PSMA IS A UNIQUE FOLATE HYDROLASE AND THERAPEUTIC TARGET IN TUMORS.

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The human prostate is unique in the types of proteins that it produces in high concentration. PSA, prostate specific antigen and PAP, prostatic acid phosphatase are found in high concentrations in the normal and tumorous prostates and are found in the serum of patients with prostate cancer. Like most differentiated products produced by normal prostate cells these prostate biomarkers decrease in amount in cancers relative to their production by normal cells. Our laboratory cloned the gene that encodes a protein that we designated prostate-specific membrane antigen, PSMA. PSMA is also produced in high concentrations by the normal prostate, but unlike the other proteins, it is further increased in prostate cancer.

We established that PSMA functioned as a glutamate preferring carboxypeptidase that hydrolyzed glutamate from peptide linkages of polygammaglutamated folic acid. Thus PSMA is a unique folate hydrolase. In order for humans to use the vitamin folate from food sources the PSMA enzyme is required to remove the glutamates from polygammaglutamated folate before the intestinal folate transporters can extract folate from the digestive tract. Inside the cell, polygammaglutamates prevents the folate from being able to readily diffuse through the membrane of the cell, thus trapping folate inside the cell. We also determined that in the prostate there was an alternatively spliced version of PSMA, PSMA'. PSMA' was shorter and was lacking the transmembrane domain and the intracellular domain of PSMA. Indeed PSMA' protein is found inside the cytoplasm of the cell. Inside of the cell, PSMA still serves as a folate hydrolase. This has implications for the prostate because PSMA can keep folate in the "free" form and free folate can diffuse from the cell. Thus the prostate because of its high content of PSMA' is a tissue at risk for "micro environmental" folate deficiency. In men, the prostate is the most common site for development of cancer, indeed nearly 50% of men by the age of 50 will have microscopic foci of prostate cancers, scattered in their prostates. Folate deficiency, even relative deficiency, is a state which increases the cells susceptibility to DNA damage by DNA damaging agents, increasing double strand breaks in DNA. We hypothesize that PSMA plays a part in this high level of cancer in the prostate. Mice don't ordinarily develop cancer in their prostates. Neither do they express the mouse homologue for PSMA in their prostates. We have used prostate-specific promoters to develop transgenic animals expressing PSMA in their prostates and are currently exploring how this changes the folate environment and cancer susceptibility of the prostate cell.

In the normal prostate the dominant mRNA encodes for the cytosolic form of PSMA, while in the cancer cell the predominant expressed mRNA encodes for the membrane form of PSMA with the folate hydrolase activity outside of the cell. It is not clear why this happens. We are currently exploring ways to develop ligands to target the extracellular portion of PSMA. These targeting ligands may be even more useful than strictly as potential treatments for prostate cancer, since we discovered that another site in which PSMA is strongly expressed is in the tumor associated vasculature of all solid tumors. Because the solid tumors, lung, breast, colon, melanoma, head and neck, bladder, kidney, brain, etc, all require blood vessel for growth, it is considered that the tumor associated vasculature represents a common "Achilles Heel" target for these cancers. Antibodies against the external domain of PSMA carrying radiation or cytotoxics are proving very effective in imaging prostate cancer and have generated some dramatic tumor regressions in early clinical trials, thus providing additional encouragement that further therapeutic ligand development of target for PSMA will be useful clinically.

We are exploring the control of PSMA gene expression as well. We have found that there are two highly homologous genes on chromosome 11, with PSMA being found on chromosome 11p11.2 and a PSMA-like gene residing on 11q14. The homology between these human genes is 97%.

We have identified an enhancer region responsible for PSMA's strong expression in LNCaP prostatic tumor cells. Because of the exceptional increase in activity provided by the PSMA promoter/enhancer in prostate cancer we are utilizing it in the creation of new gene therapy strategies for preclinical development of cancer specific gene therapies.