Understanding Why Obesity is a Risk Factor for Cancer

Dr Aliccia Bollig-Fischer

Scientia

UNDERSTANDING WHY OBESITY IS A RISK FACTOR FOR CANCER

Cancer can be caused by genetic mutations or epigenetic alterations, which are changes to the way DNA is processed, rather than to the DNA itself. These changes can be brought about by obesity, and more specifically, oxidative stress and consequent reactive oxygen species. However, the molecular mechanisms by which this occurs are not well understood. **Dr Aliccia Bollig-Fischer** from Wayne State University School of Medicine in Michigan is studying these processes and paving the way for the development of novel cancer therapeutics.

DNA Methylation and Cancer

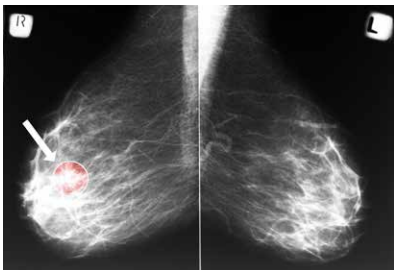
Many people will be familiar with the concept that cancer is caused by DNA mutations. When DNA is damaged and its structure is altered, the process of protein synthesis via transcription and translation is altered. This can either mean that the genes are expressed and the resultant proteins are faulty, or that the wrong amount of protein is produced. Through complex molecular mechanisms, the eventual result can be a tumour.

However, a lesser-known aspect of cancer formation is the field of epigenetics. This is the process by which the way a cell reads the DNA and a gene is expressed is altered, rather than the DNA itself. Whereas DNA mutation is permanent, an epigenetic modification can be reversed. This is a vital part of normal cell function because it helps to control healthy gene expression.

One important example of epigenetics is DNA methylation – the addition of a methyl group onto a base of the DNA. Often, this silences (or represses) the gene, meaning that it is not expressed at all or is expressed at a lower level and less protein is produced from it. This usually occurs on CpG islands, which are areas of DNA where there is a high concentration of cytosine nucleotides followed by guanine nucleotides.

CpG islands are usually found just before the beginning of a gene, at the transcription start site. Therefore, when a CpG island is methylated, the adjacent gene is silenced. Although this is a normal part of protein production, when it goes wrong, it can have serious consequences. If a tumour suppressor gene is silenced due to methylation, or a CpG island is altered and consequently, oncogenes are activated, this can lead to cancer.

