CLINICAL INVESTIGATION

Prostate Cancer Cell Lines Treated with Hydralazine and Panobinostat have less Malignant properties

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Introduction

Prostate Cancer (PCa) is the second most frequent malignancy in males and the fifth leading cause of death from cancer worldwide. More than 80% of PCa cases are now identified as localised illnesses, but up to a third of these individuals will experience recurrence and progression in the future. Androgen Deprivation Therapy (ADT) is the most prevalent treatment for advanced PCa because androgens and Androgen Receptor (AR) signalling are so important in normal prostate development and PCa progression. Despite an early response to ADT, patients usually become resistant and progress to Castration-Resistant Prostate Cancer (CRPC) between 12 months and 30 months. Despite the fact that next-generation androgen signalling inhibitors have improved the prognosis, these patients still lack curative drugs, necessitating the urgent development of novel therapeutic approaches.

There are various and intricate molecular mechanisms that lead to the development of CRPC. Epigenetic dysregulation has been shown to be a prominent factor in PCa, as well as other cancer types. By reducing gene silence, which contributes to ADT resistance, DNA Methyltransferases Inhibitors (DNMTIs) may re-sensitize malignant cells to antineoplastic medicines. Changes in specific histone marks, on the other hand, characterise the epigenetic profile of PCa, impacting key signalling pathways and transcriptional regulation and thereby contributing to prostate cancer. Histone Deacetylases (HDAC) regulate a number of genes in prostate cells, including AR. Furthermore, HDAC inhibitors (HDACIs) impede histone deacetylation, resulting in a more open chromatin structure that allows for DNA access and, as a result, DNMTis to reverse epigenetically silenced genes.

HDACIs are being explored in CRPC and chemotherapy-resistant PCa patients due to their impact on histone modifications. Although the intrinsic toxicity of DNMTIs and HDACIs did not support their use as single agents in clinical studies for the treatment of CRPC, data in pancreatic, lung, and breast cancer models suggest that utilising both epidrugs at the same time is more effective than using each epidrug separately.

So far, the FDA has approved two epigenetic drugs that target DNA Methyltransferases (DNMT) and four epigenetic treatments that target Histone Deacetylase (HDAC). Cedazuridine, a DNMTI/cytidine deaminase inhibitor combo, was recently approved for the treatment of myelodysplastic syndromes and chronic myelomonocytic leukaemia. Multiple solid tumour clinical trials are now underway, despite the fact that DNMTIs and HDACIs are only licenced for haematological malignancies. Both FDA approved DNMT inhibitors, 5-azacytidine (5-Aza-CR) and (5-Aza-CdR), are nucleoside analogues that are integrated into DNA and demethylate DNMTs by covalently sequestering them. However, this inclusion has a stronger effect in proliferative tumours than indolent tumours because it is dependent on DNA replication. PCa belongs to the second group, which could explain why clinical trials of 5-Aza-CR for CRPC reported no significant benefits for patients.

Hydralazine hydrochloride, an FDA approved medication for severe hypertension and heart failure, has also been investigated as a cancer treatment. Several in vitro studies in cancer cell lines and real tumours revealed that hydralazine has DNMTI properties and can restore the expression of Tumour Suppressor Genes (TSG) that have been suppressed by promoter hypermethylation without producing significant cytotoxicity. Hydralazine is a non-nucleoside analogue that targets the DNMT1A and DNMT3A/3B catalytic regions without integrating itself into DNA. Hydralazine's efficacy in treating solid tumours such as cervical, breast, lung, and ovarian cancer has already been demonstrated in clinical trials. Almost all of the previously mentioned clinical trials used hydralazine in

combination with valproic acid, a treatment approach that increased therapeutic efficacy in vitro while simultaneously triggering TSG reactivation. Antiepileptic medication valproic acid is also used to treat bipolar disorder. It's a fatty acid inhibitor with a short-chain.

We expected that epidrugs could be an effective treatment for advanced PCa patients because DNMTs are known to be increased in the disease. The study focused on the DNMTI hydralazine, as well as the HDACIs panobinostat and valproic acid. As a result, we sought to see how effective these epigenetic therapies were in PCa cell lines, both alone and in conjunction with other treatments. This is the first study that we are aware of that looks at the effects of hydralazine and panobinostat in human PCa cells combined.