

Targeting the tumor-associated autoantigen alpha-enolase in prostate cancer

Prostate cancer (PCa) is the most commonly diagnosed cancer and is the second leading cause of cancer-related deaths in American men. African American (AA) men are more likely to be diagnosed with more aggressive PCa at a younger age and twice as likely to die from the disease as European American (EA) men. In order to reduce PCa disparities and mortality, there is a critical need to identify and target pathways that drive molecular processes responsible for PCa aggressiveness. An unexplored target is the plasminogen system, a biological pathway that is key to PCa cellular migration and tissue invasion during metastasis. During inflammation, activation of the plasminogen pathway degrades extracellular fibrin networks. In the context of cancer, this activation promotes cancer tissue invasion and metastasis. Mounting evidence shows that alpha-enolase plays a vital role in not only increased energy metabolism but also plasminogen activation during cancer progression and metastasis. In our preliminary studies using immunoseroproteomic profiling of AA and EA men with PCa, we identified PCa tumor-associated autoantigens from members of the glycolysis and plasminogen pathways including ENO1, annexin A2, fructose biphosphate aldolase, glucose-regulated protein 78 kD, glyceraldehyde-3-phosphate dehydrogenase and phosphoglycerate kinase. In a large cohort of PCa sera (N=157) compared to non-PCa sera (N=183), we found a significantly higher frequency of autoantibodies to ENO1 in patients with PCa ($p<0.05$). Surprisingly, when we probed a panel of non-PCa and PCa cell lines with AA and EA anti-ENO1 positive sera, we saw increased immunoreactivity in metastatic PCa cells and a decrease in docetaxel-resistant cell lines that was associated only with the AA-PCa sera. The anti-ENO1 EA-PCa sera and a commercial monoclonal anti-ENO1 showed uniform immunoreactivity across the same panel cell lines suggesting the cohort of AA patients with PCa are producing autoantibodies to a different ENO1 protein than the EA patients with PCa. ENO1 proteomic analysis of post-translational modifications showed there are differences in ENO1 in the parental PC3 metastatic cell line compared to the PC3 docetaxel-resistant cell lines. Given that ENO1 is up-regulated in PCa tissue, its role in glucose metabolism and plasminogen activation during cancer, and that the immune system of a cohort of AA-PCa patients are recognizing an alternate form of ENO1 that is upregulated in metastatic PCa, we elected to target ENO1 in metastatic cell lines. ENO1 siRNA knockdown studies in a PC3 bone metastatic PCa cell line showed increased cell death and decreased proliferation indicating ENO1 is promising target for chemotherapy in metastasis, and using immunoproteomic approaches is a valid tool to identify new therapeutic pathways.