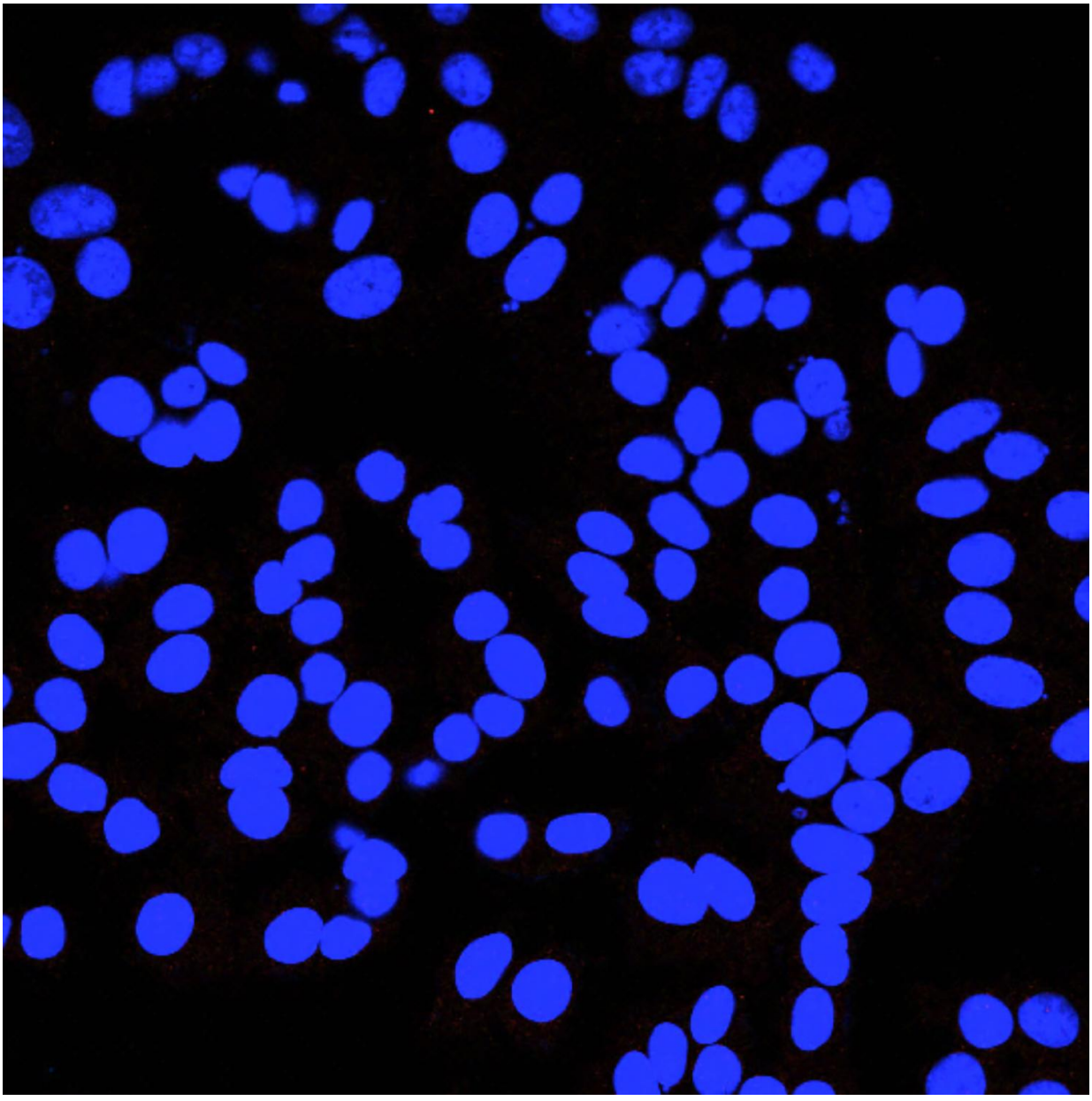
MedicalXpress

Scientists discover the 'switch' that makes breast cancer cells aggressive

November 1 2016



A study by scientists from the Cancer Science Institute of Singapore at the National University of Singapore (NUS) and NUS Yong Loo Lin School of Medicine showed that a less aggressive tumor when artificially made to increase its Manganese Superoxide Dismutase (MnSOD) levels, turns into a more aggressive tumor. The nucleus of the cells in both images are in blue while the parts in red that became more abundant (Image 2) shows the presence of a protein called Vimentin. Vimentin is often used as a marker of mesenchymal (aggressive) cells or cells undergoing an epithelial-to-mesenchymal transition (EMT), a term used to describe the process whereby a tumour converts to a different form capable of moving to distal organs in the body. Credit: National University of Singapore

A team of scientists from the National University of Singapore (NUS) has established novel insights into the relationship between breast cancer tumour intracellular redox environment and the cancer cells' ability to become invasive.

