

MEDIA RELEASE

24 SEPTEMBER 2020

SINGAPORE SCIENTISTS DISCOVER HUMAN LIVER CANCER CELLS MASQUERADING AS FETAL-LIKE CELLS

Liver cancers adopt a fetal-like environment to escape immune surveillance and grow more aggressively



From left: Dr Florent Ginhoux, Prof Jerry Chan, Prof Pierce Chow, Dr Ramanuj DasGupta, and Dr Ankur Sharma (Copyright: A*STAR's Genome Institute of Singapore)

SINGAPORE – A team of researchers and clinician-scientists from A*STAR’s Genome Institute of Singapore (GIS), Singapore Immunology Network (SIgN), National Cancer Centre Singapore (NCCS), and KK Women’s and Children’s Hospital (KKH), have identified a pivotal “fetal-like” reprogramming of the tumour ecosystem in human hepatocellular carcinoma (HCC). This study leveraged the platform established by the National Medical Research Council (NMRC) Translational and Clinical Research (TCR) Flagship Programme in Liver Cancer¹ and was recently published in [Cell](#) on 24 September 2020.

HCC, or primary liver cancer, is the sixth most common cancer in the world, and the second most common cause of cancer deaths globally². It is estimated that approximately 80% of all HCC are found in Asia. Tumours represent a complex ecosystem of diverse cell types that exhibit molecular and functional heterogeneity and plasticity. Previous studies have noted the similarities between embryonic development and tumours, specifically in the expression of fetal-like antigens in cancers. Most notably, alpha-fetoprotein (AFP) is one of the key onco-fetal proteins found to be elevated in more than 80% of HCC, especially in those with poorly differentiated cell types which are clinically more aggressive. The fetal immune system and placental-fetal system are known to be largely immunologically tolerant, allowing their co-existence within the mother until birth. It has long been suggested that cancers may have similar mechanisms to avoid rejection by the body. While it is known that HCC can undergo onco-fetal reprogramming, the relationship between HCC and its micro-environment has not been examined in detail.

In this comparative study, the researchers mapped approximately 200,000 single cells in the human liver across the timeline from fetal development to terminal liver cancer. It led to the discovery of two new fetal-associated cell types in the tumour ecosystem in HCC. Specifically, the team identified the reappearance of fetal-like endothelial cells that are responsible for blood supply, and fetal-like macrophages, an immune cell type that serves as the body’s first line of defence against pathogens, but are also associated with tissue homeostasis.

The researchers discovered that during development of the fetal liver (a process that shares many characteristics typically associated with cancer growth), these cell types (fetal endothelial and macrophages) help in organ growth and protect the tissue against the body’s own immune system. The team identified the sequential activation of VEGF and Notch signalling pathways that led to fetal-like reprogramming of endothelial cells and macrophages. Importantly, the authors showed that these signalling pathways are activated during fetal-liver growth, and switched off thereafter, but are re-activated during the development of liver cancer.

A dividing cancer cell first activates VEGF pathway in endothelial cells, which in turn communicate with macrophages in tumours via Notch-Delta interactions. The fetal-like

¹ **The National Medical Research Council (NMRC) Translational and Clinical Research (TCR) Flagship Programme in Liver Cancer** is a prospective clinical and multi-omics cohort study that leverages on multi-region sampling of surgically resected HCC. The genomics, immunomics, and metabolomics profiles of these samples are correlated to the clinical trajectories of the patients, especially to cancer recurrence and survival.

<https://clinicaltrials.gov/ct2/show/NCT03267641>

² Venook et al *The oncologist*. 2010; 15 Suppl (4): 5-13. doi: 10.1634/theoncologist.2010-S4-05

programme in tumours allows uncontrolled growth and protection from the immune system. This study provides unprecedented and fundamental insights into the processes that drive cancer development, and may provide new therapeutic strategies to re-activate the immune system in the fight against cancer.

