Loss of the Tumor Suppressor NKX3.1 in Prostate Cancer Cells is induced by Prostatitis Related Mitogens

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1. Abstract

1.1. Objective: Prostate carcinoma (PCa) is the leading causes of cancer-related death in elderly men. Although several risk factors for the development of prostate cancer have been identified, the impact of chronic prostatitis it is still a matter of debate. A key event of prostate cancer pathogenesis is the decrease of the homeo box protein NKX3.1 in the luminal epithelial cells of the prostate observed in early pre-cancerous lesions. Furthermore, inactivation of Nkx3.1 in a mouse model led to high incidence of prostatic intraepithelial neoplasia (PIN) formation underscoring the importance of NKX3.1 loss. In this study, we aimed to define the impact of diverse cytokines and growth factors known to be expressed during chronic prostatitis on NKX3.1 expression.

1.2. Methods: We determined the NKX3.1 expression in inflamed areas of prostatectomy specimens by immunohistochemistry. NKX3.1 protein and mRNA levels in cytokine and growth factor stimulated PCa cell lines were determined by western blot and RT-qPCR. Transcriptional activity of the androgen receptor (AR) was determined by luciferase reporter assays and impact of the AR on NKX3.1 expression by siRNA mediated AR knock down.

1.4. Results: Treatment of prostate carcinoma cell lines with epidermal growth factor (EGF) dramatically reduced NKX3.1 protein and mRNA levels, while TNFα or IL-1α had only a moderate effect. Moreover, EGF or a combination of PMA and ionomycin (P+I) also caused diminished levels of the AR. However, while NKX3.1 reduction is observed as early as one hour after stimulation the decrease of AR occurred with a delayed kinetic. We show that P+I-induced NKX3.1 proteolysis is proteasome-dependent and influenced by protein kinase C.

1.4. Conclusion: In summary, we provide evidences for a crucial role of inflammatory mitogenic factors leading to reduced NKX3.1 and AR levels which might contribute to the initiation of pre-cancerous PIN lesions.

2. Keywords: Prostatitis, NKX3.1, AR, mitogens, EGF, prostate cancer

3. Abbreviations: AR, androgen receptor; BIM, bisindolylmaleimide I; EGF, epidermal growth factor; FFPE, formalin-fixed paraffin embedded; IL-1, interleukin 1; PKC, protein kinase C; PMA, phorbol myristate acetate; TNFα, tumor necrosis factor alpha