

**MEDIA RELEASE
FOR IMMEDIATE RELEASE**

21 MARCH 2017

**SINGLE-CELL ANALYSIS PAVES WAY FOR CHARACTERISATION OF THE
TUMOUR MICROENVIRONMENT AND MORE ACCURATE PROGNOSIS OF
CANCER PATIENTS**

SINGAPORE – For the first time, researchers have applied single-cell transcriptomics to colorectal cancer (CRC) – the third most common cancer in the world – and discovered that this method could lead to improved patient stratification and eventually, a more accurate prognosis of CRC patients. Jointly led by scientists from A*STAR's Genome Institute of Singapore (GIS) and National Cancer Centre Singapore (NCCS), the team performed an unbiased analysis of functional heterogeneity in colorectal tumours and their microenvironment using RNA-seq profiling of unsorted single cells from 11 primary tumours and normal tissue. Over 1,500 cells taken from the 11 patients were profiled in this study, which has been published in *Nature Genetics*.

As there are no existing algorithms that can accurately identify cell-type groups from the new data type, the researchers developed their own and compared it to existing single-cell clustering algorithms using a novel benchmark data set. Called Reference Component Analysis (RCA), this novel method incorporates reference-based cell-cell similarity scores and substantially improves clustering accuracy, outperforming existing algorithms to robustly cluster single-cells. It is also the first time anyone has systematically benchmarked such an algorithm, which will serve as an important foundation for future studies.

A key conclusion of this study was that of epithelial-mesenchymal transition (EMT), which is thought to contribute to the spread of cancer cells throughout the body, or metastasis. Looking at the single-cell level, the researchers found that the mesenchymal genes that were expressed in the tumour and supposedly signatures of EMT, were not expressed in the cancer cells. Instead, these genes were expressed in the non-cancer cells – a finding that would not have been possible based on traditional bulk transcriptomics.

“The biggest advantage of single-cell analysis is that we are able to look at one cell at a time, which allows us to know exactly in which cell each gene was expressed. While we didn’t disprove EMT, we certainly found no evidence for it in the cancer cells we analysed. In fact, it appears that it’s the non-cancer cells that express mesenchymal genes in our colon tumour samples,” said Dr Shyam Prabhakar, the study’s co-corresponding author and Associate Director of Integrative Genomics at the GIS. “Our findings are consistent with some papers published recently that reached a similar conclusion. Nevertheless, this is a shift from the dominant paradigm – it really challenges our view of how cancer cells spread in the body.”

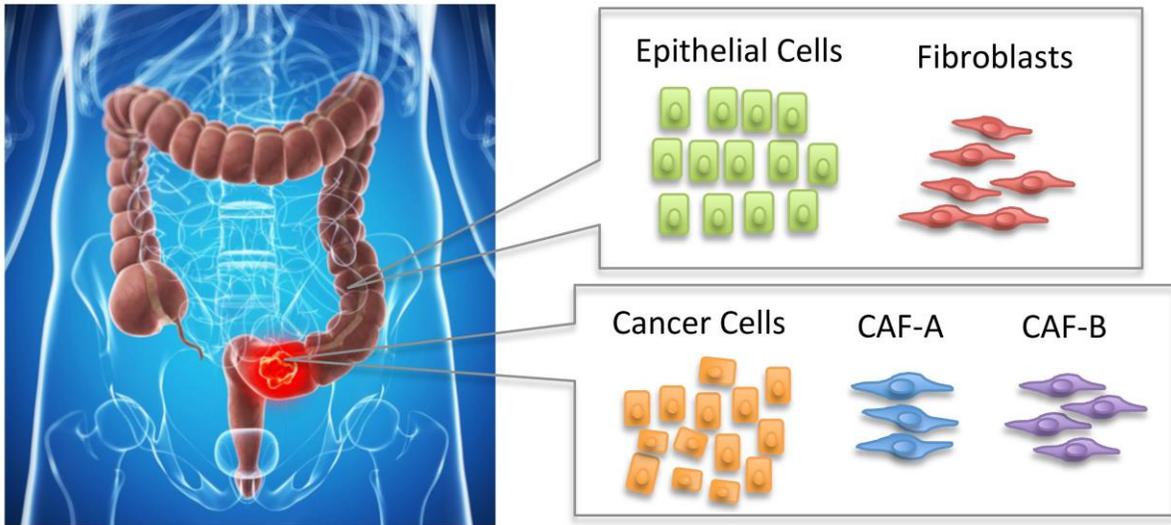
Although bulk transcriptomics is well established as a way of classifying CRC patients, the more fine-grained single-cell analysis could potentially support even more precise stratification.

