BLADDER CANCER EXOMES SEQUENCED

The vast majority of bladder cancers are transitional cell carcinomas (TCC), which arise from the transitional epithelium of the urogenital tract. TCCs are known to harbor mutations in TP53, RB1, FGFR3, HRAS, and KRAS, but this cancer has not been systematically analyzed. Gui and colleagues performed whole-exome sequencing of genomic DNA from 9 high-grade TCC patient samples and matched peripheral blood. The coding sequences of mutated genes were then analyzed in a panel of 51 high-grade and 37 low-grade TCCs, identifying 54 genes with non-synonymous mutations in at least 2 tumors. Frequent mutations in the genes previously linked to TCC were identified, but an unexpected prevalence of mutations in genes involved in chromatin remodeling was also noted. UTX, which encodes a histone demethylase, was mutated as frequently as TP53 in TCC (21% of cases). Interestingly, mutations in UTX were more frequent in low-grade tumors, suggesting that UTX-dependent epigenetic changes may play a role in the initiation of TCC. Two genes encoding histone acetyltransferases, CREBBP and EP300, and ARIDIA, encoding a subunit of the SWI/SNF nucleosome remodeling complex, were each mutated in 13% of TCCs, occurring more frequently than RB1, FGFR3, HRAS, or KRAS mutations. Loss-of-function mutations accounted for the majority of these lesions, implicating chromatin-modifying proteins as tumor suppressors in transitional cell cancers. Notably, mutations in ARIDIA and another SWI/SNF subunit, PBRM1, have respectively been identified in ovarian and renal clear cell carcinomas, hinting at a broader role of chromatin remodelers in tumor suppression. In total, 59% of TCCs had mutations in a chromatin remodeling gene, indicating that development of these tumors may especially depend on an altered epigenetic landscape. Therapeutic agents that reverse epigenetic modifications may therefore be efficacious in the treatment of bladder cancer.


CYTOKINE-GENERATED CONTRACTILITY DRIVES TUMOR CELL MIGRATION

The force generated by actin and myosin (actomyosin) contractility is crucial for tumor cell migration. Highly contractile tumor cells move in a rounded, “amoeboid” manner due to an ability to deform the extracellular matrix and associate with entry into the blood supply. Contractile force is also required for stromal cells to remodel the extracellular matrix and create tracks along which aggregates of cancer cells can invade surrounding tissue. However, the signaling pathways responsible for generation of actomyosin contractility in tumor and stromal cells are not well characterized. A collaboration of the Marshall and Gaggioli groups now demonstrates that JAK1-mediated cytokine signaling, a component of the inflammatory response, regulates contractile forces in both tumor and stromal cells. In response to inflammation, cytokine receptors activate JAK1, which phosphorylates multiple substrates, including STAT transcription factors. Phosphorylation of regulatory myosin light-chain 2 (MLC2), which is required for myosin II-mediated contraction, also occurs downstream of JAK1, and plays a role in actomyosin contractility and migration in squamous cell carcinoma and melanoma cell lines. Interestingly, the Rho kinase ROCK, a known contributor to actomyosin contractility, is required for STAT3 phosphorylation and activation, suggesting that a positive feedback mechanism drives cell contractility and cytokine signaling. To determine the clinical relevance of these findings, STAT3 expression and cell morphology was assayed in 19 primary human melanomas and 16 metastases. High STAT3 expression was associated with a contractile phenotype, demonstrated by a round cell morphology. Round cells with high STAT3 intensity predominated at the invasive front of tumors and often comprised the majority of metastases. These findings extend our understanding of the link between inflammation and cancer and identify potential therapeutic targets for metastatic cancers.

Cytokine-Generated Contractility Drives Tumor Cell Migration


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