The study by Dr Alan Prem Kumar from the Cancer Science Institute of Singapore (CSI Singapore) at NUS and NUS Yong Loo Lin School of Medicine, together with Professor Shazib Pervaiz and Associate Professor Marie-Veronique Clement from NUS Yong Loo Lin School of Medicine, found that high levels of Manganese Superoxide Dismutase (MnSOD), a key enzyme involved in regulating the cellular redox milieu, has a role to play in causing breast cancer cells to turn aggressive, especially in triple negative breast cancer subtype tumours. These aggressive cells are able to invade other sites in the body, resulting in secondary tumours.

"Our group's work over the years has highlighted the critical role of cancer cells' oxidative metabolism in drug resistance and cell survival. This study underscores the importance that MnSOD plays in the biology of breast cancer," said Assoc Prof Clement.

The new findings build on the group's previous discovery of the presence of a significantly higher MnSOD levels in triple negative breast cancer patients.

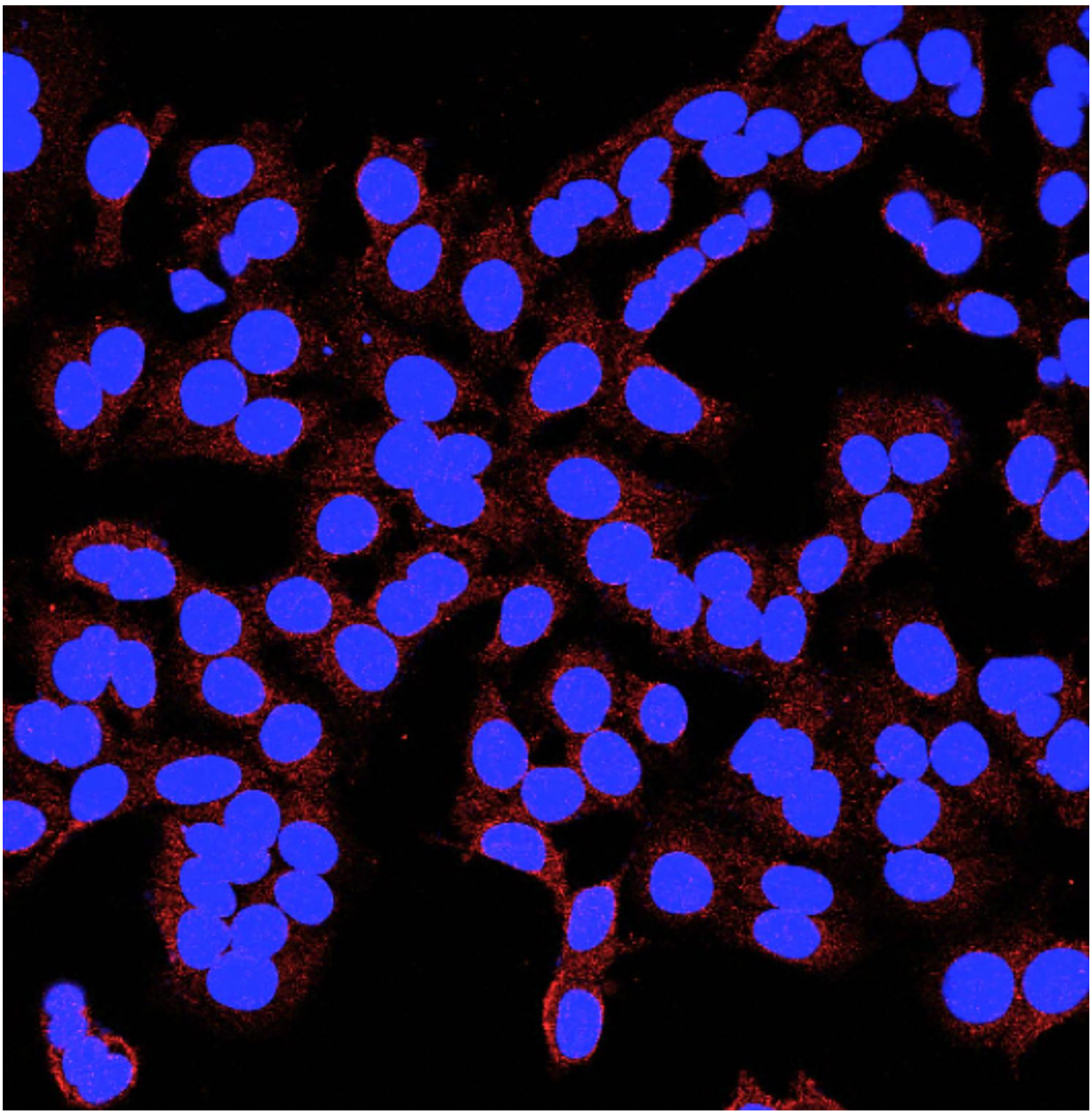
"MnSOD expression is decreased during the initial stages of cancer development. However, as the cancer advances, MnSOD expression increases and such high MnSOD levels are typically observed in triple negative breast cancer patients. In fact, we have shown that less aggressive tumours, when artificially made to increase MnSOD protein levels, adopt an aggressive behaviour. Our study shows that the amount of MnSOD levels in the tumour cell determines the predominant reactive oxygen species that will tell the tumour cells whether to stay put or to transform into an invasive form that is capable of moving to distal parts of the body," explained Dr Loo Ser Yue, a former graduate student from NUS Yong Loo Lin School of Medicine and the first author of the study.

