Inflammation and prostate cancer

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There is emerging evidence that prostate inflammation may contribute to prostatic carcinogenesis. Chronic inflammation has been associated with the development of malignancy in several other organs such as esophagus, stomach, colon, liver and urinary bladder. Inflammation is thought to incite carcinogenesis by causing cell and genome damage, promoting cellular turnover, and creating a tissue microenvironment that can enhance cell replication, angiogenesis and tissue repair. Epidemiological data have correlated prostatitis and sexually transmitted diseases with an increased risk of prostate cancer and intake of anti-inflammatory drugs and antioxidants with a decreased risk. Evidence from genetic and molecular studies also support the hypothesis that prostate inflammation and/or infection may be a cause of prostate cancer. In 1999 De Marzo et al proposed that proliferative inflammatory atrophy (PIA) is a precursor to PIN and cancer. Further research will provide opportunities for the discovery and development of strategies for treatment and prevention of prostate cancer.

Key Words: prostate cancer, inflammation, proliferative inflammatory atrophy, prostatic carcinogenesis

Chronic inflammation has been associated with the development of malignancies in several organs, including the esophagus, stomach, colon, liver and urinary bladder. Inflammation is thought to incite carcinogenesis by

(i) causing cell and genome damage,
(ii) promoting cellular turnover and
(iii) creating a tissue microenvironment rich in growth factors and cytokines that can enhance cell replication, angiogenesis and tissue repair.

Several epidemiological studies have suggested an increased risk of prostate cancer in patients with a clinical history of prostatitis. The difficulty with such studies is that prostatitis is ubiquitous and that men with symptomatic prostatitis are more likely to be diagnosed with prostate cancer. Despite these limitations, a recent meta-analysis found a small increase in the relative risk of prostate cancer in men with a prior history of clinical or symptomatic prostatitis.

There is a known increased risk of prostate cancer associated with a clinical history of STIs – gonorrhea and syphilis and more recently, HPV, CMV, and HSV. Infection with HPV 16 and 18 have been found to be risk factors. Recent epidemiological studies have looked at associations between STIs and prostate cancer by serology. One study found a statistically significant higher risk of prostate cancer among HPV-16 seropositive and HPV-18 seropositive men, known high-risk serotypes for cervical cancer.

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Changes in the activity of proteins encoded by genes involved in the immune response may result in an impaired ability to fight infection. This may result in infection-mediated damage, chronic persistent infection and consequently chronic inflammation. Genetic studies have identified RNASEL, encoding an interferon-inducible ribonuclease and MSR1, encoding subunits of the macrophage scavenger receptor, as inherited susceptibility genes for familial prostate cancer. The RNASEL gene encodes a latent endoribonuclease that is involved in interferon-induced RNA degradation. Once activated by interferon, cells with a RNASEL gene produce an enzyme that degrades single-stranded RNA leading to apoptosis. This is thought to be one mechanism that cells use to fight viral infections.

Besides infection, the decreased risk of prostate cancer associated with NSAID use and the apparent protective effective of anti-oxidants such as vitamin E, selenium and lycopene, also support a possible association between inflammation and prostate cancer.

In 1999 De Marzo et al proposed that "proliferative inflammatory atrophy" is a precursor to PIN and prostate cancer. Proliferative inflammatory atrophy (PIA) refers to focal atrophic lesions that are associated with inflammation. PIA occurs in the periphery of the prostate where cancers most commonly arise. PIA lesions are often directly adjacent to lesions of PIN and/or cancer and contain similar somatic genomic abnormalities. Their association with chronic inflammation suggests that these lesions arise as a result of the regenerative proliferation of prostate epithelial cells in response to injury caused by inflammatory oxidants. Staining for proliferation associated markers supports this: PIA luminal cells show increased Ki-67 and BCL-2 expression. They also show molecular signs of stress: high levels of GSTP1, GSTA1 and COX-2.

Chronic insult to normal prostate epithelial cells due to infection, ischemia or a toxin, can result in the influx of macrophages and lymphocytes. These inflammatory cells may produce reactive oxygen and nitrogen species that can cause epithelial damage.

GSTP1 is a detoxification enzyme that has decreased expression in almost all prostate cancer cells. In normal prostate epithelium, GSTP1 expression is generally confined to the basal cell compartment. Benign luminal cells may be induced to express GSTP1 in response to environmental stress, a finding characteristic of PIA.

Hypermethylation of the GSTP1 promoter CpG island results in inactivation of GSTP1, leaving cells vulnerable to oxidative DNA damage. Loss of GSTP1 may define the transition from PIA to PIN or prostate cancer. In a recent study by Nakayama et al, hypermethylation was found in 91% of adenocarcinoma lesions and 69% of high-grade PIN lesions in contrast to 6% of PIA lesions.

Conclusion

There is emerging evidence that prostate inflammation may contribute to prostatic carcinogenesis. Further research will provide opportunities for the discovery and development of strategies for treatment and prevention. □

References

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