Genomics

Major Finding: A global prostate cancer molecular taxonomy was described showing divergent evolution and clinical outcomes.

Concept: African individuals with prostate cancer have more acquired genetic alterations and worse clinical outcome.

Impact: This study supports a global definition of genetic and clinical heterogenicity within prostate cancer.

GLOBAL MOLECULAR TAXONOMIES WERE GENERATED FOR PROSTATE CANCER

Genomic studies of prostate cancer are lacking in individuals from sub-Saharan Africa despite this patient population demonstrating much greater mortality rates. To determine both genetic and nongenetic factors associated with the increased mortality of prostate cancer in individuals of African ancestry, Jaratlerdsiri and colleagues used high-depth whole-genome sequencing and described the largest prostate cancer genomics data involving 123 South African men, as well as 53 Australian and seven Brazilian men to control for study artifacts. Two-million somatic variants were generated and assessed using genetic ancestral classification and revealed a greater number of acquired genetic alterations in African individuals as well as a greater percentage of genome alteration. Evaluation of oncogenic drivers revealed that Africans display a greater number of protein-coding mutations, with *FOXA1*, *PTEN*, *SPOP*, and *TP53* being the most commonly mutated driver genes, while copy-number alterations and mutations in *SETBP1*, *DDX11L1*, *STK19*, and *NCOA2* were also more likely to occur in African individuals. Moreover, four global mutational subtypes (GMS) were generated, with these taxonomies indicating African individuals were dispersed among all four subtypes, with GMS-B (high copy-number gain) and GMS-D (highest mutational density) being specific to African populations. Conversely, European patients from Australia and Brazil were limited to GMS-A (mutationally silent) and GMS-C (high copy-number loss), while Chinese-Asian individuals were included in GMS-A, suggesting the universal nature of GMS-A. Additionally, these taxonomies were associated with clinical outcome, with the universal (GMS-A) demonstrating better results than the European-African GMS (GMS-C). Mutational timelines for these GMS subtypes were also generated and showed each follows a specific evolutionary pattern, suggesting tumors can differ in the time needed to reach full malignant potential. In summary, this study offers both a global whole-genome resource and molecular taxonomies for prostate cancer that provide evolutionary history and a greater understanding of disease etiology. ■

Jaratlerdsiri W, Jiang J, Gong T, Patrick SM, Willet C, Chew T, et al. African-specific molecular taxonomy of prostate cancer. Nature 2022;609:552–9.

doi: 10.1158/2159-8290.CD-RW2022-166

Immunometabolism

Major Finding: M2-like tumor-associated macrophages (TAM) are addicted to glucose, which promotes their protumor function.

Concept: TAM glucose uptake facilitates Cathepsin B O-GlcNAcylation and subsequent metastasis and chemoresistance.

Impact: This study establishes the significance of TAM glucose metabolism and indicates a correlate of chemotherapy response.

GLUCOSE METABOLISM IN TAMs PROMOTES METASTASIS AND DRUG RESISTANCE

Within the tumor microenvironment (TME), tumor-associated macrophages (TAM) have been shown to have the highest glucose consumption per cell but how glucose can affect their polarization and tumor-promoting function remains undetermined. Shi, Shen, and colleagues sought to determine the role that glucose plays in establishing the protumor function of macrophages and showed that protumor M2-like TAMs in the TME have high glucose uptake capability as compared to other immune cells and tumor cells. Analysis of metabolic enzyme levels between M2-like and M1-like TAMs indicated an increase in the expression of enzymes critical for hexosamine biosynthesis and other glucose uptake/metabolism–related pathways as well as the upregulation of O-GlcNAc transferase (OGT), which correlates with the observed increase in OGT-mediated protein O-GlcNAcylation. Inhibition of glucose uptake in M2-like TAMs led to a concomitant reduction in total protein O-GlcNAcylation levels, with IL4 being shown to stimulate this glucose uptake and subsequent protein O-GlcNAcylation. Investigation into the role that O-GlcNAcylation plays in altering TAM function revealed lysosomal localization of OGT and an enrichment of lysosome-associated proteins like Cathepsin B. Moreover, Cathepsin B was found to undergo O-GlcNAcylation at serine 210 (S210), which was increased by IL4 treatment and by elevated levels of glucose. Evaluation of the effects of OGT and Cathepsin B on the protumorigenic functions of M2-like TAMs, including metastasis and chemoresistance, indicated decreased cell invasion as well as metastasis upon OGT or Cathepsin B deficiency as shown in a mouse model of melanoma in which OGT-deficient macrophages had reduced S210 O-GlcNAcylation of Cathepsin B, which reduced secreted mature Cathepsin B, inhibited lung metastases, and prolonged survival. Additionally, Cathepsin B or OGT deficiency also blocked the protective effect of macrophages after paclitaxel or oxaliplatin treatment, which was further shown in patients with colorectal cancer who received chemotherapy. In summary, this study shows that the enhanced glucose uptake of TAMs supports their protumorigenic function as well as suggests a potential correlate of response to chemotherapy. ■

Shi Q, Shen Q, Liu Y, Shi Y, Huang W, Wang X, et al. Increased glucose metabolism in TAMs fuels O-GlcNAcylation of lysosomal Cathepsin B to promote cancer metastasis and chemoresistance. Cancer Cell 2022 Aug 30 [Epub ahead of print].

doi: 10.1158/2159-8290.CD-RW2022-171