“Using the data from our study, we found that our single-cell signatures were able to classify patients more accurately, enabling an improved prognosis of how likely they are to survive over a five-year window. The tumour microenvironment is critical to the biological behaviour of cancers. Using the technologies in our study, we have elucidated, identified and characterised different cell populations that comprise the tumour microenvironment and are now moving to further studies to experimentally characterise the interactions between these cells,” said co-corresponding author, Dr Iain Tan, Senior Consultant, Medical Oncologist at NCCS and clinician scientist at the GIS.

GIS Executive Director Prof Ng Huck Hui added, “This is a first step towards understanding how patients with the same diagnosis are actually very different. We hope methods like RCA can be used to obtain a more accurate prognosis of patient survival rate and help us understand why the patients’ prognoses are different from one another. This will eventually lead to individualised and more targeted treatments for these different, further stratified groups of patients.”

Targeting to reach a million single-cell transcriptomes, the research team will next scale up and expand their research by applying single-cell analyses to other domains, such as lung cancer, leukemias, ageing tissues and host response to infection.

IMAGE



(Image source: A*STAR's Genome Institute of Singapore)

Colorectal cancer is a heterogeneous disease, and all cell types play important roles in the tumour microenvironment. Using single-cell RNA sequencing (scRNAseq) and newly developed algorithms, we measured the gene expression of various cell types and compared the tumour cells with their matched normal cell type. These analyses led to the discovery of two different fibroblast populations in CRC (CAF-A and CAF-B) and also identification of prognostic expression signatures.

Notes to Editor:

The research findings described in this media release can be found in the scientific journal *Nature Genetics*, under the title, “*Reference component analysis of single-cell transcriptomes elucidates cellular heterogeneity in human colorectal tumors*” by Huipeng Li^{1,*}, Elise T. Courtois^{1,2*}, Debarka Sengupta^{1,3}, Yuliana Tan¹, Kok Hao Chen⁴, Jolene Jie Lin Goh⁴, Say Li Kong⁵, Clarinda Chua⁶, Lim Kiat Hon⁷, Tan Wah Siew⁸, Mark Wong⁸, Paul Jongjooon Choi⁴, Lawrence Wee⁹, Axel M. Hillmer⁵, Iain Beehuat Tan^{5,6,10,+}, Paul Robson^{2,11,12,13,+}, and Shyam Prabhakar^{1,+}

¹Computational and Systems Biology, Genome Institute of Singapore, Singapore

²Developmental Cellomics Laboratory, Genome Institute of Singapore, Singapore

³Department of Computer Science and Engineering and Center for Computational Biology, Indraprastha Institute of Information Technology, Delhi, India

⁴Synthetic Biology, Genome Institute of Singapore, Singapore

⁵Cancer Therapeutics and Stratified Oncology, Genome Institute of Singapore, Singapore

⁶Department of Medical Oncology, National Cancer Centre Singapore, Singapore

⁷Department of Pathology, Singapore General Hospital, Singapore

⁸Department of Colorectal Surgery, Singapore General Hospital, Singapore

⁹Data Analysis Department, Institute for Infocomm Research, Singapore

¹⁰Program in Cancer and Stem Cell Biology, Duke-NUS Medical School, Singapore

¹¹Single Cell Biology Laboratory, The Jackson Laboratory for Genomic Medicine, Farmington, CT 06032 USA

¹²Department of Genetics and Genome Sciences, Institute for Systems Genomics, University of Connecticut, Farmington, CT 06032 USA

¹³Department of Biological Sciences, National University of Singapore, Singapore

* These authors contributed equally to this work.

+ Correspondence authors

Email: I.B.T. (iain.tan.b.h@singhealth.com.sg); P.R. (Paul.Robson@jax.org); S.P. (prabhakars@gis.astar.edu.sg)

For media queries and clarifications, please contact:

Joyce Ang

Senior Officer, Office of Corporate Communications

Genome Institute of Singapore, A*STAR

Tel: +65 6808 8101

Email: angji@gis.a-star.edu.sg

Siti Zawiyah

Senior Executive, Corporate Communications

National Cancer Centre Singapore

Tel: +65 6236 9429

Email: siti.zawiyah.aboo@nccs.com.sg

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.gis.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 National Cancer Centre Singapore

National Cancer Centre Singapore (NCCS) provides a holistic and multi-disciplinary approach to cancer treatment and patient care. We treat almost 70 per cent of the public sector oncology cases, and they are benefiting from the sub-specialisation of our clinical oncologists. NCCS is also accredited by the US-based Joint Commission International for its quality patient care and safety. To deliver among the best in cancer treatment and care, our clinicians work closely with our scientists who conduct robust cutting-edge clinical and translational research programmes which are internationally recognised. NCCS strives to be a global leading cancer centre, and shares its expertise and knowledge by offering training to local and overseas medical professionals. www.nccs.com.sg