Nuclear pore composition contributes to prostate cancer progression.

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Nuclear abnormalities such as nuclear pore (NPC), envelope and chromosomal defects are frequent in human tumors, and correlate with aggressiveness. However, the underlying mechanisms inducing these errors and their contribution to cancer pathogenesis remain poorly understood. Nucleoporins (Nups) are the main building blocks of NPCs, and play essential functions in nuclear transport, transcription and genome integrity in the eukaryotic cell, processes that can be impaired when the molecular identity of the NPC is compromised. Here we investigated the specific Nups and Nup-based mechanisms promoting lethal prostate cancer. Interrogation of public transcriptomic patient datasets and experimental models identified striking evolutionary changes in NPC composition during prostate cancer disease progression towards a lethal state and identified POM121 as a key contributor to the aggressiveness of prostate cancer cells. Importantly, POM121 transcriptomic studies enriched for gene signatures of important oncogenic and cell cycle control pathways. Mechanistically, we observed POM121 enhanced the nuclear transport and signaling activity of MYC, E2F1, AR and GATA2 transcription factors through direct Importin β interaction. These studies uncovered a pharmacologically targetable axis that when inhibited decreased tumor growth, restored efficacy of standard-of-care therapy and improved survival in pre-clinical models. These findings revealed a mechanism that promotes the signaling activity of oncogenic and PC related transcription factors, providing a rationale for NPC-import targeting as a therapeutic option in advanced lethal prostate cancer. Based on our current and previous findings showing that NPCs regulate chromosomal stability pathways in human cells we are currently investigating the mechanistic role of NPC components and genome integrity maintenance pathways in prostate cancer.

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