Background: In its later stages prostate cancer (PC) is often characterized by neuroendocrine features, an evolution that has led to use of the term neuroendocrine prostate cancer (NEPC) – a variant commonly treated with platinum containing regimens, that is nearly always fatal, allowing one to characterize NEPC as a disease with unmet therapy needs. Although clinically and biologically heterogenous, NEPC are histologically similar to other neuroendocrine carcinomas (NECs) and express neuroendocrine markers including chromogranin and the somatostatin receptor (SSTR), suggesting SSTR-targeting agents such as lanreotide, octreotide, or Lutathera (^{177}Lutetium 177-DOTATATE) may offer therapeutic benefit. While we lack a consensus on how NEPC emerges, animal models and clinical data are gradually providing a greater understanding including evidence of frequent inactivation of TP53 and PTEN. Increasing evidence points to NEPC as a treatment emergent histologic subtype following treatment with an androgen receptor-targeting agent, such as abiraterone, enzalutamide or darolutamide. While the fraction of men who develop this invariably aggressive and lethal complication is uncertain, some studies suggest as many as 17% of all men whose tumors develop resistance to an androgen receptor–targeting agent will acquire this phenotype. Differences in estimates likely reflect both gradual evolution of the tumor neuroendocrine phenotype and our ability to detect it molecularly. Those confirmed histologically clearly represent a more distinct phenotype, while detection in DNA via a molecular signature may be more sensitive and detect the phenotype earlier in its evolution. Our analysis of the data suggests this is the case.
Materials and Methods / Experimental Approach: Standard RNA expression analysis and Virtual Inference of Protein-activity by Enriched Regulon Analysis (VIPER) analysis.
Results: NEPC express very high levels of the SSTR – most notably SSTR2. Using a pan-cancer (mostly TCGA) output as the reference point, SSTR2 is shown to be universally over-expressed in NEPC, with very high levels in small cell tumors. The levels of expression in NEPC are exceeded only by that in tumors we recognize as neuroendocrine, including common neuroendocrine tumors (NETs) arising from diverse tissues, meningiomas and pheochromocytomas / paragangliomas. Importantly, the levels are much higher than those in *de novo* PCs. Additionally, using a VIPER analysis strategy to infer functional protein levels, VIPER-inferred SSTR2 activity levels were comparable to those of mRNA expression, with only a few outliers. As observed with mRNA expression, VIPER analysis also confirms NPEC as amongst the few cohorts that demonstrate functional SSTR2 at very high levels and similarly at much higher levels than *de novo* PCs. While high SSTR levels can be detected in nearly all NEPC characterized molecularly, our analysis also finds increased SSTR2 expression in many PC samples not classified as neuroendocrine by either histology or gene expression signatures. Since this is not seen in treatment-naive PC samples in TCGA, it suggests SSTR2 expression in more advanced PC may precede overt morphological features of neuroendocrine differentiation. Finally, in preliminary experiments we examined the activity of peptide-derived drug conjugates targeting the somatostatin receptor in four NEPC models: PC3, LASCPC-01, NCI-H660, and murine NEPC organoids derived from tumors arising in NPp53 mice, a genetically engineered mouse (GEM) model with combined inactivation of TP53 and PTEN. In these assays we found marked sensitivity to our peptide drug conjugates.

Conclusions: The totality of the data suggests SSTR is likely to be broadly expressed in NEPC, implicating it as an important therapeutic target. Note here an important contrast with what occurs in the context of more traditional NECs, where SSTR expression is lower or even absent in the more advanced, aggressive and lethal high-grade tumors. The data further suggest NEPC gradually emerges with SSTR expression appearing with development of resistance to an androgen receptor (AR)-targeting agent as AR expression disappears. Because enzalutamide, apalutamide and darolutamide are increasingly being used clinically in earlier settings, one can be concerned this neuroendocrine proclivity may occur earlier in the history of treated PC. This possibility adds some urgency to addressing this unmet need. Finally, the marked sensitivity to our peptide drug conjugates suggests the SSTR can be exploited as a target in NEPC.

Lay Abstract

As prostate cancer evolves it often develops neuroendocrine features, and is referred to as neuroendocrine prostate cancer. We commonly treat this variant with platinum containing regimens, but unfortunately it is nearly always fatal, allowing one to characterize neuroendocrine prostate cancer as a disease with unmet therapy needs. Although clinically and biologically very diverse, neuroendocrine prostate cancer are histologically similar to other neuroendocrine carcinomas and express neuroendocrine markers including chromogranin and the somatostatin receptor (SSTR), suggesting somatostatin receptor-targeting agents such as lanreotide, octreotide, or Lutathera (^{177}Lutetium 177-DOTATATE) may offer therapeutic benefit. While the fraction of men who develop this invariably aggressive and lethal complication is uncertain, some studies suggest as many as 17% of all men with prostate cancer will acquire this phenotype. We have characterized neuroendocrine prostate cancer at a molecular level and find it to be both unique and similar to the more common neuroendocrine cancers. The totality of the data suggests the somatostatin receptor is likely to be found in the majority of neuroendocrine prostate cancer, implicating it as an important therapeutic target. Note here an important contrast with what occurs in the context of more traditional neuroendocrine cancers, where expression of the somatostatin receptor is lower or even absent in the more advanced, aggressive and lethal high-grade tumors. The data further suggest that neuroendocrine prostate cancer gradually emerges with somatostatin receptor expression appearing with development of resistance to a commonly used androgen receptor-targeting agents. Because the latter are increasingly being used clinically in earlier settings, one can be concerned this neuroendocrine proclivity may occur earlier in the history of treated prostate cancer. This possibility adds some urgency to addressing this unmet need. Finally, marked sensitivity to peptide drug conjugates which we have developed to target the somatostatin receptor suggests the somatostatin receptor can be exploited as a target in neuroendocrine prostate cancer.

a. a critical question or barrier to progress in the field and why it is important.
b. how the proposed study addresses it.
c. how the study affects the way we understand or treat NETs.