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Prostate cancer progression attributed to autonomic nerve development

Potential for therapeutic prevention of localized and metastatic disease

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Abbreviations: PCa, prostate cancer; SNS, sympathetic nervous system; PNS, parasympathetic nervous system; PIN, prostatic intraepithelial neoplasia; *Ard*β*2* *Ard*β*3*, β_2- and β_3-adrenergic receptors; Chrm1, cholinergic receptor, muscarinic 1; 6OHDA, 6-hydroxydopamine; Carb, carbachol; PZP, pirenzepine; BPH, benign prostatic hyperplasia

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In a study recently published in *Science*, Magnon et al. show that both the sympathetic and parasympathetic components of the autonomic nervous system play an integral part in the development and dissemination of prostate cancer (PCa). Inhibition of the sympathetic nervous system (SNS) and disruption of the adrenergic receptors, specifically *Ard*β*2*, resulted in the prevention of primary PCa tumor development in mice. The authors found that inhibition of the SNS is only successful in preventing murine tumor development if completed early enough, and the parasympathetic nervous system (PNS) predominates in later stages of PCa. Inhibition of the PNS by way of the cholinergic receptor, muscarinic 1 (Chrm1), caused mice to develop less metastases to the pelvic lymph nodes, intestines, and bones. A PCa progression scheme has been outlined where initial tumor engraftment is controlled by the SNS but then becomes less prominent than the PNS, which promotes metastasis. The investigators showed the dependence of the autonomic nervous system on development of PCa and present opportunities for prevention; further studies are needed to confirm these results in humans.

Perineural invasion, the migration of tumor cells along nerves, and neurogenesis, the development of nerves in or near cancer tissue, has been shown to occur in several epithelial cancers and correlates with poor prognosis in patients with cancer.[1-4] Along with poor prognosis, neurogenesis is correlated with aggressiveness and recurrence of prostate cancer.[4] Retrospective analysis of clinical observations has suggested that patients taking β-blockers have lower mortality in various solid tumors, including melanoma, breast, and prostate cancers.[5] This observation suggests that the autonomic nervous system plays an important role in carcinogenesis, including development of primary tumors, dissemination of the tumor, and ultimately tumor cell invasion and metastasis.[5-8] Magnon et al. show in a study recently published in *Science* that both the sympathetic and parasympathetic components of the autonomic nervous system play an integral part in the initial development and dissemination of prostate cancer (PCa), respectively.[5]

It was hypothesized that the adrenergic fibers of the sympathetic nervous system (SNS) innervate and promote PCa tumorigenesis. To study the initial engraftment and development of localized PCa, the inhibition of the SNS by way of the β_2- and β_3-adrenergic receptors (*Ard*β*2, Ard*β*3*) either by genetic modification (deletion of both *Ard*β*2* and *Ard*β*3*), pharmacologic inhibition of *Ard*β*2* with 6-hydroxydopamine (6OHDA), or surgical ablation of the hypogastric nerves, was investigated in 6- to 8-week-old mice. Intensity of bioluminescence was measured in these mice and disruption of the adrenergic receptors, specifically *Ard*β*2*, resulted in the prevention of primary PCa tumor development.

Inhibition of the SNS was found to only be successful in preventing murine tumor development if initiated early enough. The study utilized Hi-Myc transgenic mice, which develop prostatic

intraepithelial neoplasia (PIN) at a faster rate than wild-type mice. Mice that underwent pharmacologic treatment of 6OHDA or surgical hypogastric nerve ablation before 2 months of age did not develop tumors, while mice treated at ages older than 2 months would still develop tumors regardless of time to treatment or type of treatment. Because these results show that the SNS predominates in the early stages of tumor development, the transition to which the parasympathetic nervous system (PNS) controls PCa progression was explored.

To demonstrate that the PNS takes over in later stages of PCa development, luciferase intensity in mouse xenografts was compared with luciferase intensity in pelvic lymph nodes (representing metastases) under different conditions. When the cholinergic receptor, muscarinic 1 (Chrm1), was knocked out, mice still developed the same sized primary tumors as mice containing the functional gene, indicating that the PNS is not involved in initial engraftment. When the same mice were treated with carbachol (Carb), a non-selective cholinergic muscarinic receptor agonist, Chrm1-positive mice developed more metastasis in the pelvic lymph nodes than Chrm1-knockout mice. However, Carb-induced malignant progression was completely inhibited with pharmacologic inhibition or genetic deletion of Chrm1.[5]

Magnon et al. further investigated the development of metastasis under the control of Chrm1 by imaging distant organs after treating Chrm1-positive and -negative mice with Carb and Chrm1 antagonists. Chrm1-negative mice and Chrm1-positive mice treated with pirenzepine (PZP), a Chrm1 selective antagonist, did not develop intestinal metastasis and exhibited prolonged survival. In humans, osteoblastic bone lesions are the most common site of PCa metastasis. The development of bone metastasis in Chrm1-positive and -negative Hi-Myc mice was examined by FDG-PET imaging, and Chrm1-positive mice developed one to three more bone metastases than Chrm1-negative mice, which did not to develop any detectable metastases.

To show how the findings of this study relate to men with prostate cancer, formalin-fixed paraffin-embedded radical prostatectomies were analyzed. Adrenergic fibers from the SNS were only found in normal prostate tissue, but cholinergic fibers from the PNS were only present in the tumor tissue.[5] This finding suggests that the SNS innervates locations where tumor engraftment will occur and the PNS innervates locations where tumor has already developed in order to signal the tumor to disseminate.

This study presents a mechanism for the development of prostate cancer, dissemination of the tumor, and ultimately the development of metastases. PIN development is controlled by the SNS with adrenergic nerves that are innervated into the basement membrane of normal prostate tissue and cause activation of *Ardβ2* and *Ardβ3* by norepinephrine. As PCa progresses, the SNS becomes less prominent than the PNS. The PNS innervates the stroma of the tumor, where Chrm1 is activated by acetylcholine, leading to metastasis.

These data give valuable insight into the development of PCa and the potential clinical opportunities in PCa prevention. One wonders whether commonly used anti-adrenergic drugs, such as β-blockers, could be used to prevent the initial development of localized disease in humans. Patients with PCa are commonly treated with α1-antagonists for the relief of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH), which affects approximately 70% of men over age 70.[9,10] Should further investigation of β-blockers in the prevention of PCa progress to clinical studies, the potential pharmacologic interaction between β-blockers and α-blockers must be considered, as concomitant use of β-blockers with α-1 antagonists may result in an exaggerated hypotensive response.

This study also raises the question whether it would be possible to prevent metastasis by giving PZP to patients with localized disease. This may prove difficult due to the lack of understanding concerning the transition of SNS to PNS control in PCa progression. Because the activation and inhibition of cholinergic signaling experiments were conducted concurrently, it is unknown if a PNS signaling inhibitor would have an effect on already developed metastases. At a certain point, inhibiting SNS signaling is ineffective in tumor engraftment; it is possible that there is a point where PNS signaling inhibition is no longer effective in preventing metastasis as well. Given these results, Magnon et al. show the neurological dependence on the development of PCa and present potential molecular targets for preventative therapy. Further studies must be completed to confirm these results in humans.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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