DNA methylation subtype classification can predict outcomes of urothelial carcinoma

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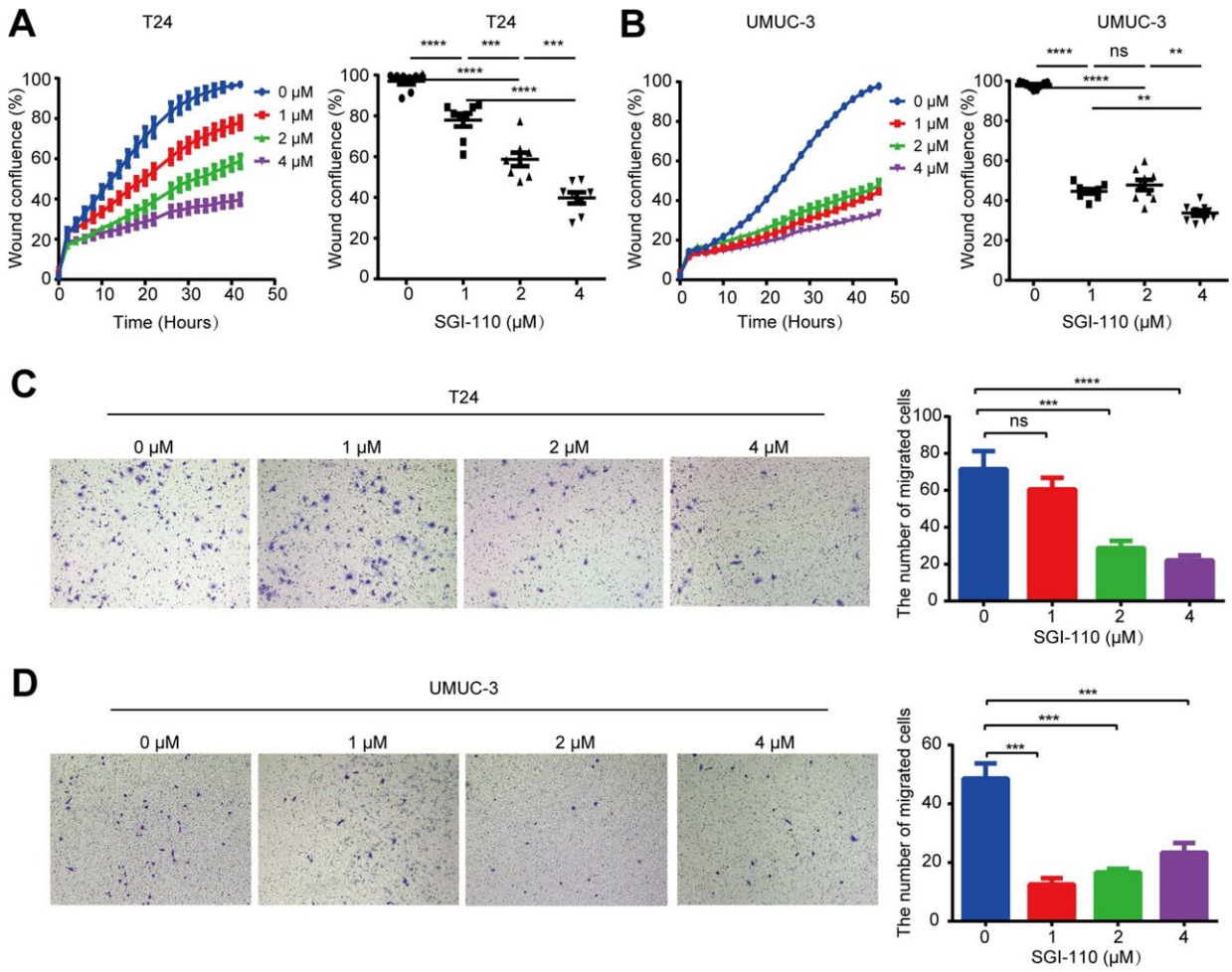

Guadecitabine (SGI-110), a DNA methyltransferase inhibitor, showed therapeutic effects in T24 and UMUC-3 cells. A, B Cell migration capacity with or without SGI-110 treatment was evaluated through wound healing assays. Values are the mean ± SD of eight independent experiments. C, D Cell invasion capacity with or without SGI-110 treatment was evaluated through Transwell

assays. The bar chart on the right represents the number of cells passing through the compartment. Data are presented as the means ± SEM. n = 3. *P BMC Medicine (2022). DOI: 10.1186/s12916-022-02426-w

Urothelial carcinoma (UC) is one of the most common malignancies genitourinary cancers, including upper tract urothelial carcinoma (UTUC) and urothelial carcinoma of the bladder (UCB).

UTUC is more malignant, with 60% of patients having muscle invasion at diagnosis, compared with only 15–25% of UCB. Increasing evidence suggests that DNA methylation is closely related to tumor progression in UCB. Unique DNA methylation patterns distinguish noninvasive and invasive UCBs. However, DNA methylation profiling in UTUC has been limited. Comparative analysis of DNA methylation alterations between UTUC and UCB would aid the development of diagnostics, prognostication, and even therapeutics for UC.

Recently, scientists from the Beijing Institute of Genomics of the Chinese Academy of Sciences (China National Center for Bioinformation) and Department of Urology, Peking University First Hospital, reported the epigenomic features and profiles of UTUC and UCB, identified DNA methylation subtypes with potential risk stratification of tumors, and evaluated therapeutic efficacy and targets of the DNA methyltransferase inhibitor SGI-110.

This study, published online in *BMC Medicine*, highlights similar management strategies for UC, and provides a roadmap for clinical practice: DNA methylation subtype classification can be used to predict the outcomes of resected UC patients.

By using the whole-genome bisulfite sequencing method, scientists

found that UTUC and UCB have very similar DNA methylation profiles, and they characterized potential links between DNA methylation and clinical outcomes.

DNA methylation classification identified two epi-clusters, Methy-High and Methy-Low, Methy-High tumors were hypermethylated, immune-infiltrated, and enriched for exhausted T cells, with poor clinical outcome. DNA methyltransferase inhibitor SGI-110 inhibited the migration and invasion of Methy-High UC cell lines by upregulating multiple antitumor immune pathways.

The study demonstrated the critical role of DNA methylation subtypes for predicting patient prognosis in UC, providing mechanistic rationale for evaluating SGI-110 in treating UC patients in the clinic.

More information: Juan Li et al, DNA methylation subtypes guiding prognostic assessment and linking to responses the DNA methyltransferase inhibitor SGI-110 in urothelial carcinoma, *BMC Medicine* (2022). DOI: 10.1186/s12916-022-02426-w

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