

A novel cancer-related gene may be important in human bladder cancer

Professor Xinghuan Wang is the President of Zhongnan Hospital of Wuhan University. He leads a team at the Department of Urology focused on human bladder cancer. The team's latest research investigates the role of a novel molecule, called CIRBP, in bladder cancer. The team's research increases understanding of the disease and allows potential targets for therapeutic interventions to be identified.

Bladder cancer is the ninth most common malignant tumour in the world, with an estimated 429,000 new cases and 165,000 deaths every year. The tumours usually develop in the bladder lining (non-invasive) but can also spread into the bladder muscle (muscle-invasive). Most cases of bladder cancer seem to develop after years of exposure to harmful substances which lead to an accumulation of changes to the bladder cells over time. For example it is estimated that 1 in 3 cases of bladder cancer is caused by smoking. It is more common in men than women and is seen more frequently in adults over 60 years old. Bladder cancer is usually treated by surgically removing the tumour, followed by chemotherapy. In severe cases, the entire bladder may have to be removed.

BLADDER CANCER BIOMARKERS

Understanding more about the disease processes involved in tumour formation not only progresses the research field for this area, but may also uncover potential therapeutic targets, such as genes which could be used for gene therapy. Previous work by the group led by Professor Wang at Zhongnan Hospital of Wuhan University (ZNWU) has identified several candidate biomarkers which correlated with tumour stage and overall survival in bladder cancer patients. These biomarkers, which are consistently found under a certain set of conditions, such as bladder cancer, could also be used as potential diagnostic markers or therapeutic targets which could ultimately be used in a clinical setting.

The team's latest discovery has been a novel oncogene (a gene with the potential to cause cancer) called cold inducible RNA binding protein, or CIRBP. CIRBP was originally identified in the testis as a mammalian cold shock protein, induced by stresses such as UV radiation, cold and low oxygen levels (hypoxia). One example of this is the ability of CIRBP to increase the stability of inflammatory molecules under cold conditions, in order to induce an airway inflammatory response. However, it has also previously been reported to be involved with the formation of tumours including colon, prostate, breast and skin, suggesting it was an ideal candidate for involvement in bladder cancer.

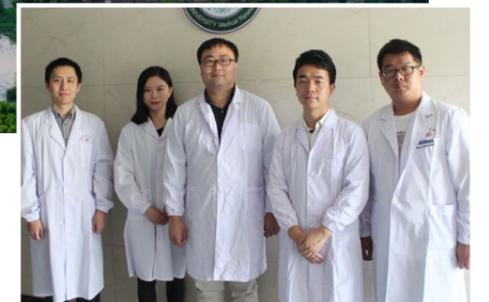
A MULTIFACETED APPROACH

Firstly, via a deep collaboration between the Department of Urology and the Department of Biological Repositories at ZNWU, the team obtained 20 bladder tissue samples from patients with bladder cancer. They also set up a system whereby they could grow bladder cells in the laboratory. Growing cells like this means that they can be altered to increase or decrease certain genes, or can be exposed to different environmental conditions, such as hypoxia. From these cells, the team were able to investigate the genes expressed by the cells under certain conditions, to assess cell proliferation and to investigate the effects of CIRBP on the sequence templates and protein stability of a molecule called HIF-1 α . The third part of the study involved a mouse model of bladder cancer.

They used transcriptome analysis, which is a way to identify genes and the mechanistic pathways that they



Zhongnan Hospital of Wuhan University was founded in 1956. It is a Grade-III Class-A (Chinese Hospital Ranking System) hospital featuring medical care, education, medical research, and public rescue service, located in the beautiful scenery of the shore of East Lake and adjacent to the Wuhan Central Cultural District (Chu River Han Street).



Professor Yu Xiao (centre) with some of the research team in the laboratory of precision medicine.

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are part of, to reveal which genes and pathways were associated with bladder cancer. This work demonstrated that CIRBP is overexpressed in both bladder tissue, and bladder cancer cells grown in the laboratory. Their transcriptome data also suggested that another molecule, MAPK, may play a role in bladder cancer. MAPK is normally associated with cell proliferation control. Professor Wang hypothesises that there may be a link between CIRBP and MAPK signalling pathways; this has been supported by several studies previously.