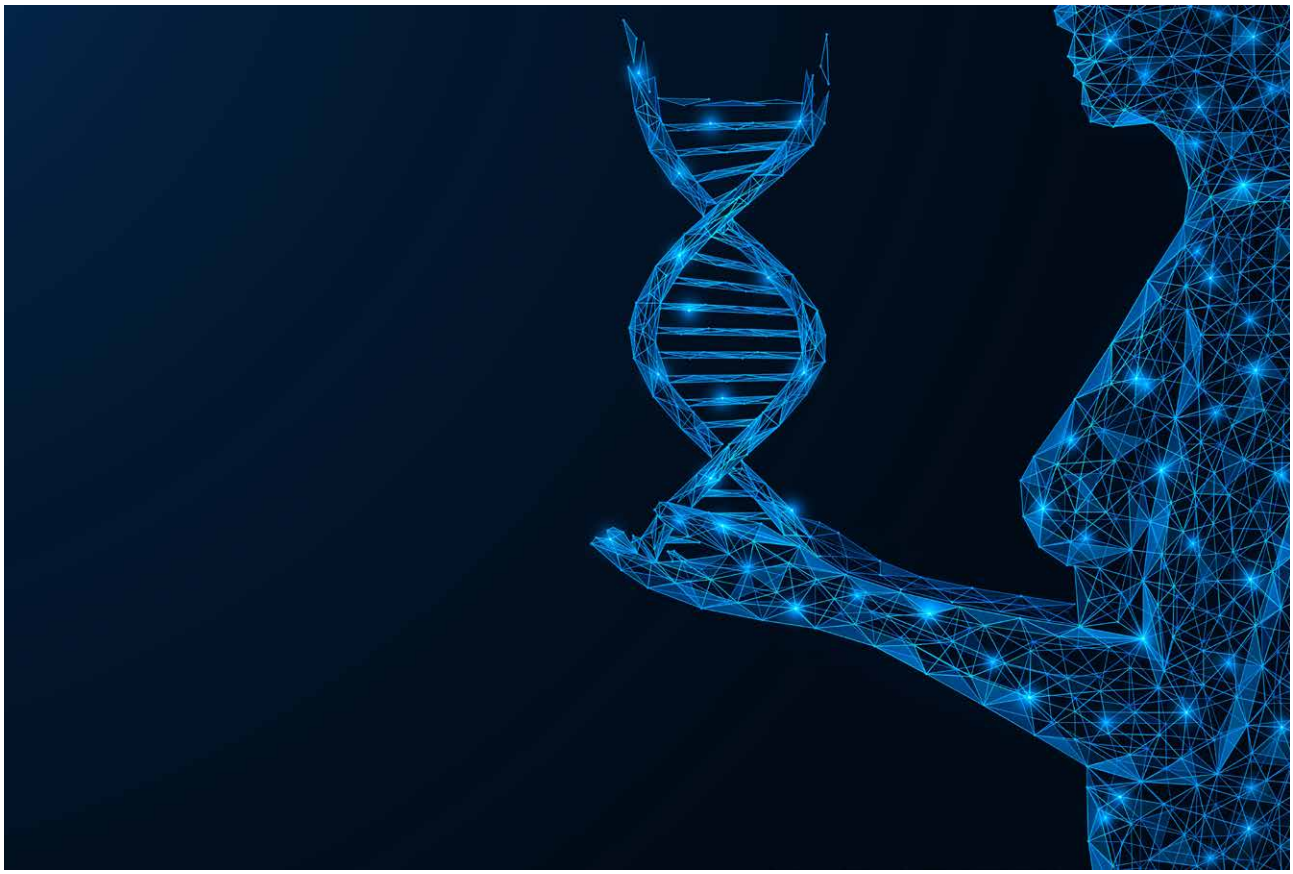
Despite extensive volumes of existing research into cancer epigenetics, there is still much more work to be done. Dr Aliccia Bollig-Fischer from Wayne State University School of Medicine in Detroit, Michigan, carries out dedicated research into the molecular and genetic reasons for how cancer develops. In addition to clarifying these underlying mechanisms, her work could help to give insight into novel therapies for cancer.



Triple Negative Breast Cancer

One specific cancer that Dr Bollig-Fischer is interested in is called triple-negative breast cancer, a type of breast cancer that presents in around 15–20% of new patients. Characterised by lack of expression of the genes for HER2, oestrogen or progesterone receptors, triple-negative breast cancer cannot be treated by standard hormone therapies or anti-HER2 therapies. Specific subtypes of this cancer can, unfortunately, be extremely difficult to treat.

For many types of cancer (including breast cancer), a methylation event known as 5mC is well-researched. This epigenetic modification occurs when a methyl group is added to a cytosine base on its fifth carbon atom.



The slight alteration of the addition of a hydroxy group to the methyl group creates a different molecule called 5hmC. Once thought to be an unimportant oxidation event, new research and improved techniques have shown it to be more interesting. Unlike most methylation occurrences like 5mC, 5hmC is associated with increased gene expression. Therefore, Dr Bollig-Fischer made this the focus of one of her studies.

She and her team scanned the available literature on 5hmC and hypothesised that it regulates the expression of genes that promote cancer stem cell-like cells in triple-negative breast cancer. Cancer stem-like cells are self-renewing cells that drive tumour progression and also lead to metastasis, the spreading of cancer to additional areas of the body. They believed this to be mediated by redox (reduction-oxidation) reactions involving reactive oxygen species (ROS).

