically, this targeted treatment comes at a time when most anticancer drugs, such as drugs included in standard chemotherapy, target normal cells at the same time as cancer cells. This leads to severe and unwanted side effects. In contrast with chemotherapy, new anticancer drugs that act on silencing JOSD2 could provide excellent alternative tools to stop cancer growth.

The pioneering work led by Norberg provided new mechanistic insights into how cancer cells differ in their metabolism to support their high glucose demands. What is left now is to use these new mechanistic tools to develop and design new future cancer treatments.

Behind the Research

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Research Objectives

Dr Norberg and his team have identified the deubiquitinase JOSD2 as a regulator of metabolism and cancer cell proliferation.

Detail

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Bio
Erik Norberg obtained his PhD at Karolinska Institute (2011), for which he was awarded the Dimitris N Chorafas Prize for the best PhD thesis. Dr Norberg then performed postdoctoral training at Harvard Medical School and, since 2019, has been Associate Professor of Metabolism at Karolinska Institute.

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References

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Personal Response

How would you design an anticancer therapy based on your findings?

"It is very challenging to design selective drugs targeting single DUBs, therefore it may be more feasible to employ a personalised medicine approach that is based on the rationale to starve the tumours of their favourite nutrients that they consume in much larger amounts than most normal cells. In this way, it has the potential to reduce tumour growth and severe side effects."