Dr Ramanuj DasGupta, cancer biologist and Senior Group Leader at GIS, and the lead corresponding author of the study, said, “Our research underscores a fundamental understanding of how early developmental processes can be hijacked by cancers in order to facilitate their own growth, and escape immune surveillance. This study also opens up exciting possibilities for the discovery of biomarkers and novel therapeutic targets associated with non-malignant cells, especially in the context of combinatorial immunotherapy with anti-angiogenic drugs. Most importantly, it highlights the power of like-minded scientists and clinicians coming together to solve big problems. I am absolutely thrilled to be working with this dream-team of exceptional scientists and clinicians.”

Dr Ankur Sharma, Research Scientist at GIS, the first and co-corresponding author of the study, said, “Our research provides insights into the mirror worlds of fetal and tumour ecosystem, where certain cell types first appear during organ development and later reappear in cancer. The ‘reappearance’ of fetal-like cells provides the perfect environment for tumour growth by suppressing the immune system. Our work demonstrates the importance of embryonic macrophages in tumour growth and immune suppression. This study opens new avenues to understand the embryonic origin of cancers and its implication in discovering new therapeutic approaches, especially in the realm of immunotherapy.”

Dr Florent Ginhoux, scientist and Senior Principal Investigator at SlgN, and co-corresponding author of the study said, “The macrophages are one of the first immune cells to arise during development as their *raison d’être* is to provide adequate organ building and tissue maintenance. These embryonic macrophages are endowed with immune-suppressive properties as inflammation too early would be detrimental to the correct development of fetal tissues. Our work uncovers that tumour cells exploit embryonic macrophage’s *raison d’être* for their own growth, by recreating an artificial fetal-like environment and taking macrophages ‘back in time’ mimicking early developmental settings. This study will help to understand the importance of macrophage ontogeny in cancer development and open new strategies to eradicate cancer.”

Prof Pierce Chow, Clinician-Scientist and Liver Surgeon at NCCS, Principal Investigator of the NMRC TCR Flagship Programme in Liver Cancer, and co-corresponding author of the study, said, “This study provides mechanistic confirmation of what many liver cancer specialists have suspected – regression to a fetal state allows HCC to grow aggressively. The findings potentially opens up new approaches in the prevention and treatment of HCC. It is also a showcase of what multi-disciplinary collaborative research between clinician-scientists from different specialities and scientists with different expertise can achieve.”

Prof Chow who is also a Programme Director with Duke-NUS Medical School added that he may include the investigation for proteins uncovered by this study in a prospective cohort study of patients at high risk of developing liver cancer, which has been planned to start at the end of 2020.

Genome Institute of Singapore

60 Biopolis Street #02-01 Genome Singapore 138672

T + 6808 8000 W www.a-star.edu.sg/gis

Prof Jerry Chan, Clinician-Scientist and Senior Consultant at KKH's Department of Reproductive Medicine and co-author of the study, said, "Globally, cancer cases have risen rapidly over the years. Understanding the behaviour of how cancer cells reprogramme their environment to simulate a fetal environment, and thereby promoting their growth and avoiding immune destruction, may be key to developing a cure. KKH is proud to contribute to this novel discovery through underlying expertise in the developing fetal immune system³, in collaboration with A*STAR and others."

Prof William Hwang, Medical Director at NCCS, said, "Indeed, the multi-institutional collaboration has allowed the team to leverage on each other's expertise, leading to the discovery of onco-fetal reprogramming in liver cancer. I'm glad we are one step closer to understanding and treating liver cancer."

Prof Patrick Tan, Executive Director of GIS, said, "The discovery of onco-fetal reprogramming in liver tumours opens up new avenues of investigating this process in other cancers and inflammatory diseases. This work also demonstrates the power of single-cell and spatial genomics in uncovering fundamental biological insights. It is a true example of 'SG United' where scientists across the different Singapore institutions formed a team to discover new biological processes with translational implications in the clinic."

