INFLAMMATION AND PROSTATIC CARCINOGENESIS - A MORPHOLOGICAL STUDY OF THE HUMAN PROSTATE

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av

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Avhandlingen baseras på följande delarbeten:

I. Wanzhong Wang, Anders Bergh, and Jan-Erik Damber. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. *The Prostate 61:60 - 72 (2004).*

II. Wanzhong Wang, Anders Bergh, and Jan-Erik Damber. Cyclooxygenase-2 expression correlates with local chronic inflammation and tumor neovascularization in human prostate cancer. *Clin Cancer Res 11:3250 - 3256 (2005).*

III. Wanzhong Wang, Anders Bergh, and Jan-Erik Damber. Increased expression of CCAAT/enhancer-binding protein beta in proliferative inflammatory atrophy of the prostate: relation with the expression of COX-2, the androgen receptor, and presence of focal chronic inflammation. *The Prostate 67:1238 -1246 (2007).*

IV. Wanzhong Wang, Anders Bergh, and Jan-Erik Damber. Morphological evidence for the transition of proliferative inflammatory atrophy to high grade prostatic intraepithelial neoplasia and prostate carcinoma. *Manuscript.*

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INFLAMMATION AND PROSTATIC CARCINOGENESIS – A MORPHOLOGICAL STUDY OF THE HUMAN PROSTATE

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ABSTRACT: Chronic inflammation has been suggested to be linked to cancers. Inflammatory infiltrates are often found in and around foci of prostatic atrophy. These foci, called proliferative inflammatory atrophy (PIA), are proposed as precursors of prostate cancer (PCa) or prostatic intraepithelial neoplasia (PIN). Up-regulated cyclooxygenase-2 (COX-2) may play a role in influencing cell proliferation, differentiation, apoptosis, and angiogenesis. In the present studies, we found that COX-2 was overexpressed in the PIA lesions. Epithelium in these PIA lesions had high proliferation index and increased level of anti-apoptosis protein Bcl-2. The association between COX-2 and the focal chronic inflammation, dominant T-lymphocytes and macrophages infiltration, was clearly shown. This study suggests that chronic inflammation and the related oxidative stress might play crucial roles in inducing COX-2 overexpression, which could be involved in the pathogenesis of prostate disorders.

Transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) plays a major role during the initial stage of COX-2 transcription. In the present study we report a novel finding that C/EBPβ was overexpressed in PIA lesions and in relation to COX-2. The data also demonstrates that chronic inflammation appeared to play a role in inducing C/EBPβ expression in atrophic prostate epithelial cells.

Using a similar technique, we investigated COX-2 expression in human PCa tissue and found that COX-2 expression correlated with Gleason score. The focal chronic inflammation in the cancer areas seems to induce COX-2 expression, since the COX-2 expression was significantly related to inflammation density. This study provides the first evidence of a direct link between COX-2 and angiogenesis in PCa tissues.

Morphological transition from PIA to HGPIN and PCa was found in radical prostatectomy specimens, although it was not very common. Atrophic epithelial cells are easy to recognize and clearly delineated by CK5 and GSTP1 immunostaining. One striking finding of this study is that clusters of cells that show nuclear atypia were found in some PIA lesions. Such focal atypical epithelial cells fulfil the criteria for HGPIN and expressed both CK5 and GSTP1. This study suggests that PIA lesions may develop into HGPIN and prostate cancer directly or via some intermediate process.

Key words: prostate, carcinogenesis, chronic inflammation, atrophy, morphology, immunohistochemistry

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