WHAT THE RESEARCH REVEALED

The role of CIRBP is to promote proliferation and migration of cells. Interestingly, there were no differences in CIRBP expression between the bladder cancer tissues and the paracancerous samples which were also collected. Paracancerous tissue is located near the cancerous cells or tissue but is not directly involved. However, when they investigated the expression levels of CIRBP at the tumour stage of the cancer, they found that CIRBP expression levels were positively correlated with the T stage in bladder cancer. The T stage

indicates that although a tumour has developed, it has not yet spread into the lymph nodes or metastasised (when chunks of tumour break off and move around the body to form new tumours). In the mouse model of bladder cancer, they found that reduction of CIRBP inhibits the progression of bladder cancer, as well as pulmonary metastasis.

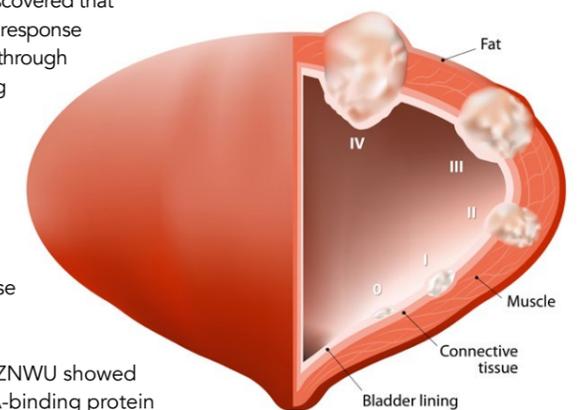
As Professor Wang's team investigated CIRBP further, they discovered that the gene increased in response to decreased oxygen through a mechanism involving a molecule which responds to hypoxia, called HIF-1 α . Other members of the HIF family are involved in the activation of over 1000 genes in response to hypoxia.

In fact, the group at ZNWU showed that CIRBP is an RNA-binding protein and could induce expression of HIF-1 α by binding to one end of the template used to produce HIF-1 α . By doing this, the template becomes more stable,

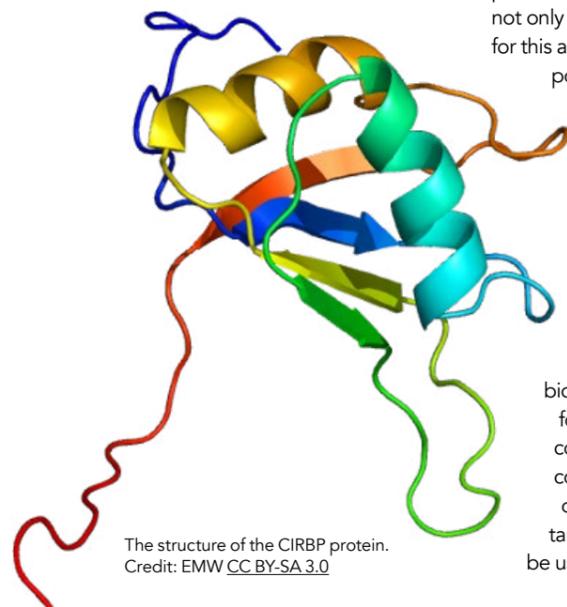
hence allowing more HIF-1 α to be expressed under hypoxic conditions. Previous studies have also shown that other proteins induce HIF-1 α by a similar method.

It is already known that HIF-1 α is involved in activation of several oncogenes; the HIF-1 α gene has been seen at

STAGES OF BLADDER CANCER



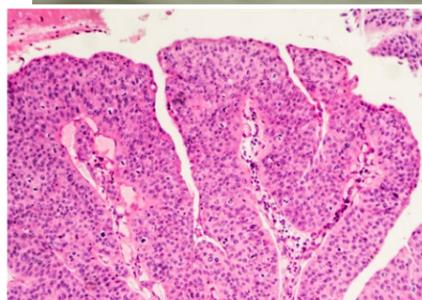
Tumours usually develop in the bladder lining but can spread to the muscle.