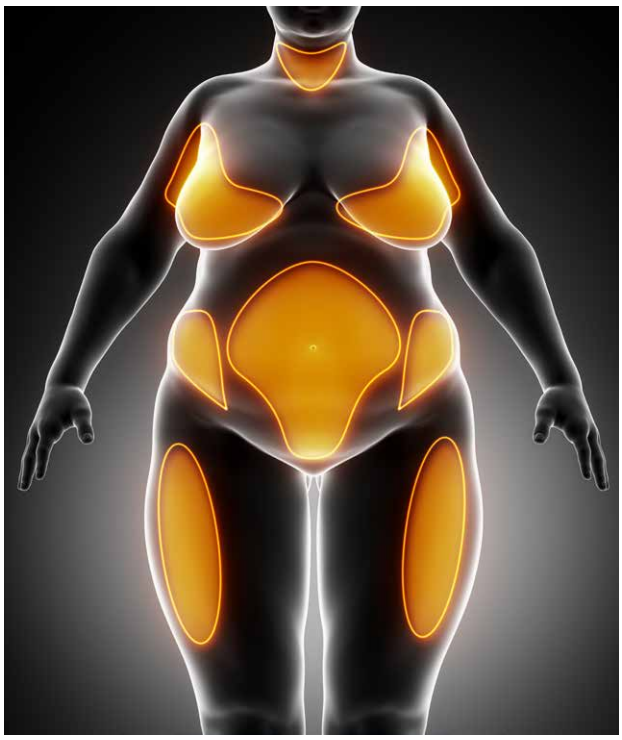
They set out to find the genes that are the target for these processes, looking for those that are regulated by ROS and therefore, sensitive to antioxidants and when 5hmC occurs, associated with the gene expression changes in triple-negative breast cancer. By developing a novel approach for their experiments, Dr Bollig-Fischer and her colleagues discovered a set of genes whereby the 5hmC level was coordinated with the relevant gene expression changes. Critically, these genes could potentially be regulated via a selective or targetted antioxidant treatment.

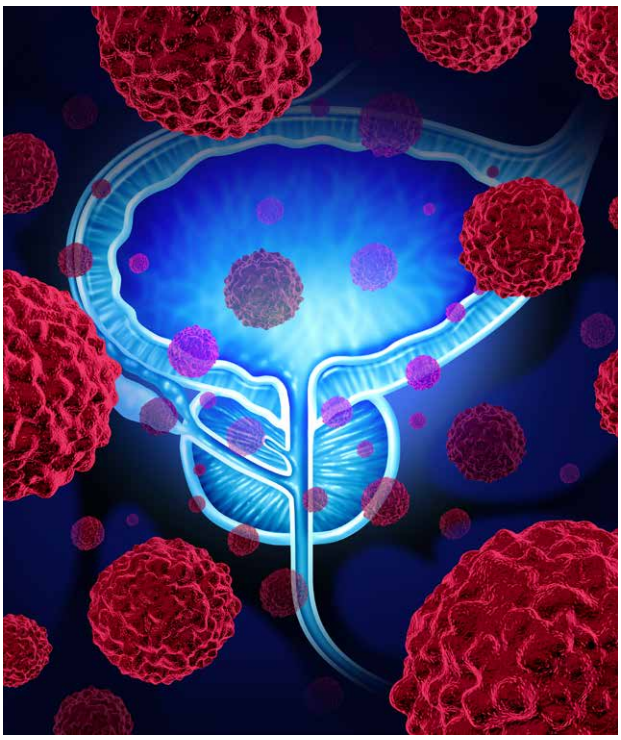
The Role of MBD2-v2 in Breast Cancer

A major risk factor for cancer is obesity and once cancer has formed, it also often leads to poor outcomes. The theory behind this is that the adipose (fat) tissue that builds up results in an immune response in the form of local and system-wide chronic inflammation. One consequence of this is an increase in oxidative stress and ROS which can incite breast cancer, including triple-negative breast cancer. However, the exact underlying mechanisms of this progression are unclear, and Dr Bollig-Fischer wanted to elucidate the issue.

