Title: Loss of GATA2 promotes invasion and predicts cancer recurrence and survival in FIGO stage I uterine serous carcinoma

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Scientific Abstract:

Background: Uterine cancer is the 4th most common cancer in women. Its incidence is increasing and its mortality rate also is rising. Uterine serous carcinoma (USC) is an aggressive uterine cancer subtype that is responsible for 40% of uterine cancer deaths. Although 50% of USC patients present with cancer localized to the uterine body (FIGO stage I) and should be cured by staging hysterectomy, 30% of these patients later recur in the absence of adjuvant combination paclitaxel-carboplatin chemotherapy. There is no reliable method to identify which USC patients are at risk of USC recurrence, so most patients receive risk-reducing adjuvant chemotherapy associated with significant morbidity. A priori knowledge of recurrence risk would enable a risk-stratified approach to adjuvant therapy to reduce morbidity and optimize survival. GATA Binding Protein 2 (GATA2) is a transcription factor that supports progesterone receptor signaling in the uterus. We recently generated anti-GATA2 monoclonal antibodies that can routinely detect GATA2 by standard immunohistochemistry (IHC).

Methods: We assembled a retrospective multi-institutional cohort of 81 patients with primary FIGO stage I USCs. Associations between GATA2 levels and clinicopathologic metrics were evaluated using Student's t-test, Fisher's exact test, Kaplan-Meier method, and Cox proportional hazards ratio. Gene targets including GATA2 were depleted from Ark1 and Ark2 patient-derived USC cell lines using siRNA or shRNA, and cell invasion evaluated using Matrigel-coated membranes and organoid-based natural hydrogel. RNA-seq, anti-GATA2 ChIP-seq, and western blotting enabled identification of GATA2 gene targets.

Results: GATA2 expression in USC tumors ranged from 0-100% GATA2+ tumor nuclei. USCs with >15% GATA2+ nuclei were defined as GATA2-high based on an initial inflection point in the data that optimally delineated patients by outcome. The 39% of patients with GATA2-high USCs had 100% recurrence-free, 100% disease-specific, and 87% overall survival. These outcomes were significantly better than patients with GATA2-low USCs. Depletion of GATA2 in USC cell lines increased invasion in vitro. In patients who received no adjuvant chemotherapy (n=18), those with GATA2-high USCs had 100% recurrence-free survival compared to 50% recurrence-free survival in GATA2-low USC patients. A multi-omic approach identified SIN3 Transcription Regulator Family Member B as a GATA2 target gene that suppressed USC invasion in vitro.

Conclusions: GATA2 IHC identifies FIGO stage I USC patients with a greatly reduced risk of USC recurrence. A GATA2 guided personalized medicine approach using standard IHC methods could be rapidly implemented in most hospital settings, would reduce treatment-related morbidity, and may optimize survival for USC patients.

Written Lay Abstract:

Uterine serous carcinoma (USC) is an aggressive type of uterine cancer. Even when caught early and treated, up to 3 in 10 patients with USC have their cancer return later. For this reason, doctors often treat USC patients with surgery and then also give them chemotherapy to stop cancer from coming back. However, chemotherapy has serious side effects, and doctors want to know which patients truly need it.

In this study, the researchers tested whether a protein called GATA2 could tell us whether patients with USC are likely to get cancer again and need chemotherapy. The researchers studied 81 patients with early-stage USC and tested their tumors for GATA2 using a test called immunohistochemistry (IHC).

The researchers found that none of the patients with high levels of the GATA2 protein got cancer again, even without chemotherapy. The researchers also tested USC cancer cells and found that GATA2 stops cancer cells from spreading, which may be why patients with high levels of GATA2 did not get cancer again.

These findings tell us that patients with USC and high levels of GATA2 may not need chemotherapy after cancer surgery. The IHC test is already common in hospitals, so it could be used by doctors to test their patients and see if chemotherapy is needed.

Visual Lay Abstract:

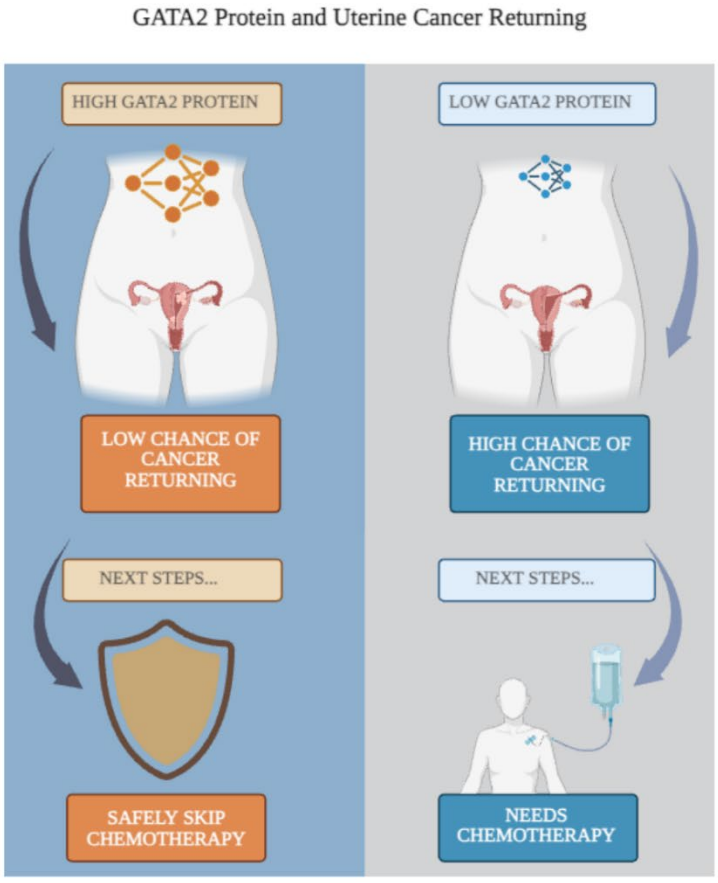
How a Tumor Protein Can Guide Cancer Care

Protein GATA2

Some uterine cancers can come back after surgery. In this study, researchers looked at whether a protein called GATA2 could tell which cancers are likely to return.

Choosing Better Treatments

The researchers found that when there was less of this GATA2 protein in a tumor, the cancer was more likely to come back. This means patients with lower levels of GATA2 could benefit from chemotherapy after surgery.



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