Triple negative breast cancer is a subtype of estrogen-independent breast cancer. Among female patients diagnosed with various subtypes of breast cancer in Singapore and worldwide, about 13 per cent of them are triple negative. While considerable progress has been made in the diagnosis and treatment of estrogen-dependent breast cancer, triple negative breast cancer is associated with poor diagnosis due to a lack of targeted therapeutic options. By studying the underlying cause of this subtype of breast cancer, the NUS research team hopes to design and develop effective therapeutic strategies to combat this disease.

"Our study provides a novel mechanism for exploiting cancer's Achilles heel with potential implications for the design of target-specific therapies against aggressive breast cancer," said Professor Pervaiz.

As part of their earlier study, the NUS team had shown a novel strategy of targeting this enhanced MnSOD expression and therefore its activity using other FDA-approved drugs to make the aggressive tumours more

sensitive to conventional anti-cancer drugs. They also showed that this strategy would re-sensitise patients who develop resistance to conventional breast cancer drugs such as Docetaxel or Doxorubicin.



A study by scientists from the Cancer Science Institute of Singapore at the National University of Singapore (NUS) and NUS Yong Loo Lin School of Medicine showed that a less aggressive tumor when artificially made to increase

its Manganese Superoxide Dismutase (MnSOD) levels, turns into a more aggressive tumor. The nucleus of the cells in both images are in blue while the parts in red that became more abundant (Image 2) shows the presence of a protein called Vimentin. Vimentin is often used as a marker of mesenchymal (aggressive) cells or cells undergoing an epithelial-to-mesenchymal transition (EMT), a term used to describe the process whereby a tumour converts to a different form capable of moving to distal organs in the body. Credit: National University of Singapore

The novel findings were published in the leading journal *Antioxidants & Redox Signaling* in August 2016. Their earlier findings were also published in the same journal in May 2014.

The "switch" to aggression

Compared to normal cells, cancer cells experience higher oxidative stress, which is the imbalance between the production of free radicals and the body's antioxidant defences. MnSOD, which is a major antioxidant protein, is especially essential for cancer cells to cope with their high oxidative stress. However, the NUS research team found that too much of the MnSOD protein - as a result of the advancement of the cancer - activates a molecular program to convert a localised tumour to become aggressive and spread to neighbouring organs.

The team's findings also suggest MnSOD as a potential target for treatment of aggressive cancers, beyond breast cancer.

Good news for breast cancer treatment

Breast cancer is the most frequently diagnosed cancer in Singaporean women, making up about 30 per cent of all female cancers. The increase

in breast cancer incidence rate in Singaporean women is also amongst the highest globally.

Different subtypes of breast cancer are inherently genetically diverse and different treatment strategies need to be devised against each subtype. Due to the lack of well-defined molecular targets in triple negative breast cancer patients, current treatment options rely heavily on chemotherapy, which is highly non-specific and has adverse side effects. "By suppressing MnSOD expression or its activity in triple negative breast cancer patients, we are able to make the tumour cells less aggressive and more sensitive to chemotherapy," said Dr Kumar.

Moving forward, the NUS team is looking into selective killing of cancer cells by designing small molecules targeting MnSOD, to diminish the invasive properties of such tumours.

More information: Ser Yue Loo et al, Manganese Superoxide Dismutase Expression Regulates the Switch Between an Epithelial and a Mesenchymal-Like Phenotype in Breast Carcinoma, *Antioxidants & Redox Signaling* (2016). DOI: 10.1089/ars.2015.6524

Provided by National University of Singapore