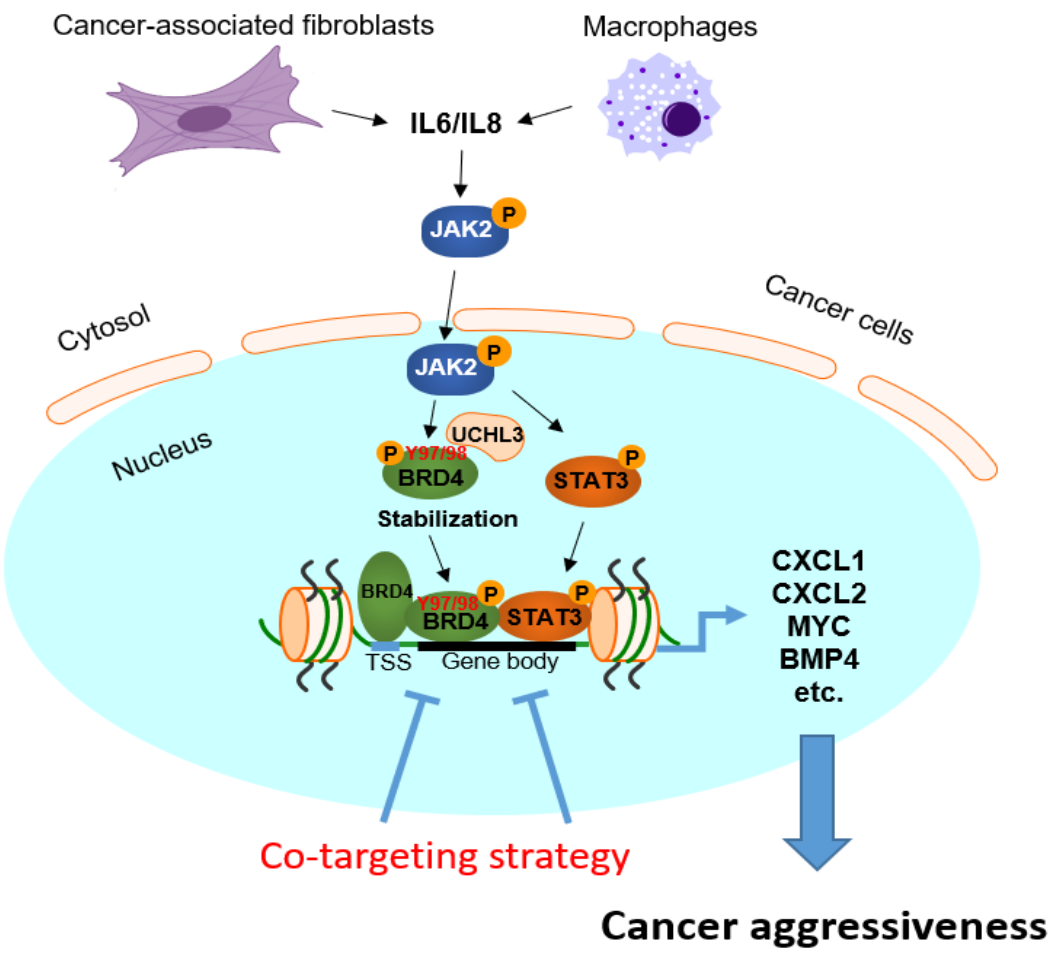
HOW TUMOUR MICROENVIRONMENT CAUSES CANCER CELLS TO BE RESISTANT TO DRUG TREATMENT



Cancer-associated fibroblasts secret inflammatory cytokines IL6 and IL8 to induce chromatin remodeling in cancer cells through BRD4 phosphorylation, and resistance to BET inhibitor treatment.

The tumour microenvironment is the ecosystem that surrounds a tumour inside the body. In addition to the tumour cells, there are also other cell types such as immune cells and fibroblasts. A tumour and its microenvironment constantly interact with each other to promote cancer growth.

Our study identified a new way in which fibroblast cells secrete cytokines to change the cancer cells' behaviour. This change in behavior causes resistance to **B**romodomain and **E**xtra-**T**erminal motif (BET) inhibitors such as JQ1, a new type of cancer therapy which is currently in clinical development.

In particular, our work showed that cancer-associated fibroblasts can produce cytokines IL6 and IL8 to induce cancer cell chromatin dysregulation via modification of BRD4, a chromatin reader, which leads to reduced response to BET inhibitor that targets BRD4. The inhibition of this new pathway improves the efficacy in BET inhibitor treatment in preclinical models.

Moving forward, our long term goal is to develop a combination therapy approach to facilitate the clinical development of BET inhibitors in the clinic.

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"There are other groups in the world studying BET inhibitor resistance, but they mostly focus on cancer cells (cancer intrinsic manner). On the other hand, our study focuses on the stromal cells in the tumour environment, and seeks to understand how the stromal cells can be a factor that causes resistance to cancer treatments."

Dr Yu Qiang, Senior Group Leader,
Laboratory of Precision Cancer Medicine, GIS

"BET inhibitors have been pursued as a new therapy for cancer, but the clinical efficacy in solid tumours like colorectal cancer is lower than expected. This study provides a possible explanation about how the tumour microenvironment in the solid tumors causes resistance to the BET inhibitor treatment, and possibly provide a new approach to overcome the resistance."

Prof Patrick Tan, Executive Director, GIS