Targeting essential protein could lead to new breast cancer treatments

31 March 2021

Credit: CC0 Public Domain

A protein frequently found in high levels in breast cancer cells helps tumors to survive and grow, and could be targeted with a new type of drug that is already being tested for other cancers, new research reveals.

The new study confirms that a protein called MCL-1 helps breast cancer cells survive, by hindering cells' natural ability to die through a process called apoptosis, and proves that breast cancer tumors in fact rely on this protein to help them grow more aggressively, by blocking this natural cellular self-destruct function. The research was funded by Breast Cancer Now, in partnership with the Scottish Government's Chief Scientist Office, and took place at the University of Glasgow.

Apoptosis is a natural process by which unwanted, harmful or damaged cells are removed from our bodies and plays an important part in our growth and development. Apoptosis can also play a key role in preventing cancer; however, cancer cells will often evolve to avoid this process.

Current breast cancer treatments target a range of proteins, but this study could be an important step towards targeting MCL-1 as a way to treat people with breast cancer and developing urgently needed new treatments for the disease. The study has also discovered that breast cancer stem cells, which are thought to be responsible for the disease spreading and becoming resistant to treatments, are especially dependent on MCL-1 for growth and survival.

Excitingly, the study suggests a new type of drug called BH3 mimetics, which target the MCL-1 protein, could be used to 'kick-start' apoptosis in breast cancer cells to help treat people with breast cancer, and slow the growth of tumors.

BH3 mimetics are already undergoing clinical trials for some blood cancers. While further testing is needed, this new study presents a strong case to test this emerging new therapy in breast cancer too.

This new research, published in *Cell Death & Differentiation*, was led by Professor Stephen Tait and Dr. Kirsteen Campbell at the Institute of Cancer Sciences at the University of Glasgow, in collaboration with Professor Karen Blyth from the Beatson Institute for Cancer Research, Glasgow.

In experiments with mice, the team showed that MCL-1 is critical for the growth and survival of breast cancer. When MCL-1 was removed from existing breast tumors in mice, it led to tumors shrinking. The results suggest that targeting MCL-1 with drugs could work as a treatment strategy for breast cancer.

The team then tested whether BH3 mimetic drugs, targeting the MCL-1 protein, could stop the growth of breast cancer in mice. The results showed that the growth of tumors was significantly slowed down and suggests that with further testing, BH3 mimetic drugs have the potential to treat people affected by breast cancer.

The study also found that in the absence of the BAX and BAK proteins—which are essential for

apoptosis—targeting MCL-1 did not slow the growth of tumors. This strongly suggests that MCL-1, which has more than function, is helping breast cancer survive specifically by stopping apoptosis.

Professor Stephen Tait at the Institute of Cancer Sciences at the University of Glasgow, said, "Our study further highlights the importance of MCL-1 protein in breast cancer. Our demonstration that MCL-1 acts in breast cancer by keeping cells alive (as opposed to other MCL-1 functions) is important, because drugs that target MCL-1 survival function are now in clinical development"

"The next steps will be to determine the effectiveness of MCL-1 targeting drugs, that are in clinical development, to treat breast cancer in combination with existing therapies"

Dr. Simon Vincent, director of research, support and influencing at Breast Cancer Now, said, "It's hugely exciting that this study could confirm the role that the MCL-1 protein plays in allowing breast cancer cells to survive and grow. With this understanding we can now explore targeting the protein with drugs that are already being tested for treating other types of cancer.

"With around 55,000 women being diagnosed with breast cancer every year in the UK, we urgently need to find new ways to treat people and prevent deaths from this devastating disease. As such, while further research is needed, we hope this study leads to new and effective treatments being available for people affected by breast cancer.

"We're hugely proud to have funded this exciting discovery, especially at a time when we are all too aware of the profound effects the COVID-19 pandemic has already had on our world-class research. We are now less able to fund new research that could transform the lives of people affected by breast cancer and this is why now, more than ever, we need your support so we can continue to bring hope for the future through our research."

More information: Kirsteen J. Campbell et al. Breast cancer dependence on MCL-1 is due to its canonical anti-apoptotic function, *Cell Death & Differentiation* (2021). DOI: 10.1038/s41418-021-00773-4

Provided by University of Glasgow