Genome Institute of Singapore
A*STAR

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SINGAPORE SCIENTISTS DISCOVER A NUTRITION PATHWAY TO STAMP OUT THE START OF CANCER

Singapore – In a landmark study, scientists at the Agency for Science, Technology and Research's (A*STAR) Genome Institute of Singapore (GIS), Bioprocessing Technology Institute (BTI) and oncologists at the National Cancer Centre Singapore (NCCS), have discovered that cancer stem cells, the founder cells of a tumour, have unique nutrient requirements. Unlike the rest of the tumour cells, cancer stem cells are addicted to a type of dietary amino acid – methionine – which is linked to their ability to form tumours.

Methionine is an essential amino acid absorbed from diet for normal cell growth. However, a metabolite produced from it, S-adenosylmethionine (SAM), is involved in the regulation of critical gene functions in cancer stem cells. Importantly, this methionine metabolism pathway is controlled by a critical metabolic enzyme known as MAT2A (methionine adenoyltransferase 2A) that converts methionine to SAM.

This surprising discovery has implications on how one can develop better drugs against cancer. By specifically drugging this metabolic pathway, laboratory models of tumours are more effectively targeted compared to conventional treatment regimes. These findings were published online in the medical journal, *Nature Medicine*, on 06 May 2019. The research is supported by A*STAR, and the National Medical Research Council's Large Collaborative Grant for fighting lung cancer.

Cancer cases have been rising over the years. One in every four to five people in Singapore may develop cancer in their lifetime, and the number of people living with cancer will continue to increase.[1] Tumours start from cancer stem cells. They are able to resist many forms of therapies, leading to the problem of resistance and relapse in patients. This has given rise to an urgent need for more precise methods to eliminate these recalcitrant cells. Through the integration of advanced genomics and metabolomics technologies housed at A*STAR, scientists are able to accurately pinpoint the unique nutritional requirements of cancer stem cells. This provides new insights and methods to avoid the problem of cancer resistance caused by cancer stem cells.

Dr Tam Wai Leong, the senior author of the study, Group Leader at the GIS and faculty member at Cancer Science Institute of Singapore, explained, "Cancer cells within a tumour are quite different from one another. Like human beings, they have different dietary preferences from each other. Through this study, we discovered that the cancer stem cells are addicted to a particular nutrient – methionine. By blocking the ability of the cancer stem cells to use this

[1] https://www.nccs.com.sg/patient-care/cancer-types/cancer-statistics

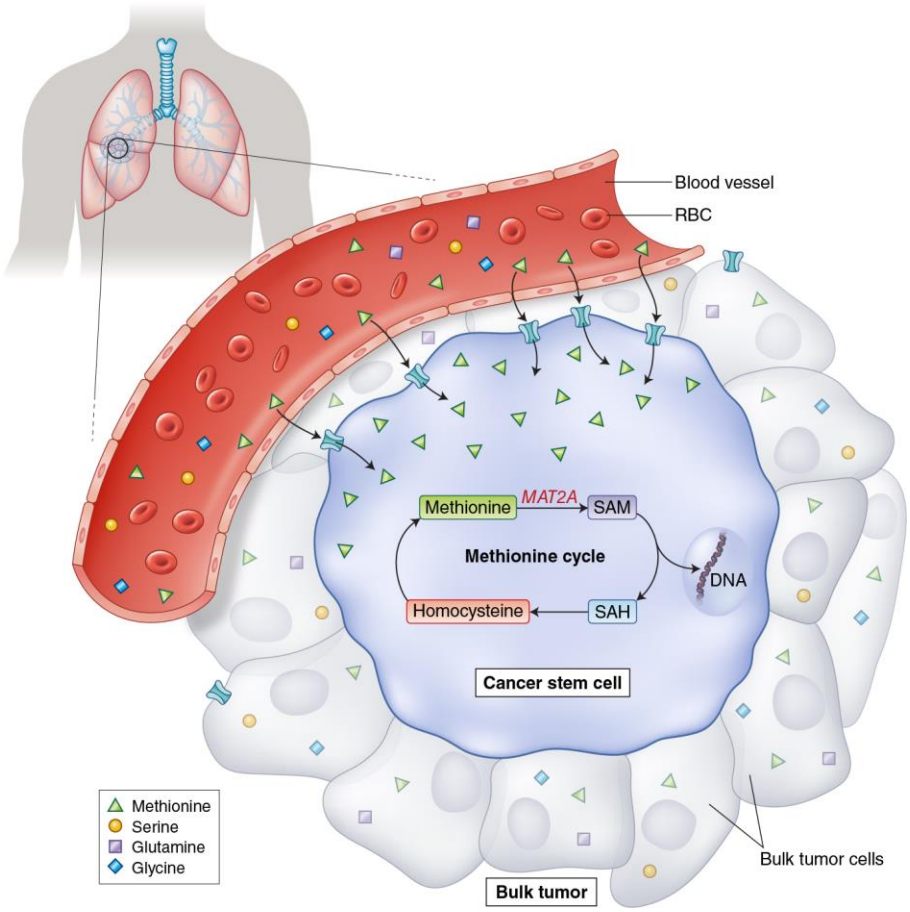
amino acid with potential anti-cancer therapeutics, we are able to effectively halt the growth of a tumour."

