

MEDIA RELEASE

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SINGAPORE TEAM'S DISCOVERY OF NEW GENOMIC ABERRATIONS OF GASTRIC CANCER COULD PAVE THE WAY FOR PRECISION MEDICINE

Findings open up possibilities for more targeted therapeutic cures for the disease

Singapore — Singapore scientists from A*STAR's Genome Institute of Singapore (GIS) and Institute of Molecular and Cell Biology (IMCB), together with colleagues from the National University Health System (NUHS) and Tan Tock Seng Hospital, have discovered a relationship between Asian gastric cancers and the fusion of two genes.

The researchers discovered that the fusion of these two genes, known as *CLDN18* and *ARHGAP26*, gives rise to the destruction of the stomach surface barrier, resulting in gastric acids affecting the stomach tissues. Moreover, *CLDN18-ARHGAP26* also hampers wound-healing.

Findings from the study were published in the scientific journal *Cell Reports*.

Structural changes of chromosomes (genome rearrangements), can result in gene fusions with properties that can cause cancer. The three-dimensional organisation of the genome, known as the chromatin structure, plays a role for the generation of rearrangements. Using a technique known as DNA paired-end-tag (DNA-PET) whole genome sequencing, GIS scientists analysed 15 gastric cancers (GCs) from Southeast Asians, and observed that rearrangements were enriched in regions of active genes. They subsequently screened 100 GCs for certain fusion genes that were discovered in the 15 GCs.

Through the sequencing, the scientists identified seven hotspots across the genome which had many rearrangements as well as 136 gene fusions. In three out of the 100 GC cases, they found recurrent fusions between *CLDN18*, a tight junction gene, and *ARHGAP26*, a gene encoding an RHOA inhibitor. The functions of both genes are important for a tight inner surface (epithelium) of the stomach. Epithelial cell lines expressing the fused genes *CLDN18-ARHGAP26* displayed a dramatic loss of epithelial phenotype and long protrusions indicative of epithelial-mesenchymal transition (EMT)¹. Fusion positive cell lines showed impaired barrier

¹ EMT is a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells (multipotent stromal cells that

properties, reduced cell-cell and cell-extracellular matrix-adhesion, retarded wound healing and inhibition of RHOA. Gain of invasion, a property that contributes to metastases, was seen in cancer cell lines expressing the fusion.

Dr Axel Hillmer, Group Leader of GIS and senior author of the publication said, "We identified five different fusion genes recurrently in several tumours, one of these fusion genes is *CLDN18-ARHGAP26*. Our simulations indicate that the recurrence is unlikely to be by chance, suggesting that the other four fusion genes might also play a role in the development of gastric cancer."

Overall, *CLDN18-ARHGAP26* mediates epithelial disintegration possibly leading to leakage of gastric acids, and the fusion might contribute to invasiveness of tumours once a cell is transformed.

Dr Walter Hunziker, Deputy Director of IMCB and co-senior author of the publication, added, "CLDN18 is a critical component of the gastric epithelial barrier. Fusion of ARHGAP26 to CLDN18 not only interferes with the tethering of CLDN18 to the actin cytoskeleton, but could also affect the actin cytoskeleton by inhibiting RHOA at the wrong location, thereby compromising barrier integrity. The resulting inflammation and gastritis are well known risk factors for gastric cancer."

"Gastric cancer has a high incidence in Asia, and it is important for Asian scientists to improve our understanding of diseases which are important in our population. This joint study combines the efforts of scientists and clinicians in multiple institutions in Singapore, including GIS, IMCB, TTSH and NUHS," said Deputy Chief Executive (Academic Enterprise) at NUHS, Assoc Prof Yeoh Khay Guan. "The present new finding describes a fusion gene which causes a breakdown of the protective gastric lining and which could help the cancer to spread. This is one more important step in advancing our understanding of gastric cancer which will ultimately lead to better treatment for this disease."

Prof Ng Huck Hui, Executive Director at GIS said, "Gastric cancer is the 5th most common cancer worldwide, with the highest incidence in Asia. This is another excellent example of how important collaborations between research institutes, academia and hospitals can result in spectacular discoveries, to advance possible cures for the disease."

