Dissecting NUP-regulated pathways in aggressive prostate cancer.

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Background: Nuclear aberrations such as nuclear pore (NPC), envelope and chromosomal defects are a hallmark of aggressive human tumors. However, the underlying source of these errors and their contribution to cancer pathogenesis remain poorly understood. Nucleoporins (NUPS) are the protein components of NPCs, and play key roles in nuclear transport, transcription and genome integrity, processes that can be impaired when the molecular identity of the NPC is compromised. Our recent work unveiled NPC deregulation promotes lethal prostate cancer and identified POM121 as a key contributor, which enhances nuclear transport of transcription factors considered drivers of aggressive disease. Based on current and previous findings showing that NPCs regulate chromosomal stability in human cells we are further investigating the role of NPC in genome integrity maintenance in prostate cancer.
Methods: We utilize cell experimental models of prostate cancer, which we interrogate through gene expression and functional assays including single-cell live imaging, immunofluorescence, qRT-PCR, RNAseq and ChIP. We combine our analysis with publicly available patient databases to determine clinically relevant pathways. Further validation includes analysis of tumor tissue samples and preclinical models of aggressive disease.
Results: Our data suggest that NPCs are important hubs regulating expression of genes important for mitotic fidelity and centrosome biology. We are functionally dissecting actionable components of these pathways to define novel biomarkers and targetable avenues for aggressive prostate cancer. We have also found that off-pore NUPS play a role in prostate cancer cell biology by direct chromatin binding. Future work will address the specific contribution of NPC-associated and soluble NUPS to advanced prostate cancer.
Conclusions: NUP-regulated pathways play a role in aggressive prostate cancer and may inform on novel targetable mechanisms and biomarkers for aggressive disease.

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