Researchers pioneer novel strategy to prevent progression of inflammation-associated cancers

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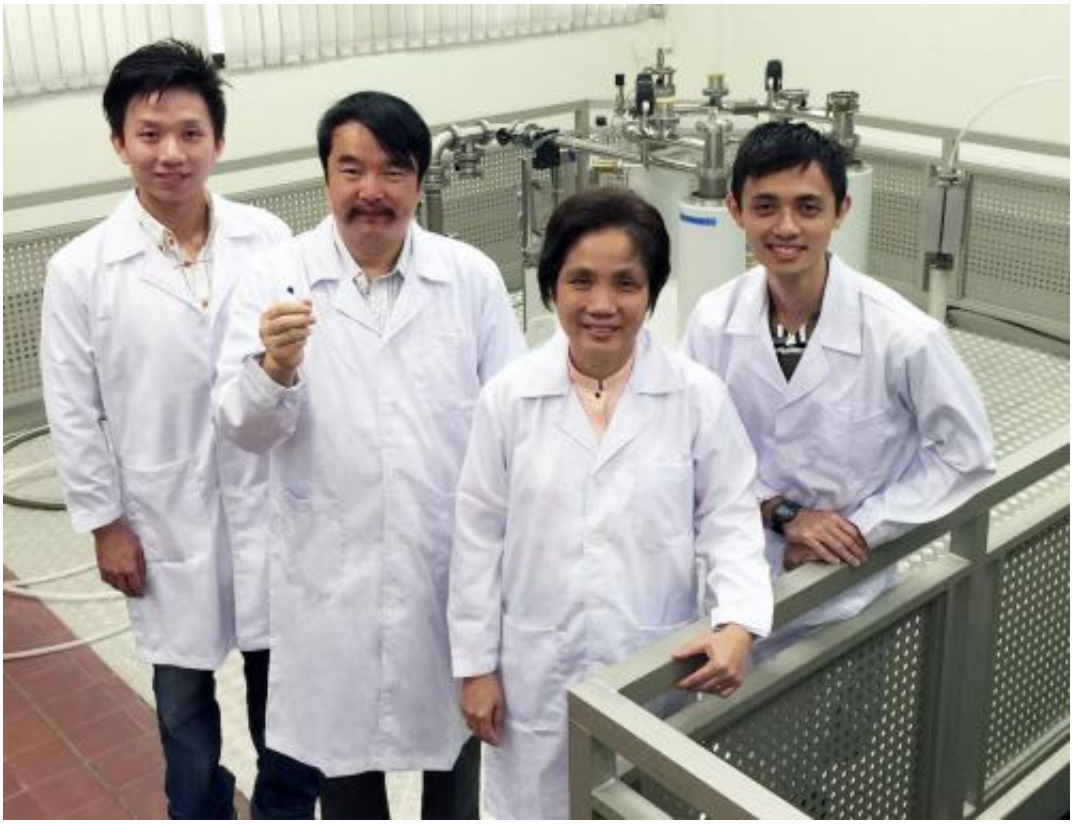

A research team led by Associate Professor Caroline Lee (third from left), in collaboration with Associate Professor Song Jianxing (second from left), has developed a novel strategy in the fight against cancer.

A team of researchers led by Associate Professor Caroline Lee from the

Yong Loo Lin School of Medicine at the National University of Singapore (NUS), in collaboration with Associate Professor Song Jianxing of the Department of Biological Sciences at the NUS Faculty of Science, has developed a novel strategy in the fight against cancer. They discovered that the interaction between two proteins, namely FAT10 and MAD2, leads to inflammation-associated cancers, such as liver (hepatocellular carcinoma) and colorectal cancers. A disruption of this unique interaction can prevent cancer.

This novel breakthrough paves the way for the design of drugs that targets the specific interaction without affecting other important cellular functions of the molecule that causes cancer, thereby minimising undesirable side effects.

The findings were published in the prestigious US journal, *Proceedings of the National Academy of Sciences* (*PNAS*), on 24 November 2014.

Interaction between FAT10 and MAD2

FAT10 is a protein that is expressed mainly in tissues of the immune system, including the spleen and thymus. In their previous studies, Assoc Prof Lee, who also holds joint appointments at Duke-NUS Graduate Medical School and the National Cancer Centre Singapore, and her team had found that overexpression of FAT10 promotes tumour formation, growth and progression. However, the mechanism underlying FAT10's promalignant characteristics remains unclear, and the team sought to address this.

In this latest study, the NUS research team discovered that FAT10 interacts with a protein called MAD2, which serves as a gatekeeper of cell-division to ensure that each cell receives the same number of chromosomes. When FAT10 interacts with MAD2, it pulls MAD2 away from its gate-keeping function, causing many cells to carry abnormal

number of chromosomes, which leads to cancer. The researchers determined the three-dimensional structures of FAT10 using the state-of-the-art nuclear magnetic resonance (NMR) spectroscopy, and further examined the relationship between the two proteins.

Through the use of genetic mutation manipulation, the researchers discovered that when the interaction between FAT10 and MAD2 is disrupted, the number of chromosomes in the affected cells is restored and tumour progression is curtailed, without affecting FAT10's interaction with its other known key interaction partners.

The results present a new paradigm for drug targeting and pave the way for the development of a novel small-molecule anti-cancer inhibitor targeting the specific interaction between FAT10 and MAD2.

Explaining the significance of the team's work, Assoc Prof Lee said, "Many current strategies target over-expressed genes to inhibit their expression. As these cellular genes perform other functions besides causing cancer, inhibiting their expression in a blanket fashion may result in undesirable side effects as the physiological function of these genes may be affected as well. Our strategy works differently as it targets a specific pathological function of the 'culprit' molecule without affecting its other physiological functions. This is especially important for a molecule like FAT10 which is not only over-expressed during cancer formation but is also over-expressed during immune response."

Designing cancer drugs with fewer side effects

Assoc Prof Lee and her team will further explore the relationship between FAT10 and MAD2. They aim to identify and design drugs that can specifically disrupt their interaction to prevent formation of inflammation-associated cancer.

More information: "Disruption of FAT10-MAD2 binding inhibits tumor progression." *Proceedings of the National Academy of Sciences* (*PNAS*), 24 November 2014. DOI: 10.1073/pnas.1403383111