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Enclosed:

ANNEX A – Notes to Editor

For media queries and clarifications, please contact:

Lyn Lai
Officer, Office of Corporate Communications
Genome Institute of Singapore, A*STAR
Tel: +65 6808 8258
HP: +65 8755 8759
Email: laiy@gis.a-star.edu.sg

³ McGovern et al Nature. 2017 Jun 29;546(7660):662-666. doi: 10.1038/nature22795



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 pursues the integration of technology, genetics and biology towards academic, economic and societal impact, with a mission to "read, reveal and write DNA for a better Singapore and world".

Key research areas at the GIS include Precision Medicine & Population Genomics, Genome Informatics, Spatial & Single Cell Systems, Epigenetic & Epitranscriptomic Regulation, Genome Architecture & Design, and Sequencing Platforms. The genomics infrastructure at the GIS is also 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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ANNEX A – NOTES TO EDITOR

The research findings described in this media release can be found in the scientific journal Cell, under the title, "[Onco-fetal reprogramming of endothelial cells drives immunosuppressive macrophages in Hepatocellular Carcinoma](#)" by Ankur Sharma^{1,2*}, Justine Jia Wen Seow^{1,15}, Charles-Antoine Dutertre^{3,4,15}, Rhea Pai¹, Camille Blériot³, Archita Mishra³, Regina Men Men Wong¹, Gurmit Singh Naranjan Singh³, Samyururai Sudhagar¹, Shabnam Khalilnezhad³, Sergio Erdal³, Hui Min Teo¹, Ahad Khalilnezhad³, Svetoslav

Genome Institute of Singapore

60 Biopolis Street #02-01 Genome Singapore 138672

T + 6808 8000 W www.a-star.edu.sg/gis

Chakarov³, Tony Kiat Hon Lim⁵, Alexander Chung Yaw Fui⁶, Alfred Kow Wei Chieh⁷, Cheow Peng Chung⁶, Glenn Kunnath Bonney⁷, Brian Goh Kim Poh⁶, Jerry KY Chan^{8,9,10}, Pierce Chow Kah Hoe^{11,12*}, Florent Ginhoux^{3,13,14*}, Ramanuj DasGupta^{1,16,*}.

1. Genome Institute of Singapore, A*STAR, 60 Biopolis Street, Genome, #02-01, Singapore 138672, Singapore
2. School of Pharmacy and Biomedical Sciences, Curtin Health Innovation Institute, Curtin University, Perth, WA 6102, Australia
3. Singapore Immunology Network (SIgN), A*STAR, 8A Biomedical Grove, Immunos Building, Level 3 and 4, Singapore 138648, Singapore
4. Program in Emerging Infectious Disease, Duke-NUS Medical School, 8 College Road, Singapore 169857, Singapore
5. Department of Pathology, Singapore General Hospital, Singapore 169608, Singapore
6. Department of Hepato-Pancreato-Biliary and Transplant Surgery, Singapore General Hospital, Singapore 169608, Singapore
7. Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, National University of Hospital, Singapore 119074, Singapore
8. Department of Reproductive Medicine, KK Women's and Children's Hospital, Singapore 229899, Singapore
9. Experimental Fetal Medicine Group, Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, NUS, Singapore 117597, Singapore
10. Academic Clinical Program in Obstetrics and Gynaecology, Duke-NUS Medical School, Singapore 169857, Singapore
11. Division of Surgery and Surgical Oncology, National Cancer Centre, Singapore 169610, Singapore
12. Academic Clinical Programme for Surgery, Duke-NUS Medical School, Singapore 169857, Singapore
13. Shanghai Institute of Immunology, Shanghai JiaoTong University School of Medicine, Shanghai 200025, China
14. Translational Immunology Institute, SingHealth Duke-NUS Academic Medical Centre, 169856, Singapore

These authors contributed equally

Lead Contact: Ramanuj DasGupta (dasguptar@gis.a-star.edu.sg)

*Correspondence: Ankur Sharma (sharmaa@gis.a-star.edu.sg), Pierce Chow Kah Hoe (pierce.chow.k.h@singhealth.com.sg), Florent Ginhoux (florent_ginhoux@immunol.a-star.edu.sg), Ramanuj DasGupta (dasguptar@gis.a-star.edu.sg).



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