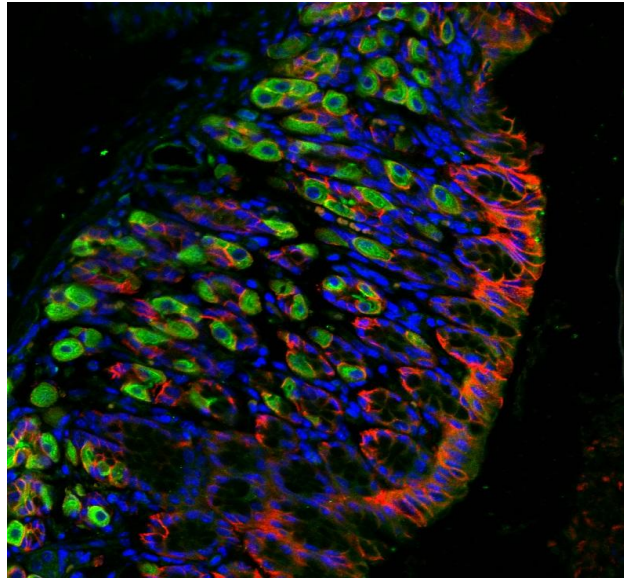
The study, made possible through collaboration between GIS, IMCB, NUHS and Tan Tock Seng Hospital and support by A*STAR, showcased the importance of such collaborative efforts between researchers and clinicians. The Translational and Clinical Research Flagship Programme – *The Singapore Gastric Cancer Consortium*² - is supported by the Singapore National Research Foundation and administered by the Singapore Ministry of Health's National Medical Research Council.

can differentiate into a variety of cell types). EMT is essential for numerous developmental processes including mesoderm formation. EMT has been shown to occur in wound healing, in organ fibrosis and in the initiation of metastasis for cancer progression.

(http://en.wikipedia.org/wiki/Epithelial%E2%80%93mesenchymal_transition)

² http://www.nmrc.gov.sg/content/nmrc_internet/home/grant/compgrants/tcrcancer.html

IMAGES



Immunofluorescence image of human stomach section stained for ARHGAP26 (green), epithelial cadherin (red) and cell nuclei (blue). Epithelial cadherin is present in all epithelial cell types of the stomach, whereas ARHGAP26 is restricted to parietal cells. Since CLDN18 has a similar expression pattern as epithelial cadherin, the fusion of ARHGAP26 to CLDN18 will result in the expression of ARHGAP16 activity in all epithelial cells.

Notes to Editor:

The research findings described in the media release can be found in the scientific journal *Cell Reports*, under the title, "Recurrent fusion genes in gastric cancer: *CLDN18-ARHGAP26* induces loss of epithelial integrity" by Fei Yao,^{1,2,19} Jaya P. Kausalya,^{3,19} Yee Yen Sia,^{1,2} Audrey S.M. Teo,^{1,2} Wah Heng Lee,⁴ Alicia G.M. Ong,³ Zhenshui Zhang,⁵ Joanna H. J. Tan,¹ Guoliang Li,⁶ Denis Bertrand,⁴ Xingliang Liu,¹ Huay Mei Poh,¹ Peiyong Guan,^{4,7} Feng Zhu,^{8,2} Thushangi Nadeera Pathiraja,^{1,2} Pramila N. Ariyaratne,⁴ Jaideep Raj Rao,⁹ Xing Yi Woo,¹⁰ Shaojiang Cai,⁴ Fabianus H. Mulawadi,⁴ Wan Ting Poh,¹⁰ Lavanya Veeravalli,¹¹ Chee Seng Chan,¹¹ Seong Soo Lim,⁵ See Ting Leong,¹² Say Chuan Neo,¹² Poh Sum D. Choi,¹² Elaine G. Y. Chew,¹ Niranjan Nagarajan,⁴ Pierre-Étienne Jacques,¹³ Jimmy B.Y. So,^{14,15,2} Xiaoan Ruan,^{10,12} Khay Guan Yeoh,^{8,15,2} Patrick Tan,^{1,2,16,17} Wing-Kin Sung,^{4,7} Walter Hunziker,^{3,18,21,*} Yijun Ruan,^{19,21,*} Axel M. Hillmer^{1,2,21,*}

¹ Cancer Therapeutics & Stratified Oncology, Genome Institute of Singapore, Singapore 138672, Singapore

² The Singapore Gastric Cancer Consortium, National University of Singapore, Singapore 119228, Singapore

³ Epithelial Cell Biology Laboratory, Institute of Molecular and Cell Biology, Singapore 138673, Singapore

⁴ Computational & Systems Biology, Genome Institute of Singapore, Singapore 138672, Singapore