Previous research with her team had found an important epigenetic reader, which is a protein that is vital for the maintenance and replication of cancer stem-like cells in triple-negative breast cancer. It has the rather long name of methyl-CpG-binding domain protein 2, variant 2 (or MBD2_v2 for short). Because of its role in cancer stem-like cell survival, Dr Bollig-Fischer believed it to be a key component in triple-negative breast cancer incidence and recurrence.

She hypothesised that obesity fuels an increase in MBD2_v2 expression which promotes cells to turn into cancer stem-like cells. Tests using obese mice and lean control mice with triple-negative breast cancer tumours confirmed her theory. The tumours of the obese mice had much higher levels of MBD2_v2 in addition to another protein called serine- and arginine-rich splicing factor 2 (SRSF2). Tumours also appeared more frequently in obese mice.





When the genes for SRSF2 were knocked down (removed) from the mice, they could no longer make the protein. The side-effect was that MBD2_v2 expression also decreased and in turn, cancer stem-like cells also diminished within the tumours. Dr Bollig-Fischer says this provides evidence for a new mechanism of cancer progression that is initiated by obesity. A majority of triple-negative breast cancer patients are overweight or obese, which emphasises the need to understand what lifestyle changes will help these patients in addition to what pharmacological interventions could be useful.

Further Proteins Involved in Breast Cancer

Delving further into triple-negative breast cancer, Dr Bollig-Fischer conducted another study linking 5hmC with obesity. The epigenetic event of 5hmC is brought about by an enzyme called tet methylcytosine dioxygenase (TET1). Although it is an important enzyme to maintain embryonic stem cells, it is not well understood how and why it can support cancer stem-like cells. This has led to extensive research in this specific area from Dr Bollig-Fischer and her team.

They have found that hydrogen peroxide, an ROS, regulates the SRSF2 needed for MBD2_v2 activity. This supports the idea that obesity leads to cancer due to inflammation, an increase in ROS and then higher SRSF2 expression. Additionally, another protein of interest called TAR DNA-binding protein was put into the mix after investigations. TET1 upregulates TAR-binding protein via 5hmC and therefore, SRSF2 is upregulated to promote cancer stem-like cells.

Furthermore, in a brand new discovery, they reported that dysregulation within triple-negative breast cancer cells allows hydrogen peroxide to form signals that increase the levels of TET1. The team found this is more severe in obese patients, which further clarifies why obesity is a risk factor for this type of cancer. As with the previous research, this new understanding could be utilised to advance prevention and treatment strategies for triple-negative breast cancer.

Different Risks of Prostate Cancer

In further studies, Dr Bollig-Fischer shifted her focus to prostate cancer. African American men are much more likely to be diagnosed with the disease compared to European American men, and they are also at higher risk of dying from it. She and her team used tissue samples from prostate cancer patients for their research and they made some interesting discoveries.

In the African American patients, the tissue adjacent to their tumours over-expressed a pro-inflammatory signalling molecule called interleukin-6 (IL-6) in comparison to the European American patients. Even though IL-6 is an immune molecule with wide-reaching roles, the team found that it inhibited the expression of the tumour suppressor, p53. The additional IL-6 also promoted cancer cells to self-renew and was associated with prostate cancer cells becoming stem-like.

As with the breast cancers she studied, these cancer stem-like cells were encouraged by MBD2_v2 whose expression had been elevated by the excess IL-6. This continually expanding knowledge of the mechanisms behind cancer incidence and recurrence will help Dr Bollig-Fischer and many other scientists to develop novel, targeted treatments. Hopefully, this will result in more positive outcomes for patients, regardless of gender or ethnicity.

Meet the researcher

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Dr Aliccia Bollig-Fischer received BScs in Biology and Chemistry from St. Cloud State University in Minnesota. She went on to achieve her PhD in Human Physiology at Michigan State University and then completed postgraduate training at the Karmanos Cancer Institute and Wayne State University in Michigan. Currently, Dr Bollig-Fischer is an Assistant Professor in the Department of Oncology at Wayne State University. She has received multiple honours and awards for her research, which is centred around understanding lifestyle factors and the molecular mechanisms that lead to cancer.

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FURTHER READING

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