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Nuclear receptor subfamily 4A2: Novel role and a potential therapeutic lead in cancers.

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Background: Perineural invasion (PNI) is a pathological process where cancer cells infiltrate surrounding nerve tissues, markedly increasing the risk of cancer recurrence, metastasis, post-surgical complications, and associated pain. Alarmingly, PNI is prevalent in 80 - 100% of Head and Neck Squamous Carcinoma (HNSCC) and Pancreatic Ductal Adenocarcinoma (PDAC) cases. In these tumors, nerve invasion often occurs as a distinct route of metastasis, bypassing the usual lymphatic or vascular routes. Despite the rigor of surgical interventions and post-operative radiation, PNI-associated tumors recurrently manifest, emphasizing an urgent need to elucidate the underlying molecular interplay between tumor cells and nerves. **Methods:** Our study focuses on the Nuclear receptor subfamily 4A2 (NR4A2) transcription factor, known for its pivotal roles in cellular homeostasis and response to pathological conditions. **Results:** Comprehensive analyses employing tissue microarrays, curated public datasets, and cell lines unveiled a consistent overexpression of NR4A2 in HNSCC and PDAC tumor cells compared to their normal counterparts. Intriguingly, genome-wide chromatin immunoprecipitation (ChIP) sequencing with an NR4A2-specific antibody highlighted an enrichment of genes linked to neuronal guidance, suggesting a probable NR4A2-mediated mechanism underpinning PNI. Further, an in-depth analysis of these ChIP-enriched neuronal genes using The Cancer Genome Atlas (TCGA) confirmed their heightened expression in HNSCC and PDAC tumor tissues relative to healthy tissues. Advancing our research with graph neural networks and sophisticated bioinformatics, we identified two potent lead compounds targeting NR4A2. Preliminary Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) assessments of these compounds indicate favorable safety and efficacy profiles for clinical application. We are currently conducting comprehensive evaluations of these compounds, deciphering their molecular mode of action and therapeutic potential in cell culture and animal models. **Conclusions:** To sum up, our findings reveal a yet unknown role of NR4A2 in the landscape of PNI in HNSCC and PDAC. The AI-driven discovery and ensuing validation of NR4A2-centric inhibitors present a novel therapeutic avenue to curb cancer progression, prevent metastasis, and potentially improve patient outcomes. Research Sponsor: None.