⁵ Human Genetics, Genome Institute of Singapore, Singapore 138672, Singapore

6 National Key Laboratory of Crop Genetic Improvement, Center for
Bioinformatics, College of Informatics, Huazhong Agricultural University,
Wuhan 430070, China
7 School of Computing, National University of Singapore, Singapore 119074,
Singapore
8 Department of Medicine, Yong Loo Lin School of Medicine, National
University of Singapore, Singapore 119228, Singapore
9 Department of General Surgery, Tan Tock Seng Hospital, Singapore 308433,
Singapore
10 Personal Genomic Solutions, Genome Institute of Singapore, Singapore
138672, Singapore
11 Research Computing, Genome Institute of Singapore, Singapore 138672,
Singapore
12 Genome Technology and Biology, Genome Institute of Singapore, Singapore
138672, Singapore
13 Département de Biologie, Université de Sherbrooke, Sherbrooke, Québec
J1K 2R1, Canada
14 Department of Surgery, Yong Loo Ling School of Medicine, National
University of Singapore, Singapore 119074, Singapore
15 National University Health System, Singapore 119228, Singapore
16 Duke-NUS Graduate Medical School, Singapore 169857, Singapore
17 Cancer Science Institute of Singapore, Yong Loo Lin School of Medicine,
National University of Singapore, Singapore 117599, Singapore
18 Department of Physiology, National University of Singapore, Singapore
117597, Singapore
19 The Jackson Laboratory for Genomic Medicine, Farmington, Connecticut
06032, USA
20 Co-first author
21 Co-senior author
* Corresponding author

For media queries and clarifications, please contact:

Ms Winnie Lim
Head, Office of Corporate Communications
Genome Institute of Singapore, A*STAR
Tel: +65 6808 8013
Email: limcp2@gis.a-star.edu.sg

Ms Dawn Sim
Assistant Director, Communications Office
National University Health System
Tel: +65 6772 3989
Email: dawn_sim@nuhs.edu.sg

About the 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.gis.a-star.edu.sg

About A*STAR's Institute of Molecular and Cell Biology (IMCB)

The Institute of Molecular and Cell Biology (IMCB) was launched on 23 January 1985, with its official opening ceremony held on 2 October 1987 at the National University of Singapore (NUS). It subsequently became an autonomous research institute (RI) of A*STAR, moving to Biopolis in 2004. IMCB's vision is to be a premier cell and molecular biology institute which addresses the mechanistic basis of human diseases and its mission is to conduct cutting-edge discovery research in disease pathways; to groom early career researchers to be future leaders in research; and to collaborate with medical and industry communities for research impact. IMCB plays an important role training and recruiting scientific talents, and has contributed to the development of other research entities in Singapore. Its success in fostering a biomedical research culture in Singapore has catalysed Singapore's transformation into an international hub for biomedical research, development and innovation.

Funded primarily by the Biomedical Research Council (BMRC) of A*STAR, IMCB's current discovery research includes cell biology in health and disease; animal models of development & disease; cancer & stem cell genetics & genomics; and structural biology & drug discovery. IMCB's translational research includes humanised model organisms for human diseases; systems approach for disease target identification & validation; and protein engineering & antibody development for diagnostics & therapeutics. Research activities in IMCB are supported by cutting edge infrastructure and facilities including quantitative proteomics; humanised mice; mouse models of human cancer; protein crystallography X-ray; zebrafish for drug metabolism & toxicology; advanced molecular histopathology; imaging & electron microscopy; and DNA sequencing.

For more information about IMCB, visit www.imcb.a-star.edu.sg.

About the Agency for Science, Technology and Research (A*STAR)

The Agency for Science, Technology and Research (A*STAR) is Singapore's lead public sector agency that spearheads economic oriented research to advance scientific discovery and develop innovative technology. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit society.

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 Institutes, the wider research community and industry. A*STAR oversees 18 biomedical sciences and physical sciences and engineering research entities primarily located in Biopolis and Fusionopolis.

For more information on A*STAR, please visit www.a-star.edu.sg.

About the National University Health System (NUHS)

The National University Health System (NUHS) groups the National University Hospital, the NUS Yong Loo Lin School of Medicine, the NUS Faculty of Dentistry and the NUS Saw Swee Hock School of Public Health under a common governance structure to create synergies for the advancement of health by integrating clinical care, research and education.

The enhanced capabilities and capacity enable the NUHS to deliver better patient care, train future generations of doctors more effectively and bring innovative treatments to patients through groundbreaking research.

For more information, please visit www.nuhs.edu.sg