"MAT2A is an interesting enzyme that controls the metabolism of cancer cells. From our findings, this enzyme represents an important new drug target, as its inhibition led to the ablation of cancer stem cells. This paves the way for the development of next-generation drugs that target this dependence on methionine," said Dr Wang Zhenxun, the first author of this study.

Professor William Hwang, Medical Director at NCCS, said, "This important research provides key clinical insights on how oncologists can better overcome the problem of cancer resistance. The discovery of MAT2A as a new drug target may add to the arsenal of next generation anti-cancer drugs in our fight against cancer."

Professor Ng Huck Hui, Executive Director at GIS, said, "This is the first study demonstrating that cancer stem cells have unique dependencies on specific pathways. It also illuminates a way where we can exploit these dependencies to eliminate these cells from a tumour, thereby reducing the chance of cancer relapse and progression."

IMAGES



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Caption: Cancer stem cells are addicted to methionine which is derived from the diet and transported to a tumour where they can be absorbed. High methionine cycle activity drives the production of S-adenosylmethionine (SAM) that is essential for tumour formation. Methionine adenosyltransferase 2A (MAT2A) is a key enzyme that regulated the methionine cycle, and an important therapeutic candidate for cancer.

Notes to Editor:

The research findings described in this media release can be found in the scientific journal *Nature Medicine*, under the title, "Methionine is a metabolic dependency of tumor-initiating cells" by Zhenxun Wang[1,*], Lian Yee Yip[2,*], Jia Hui Jane Lee[1,3], Zhengwei Wu[4,1], Hui Yi Chew[1], Pooi Kiat William Chong[2] , Chin Chye Teo[2], Heather Yin-Kuan Ang[1], Kai Lay Esther Peh[2] , Ju Yuan[1], Siming Ma[1], Li Shi Kimberly Choo[1], Nurhidayah Basri[2], Xia Jiang[1], Qiang Yu[1], Axel M. Hillmer[1], Wan Teck Lim[5,6,7], Tony Kiat Hon Lim[8], Angela Takano[8], Eng Huat Tan[5], Daniel Shao Weng Tan[5,1], Ying Swan Ho[2] , Bing Lim[9,#] and Wai Leong Tam[1,4,10,3,#].

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About A*STAR's Genome Institute of Singapore (GIS)

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS will pursue the integration of technology, genetics and biology towards academic, economic and societal impact.

The key research areas at the GIS include Human Genetics, Infectious Diseases, Cancer Therapeutics and Stratified Oncology, Stem Cell and Regenerative Biology, Cancer Stem Cell Biology, Computational and Systems Biology, and Translational Research.

The genomics infrastructure at the GIS is utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact. For more information about GIS, please visit www.a-star.edu.sg/gis.

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As a Science and Technology Organisation, A*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by contributing to societal benefits such as improving outcomes in healthcare, urban living, and sustainability.

We play a key role in nurturing and developing a diversity of talent and leaders in our Agency and research entities, the wider research community and industry. A*STAR's R&D activities span biomedical sciences and physical sciences and engineering, with research entities primarily located in Biopolis and Fusionopolis. For ongoing news, visit www.a-star.edu.sg.