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Scientists provide new insights on how cancers evade the immune system

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A team of scientists from Singapore has discovered new ways in which cancers can escape the body's immune system. Focusing on gastric cancer (GC), the third leading cause of cancer death worldwide, the team's findings may also prove applicable to other major cancers with potential implications for how cancers might be better treated with immunotherapy, one of the most promising classes of anti-cancer drugs today.

Promoters are regions in the genome that regulate the expression of genes, similar to the switch of a light bulb. Using an ultra-sensitive technique called NanoChIP-seq, the team surveyed the promoter landscape for GC to better understand the epigenetic mechanisms contributing to GC development. The team found that in GCs, gene promoters are dysregulated in a way that alters a tumour's antigenic profile to evade the body's immune system. The study, published in the leading journal *Cancer Discovery*, involved scientists and clinicians from Duke-NUS Medical School, Genome Institute of Singapore, Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS), and National Cancer Centre Singapore (NCCS).

"Using the NanoChIP-seq platform invented in Singapore, we created comprehensive epigenetic profiles for both GC and normal tissues," explained team leader Professor Patrick Tan. "Epigenetics is a process by which a cell's DNA is chemically modified by the environment, to change gene expression. By comparing the epigenetic profiles of gastric

tumours to normal tissues from the same patient, we were able to identify those promoters specifically altered in GC tissues." Professor Tan is a Faculty Member of Duke-NUS Medical School, Deputy Executive Director of the Biomedical Research Council at the Agency for Science, Technology and Research (A*STAR), and also Senior Principal Investigator at CSI Singapore and Principal Investigator at NCCS.

Just like how a light can be controlled by multiple switches to influence its intensity and colour, the team identified hundreds of genes controlled by multiple promoters, causing alternate versions of that gene to be produced. The team demonstrated that some of these gene variants are capable of stimulating cancer growth. Strikingly, the team also found that many of these alternate gene variants produced in gastric tumours were also less likely to stimulate the immune system compared with their normal counterparts.

"Our data, combining computational, experimental assays, and analyses of human gastric cancers, indicates that the use of these less immunogenic variants may enhance the ability of a tumour to bypass the host's immune system. This process is referred to as tumour immunoediting," added Ms Aditi Qamra, graduate student at the Genome Institute of Singapore and first author of this study. She is also a graduate student with the Department of Physiology at the NUS Yong Loo Lin School of Medicine.

The findings provide important insights into mechanisms used in cancer development and may have implications for cancer immunotherapy. While striking clinical responses have been seen in some patients treated with immunotherapy, these drugs are expensive, associated with side effects, and not all patients respond to the treatment. The team's results suggest that studying the promoter profiles of tumours may possibly identify those patients who would be responsive to immunotherapy.

Moreover, the team also identified cellular pathways required by the tumour cell to maintain expression of the less immunogenic gene variants. The team is now exploring if targeting these pathways, combined with immunotherapy, can increase the proportion of patients that might respond to such drugs.

Summary of key findings

- Nano-ChIPseq enables the comprehensive identification of promoter elements using small amounts of tissue, opening up the ability to analyse samples obtained directly from patients.
- Altered promoters in GC change the gene expression profile of GC cells and may confer its oncogenic properties, including cell movement and cancer signalling.
- Gene variants associated with GC altered promoters lack immunogenic N-terminal–lacking peptides, enhancing the ability of gastric tumours to evade the native body's immune response.

More information: Ester Valls et al. BCL6 Antagonizes NOTCH2 to Maintain Survival of Human Follicular Lymphoma Cells, *Cancer Discovery* (2017). DOI: 10.1158/2159-8290.CD-16-1189

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