The structure of the CIRBP protein. Credit: EMW CC BY-SA 3.0



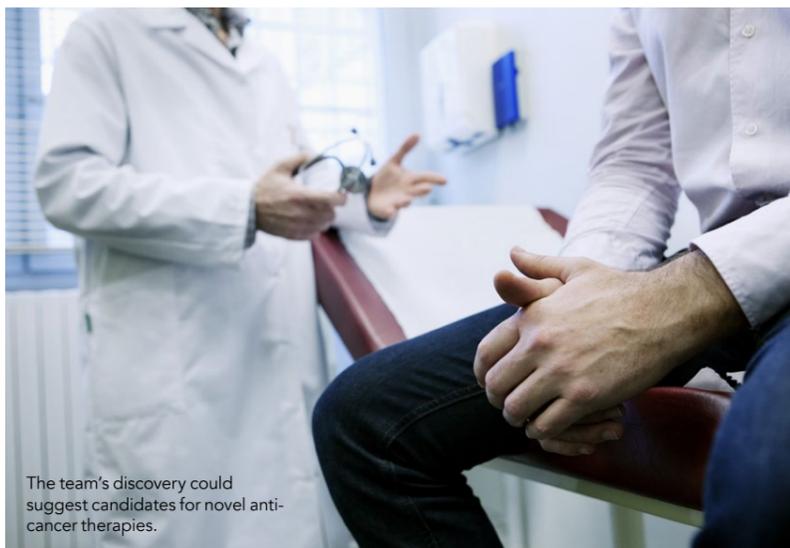
It is estimated that 1 in 3 cases of bladder cancer is caused by smoking.



A high grade papillary transitional (urothelial) carcinoma.

higher levels in many cancers compared to normal tissue. It is thought that the role of HIF-1 α in cancers is to increase expression of a factor involved in the growth of new blood vessels, which may supply the tumour.

One of the genes associated with HIF-1 α is called PTGIS. The team speculated that the reason that PTGIS expression is downregulated by HIF-1 α is that modifications are made to its DNA, in a process called DNA methylation.



The team's discovery could suggest candidates for novel anti-cancer therapies.

Indeed, the team found that overexpression of HIF-1 α may suppress the expression of PTGIS in bladder cancer cells. By stopping cells expressing CIRBP, they showed that this promoted expression of PTGIS, and also that cells without PTGIS could rescue the inhibition of migration and proliferation that was seen with CIRBP deficiency. PTGIS is usually associated with suppression of proliferation, so reducing the activity of PTGIS allows tumour cells to multiply

Overall, this study showed that CIRBP is overexpressed in 57% of bladder cancer tissues and cell lines.

uncontrollably. Their research clarified that methylation of the PTGIS gene promoter

may be important for the down regulation of PTGIS expression in a bladder cancer cell line. In theory, this means that if a way is found to prevent the inhibitory action of CIRBP, increased PTGIS expression may slow the rate of tumour cell proliferation.

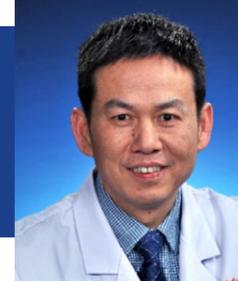
WHAT DOES THIS MEAN FOR BLADDER CANCER PATIENTS?

Overall, this study showed that CIRBP is overexpressed in 57% of bladder cancer tissues and cell lines and that

CIRBP promoted bladder cancer cell proliferation, both in patients and in a laboratory setting.

Taken together, these findings suggest a complex relationship between CIRBP and HIF-1 α . The team proposes that CIRBP may be a novel oncogene in human bladder cancer, inducing transcription of HIF-1 α , which could subsequently inhibit expression of PTGIS. This paves the way for further studies which may investigate the role of other oncogenes in human bladder cancer.

As well as increasing knowledge about the mechanisms behind the development of human bladder cancer, the work of the team at ZNWU has uncovered pathways and molecules which could theoretically be targeted by future anti-cancer therapies.



Behind the Research

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Bio

Prof Xinghuan Wang's lab aims to understand the pathogenesis of urologic neoplasms, including bladder cancer, clear cell renal cell carcinoma, and prostate cancer. Prof Wang's group has revealed several oncogenes in human bladder cancer. This research by Dr Mengxin Lu et al has investigated the role of an oncogene named CIRBP in bladder cancer.

Funding

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Collaborators

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Research Objectives

Professor Xinghuan Wang's team investigate bladder cancer and possible therapies.

References

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Personal Response

Now that you have identified that CIRBP plays an important role in bladder cancer, are you planning on investigating the role of the oncogene further in future studies?

Our future research goals are severalfold. First, as we mentioned, CIRBP is an RNA-binding protein and binds specifically to the 3'-untranslated regions (3'-UTR) of many target mRNAs, and affects their post-transcription expression. Based on this mechanism, we'd like to explore more CIRBP-targeted transcripts to study CIRBP's oncogenic function in bladder cancer. Secondly, our group has completed a transcriptome analysis using bladder cancer tissues and normal bladder epithelium, revealing several significantly affected related pathways and hundreds of genes. Our further studies also will continue to seek more oncogenes and tumour suppressor genes, and investigate the potential relationships between these key genes.