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Modulation of notch signal in prostate cancer cells under hypoxia

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Abstract

Background: Prostate cancer (PC) is the second cause of cancer-related death in men. Although the vast majority of cases are diagnosed at an early stage, even patients with clinically localized disease may have an ominous outcome. We know very little about deranged signaling pathways that may take place in localized, aggressive cancers. The elucidation of such pathways may help to develop innovative therapies aimed at specific molecular targets.

Objective: To determine whether exposure of PC cells to hypoxia induces modulation of Notch-mediated signal, contributing to cancer progression.

Methods: We exposed PC cells to chronic hypoxia (2% oxygen for up to 14 days) and analyzed the expression and activity of Notch1-3 receptors; the effect of Notch3 gene silencing was also studied. Lipid raft composition and distribution of Notch receptors and □-secretase complex was determined. The expression of Notch1-3 in human PC biopsies was detected by immunohistochemistry.

Results: We demonstrated that exposure of PC cells to chronic hypoxia resulted in a profound modulation of the Notch signaling system with a strong down regulation of Notch1 and Notch2, but without significant changes in Notch3 expression.Notch3 was activated under hypoxic conditions and sustained cell growth and colony formation in soft agar. Hypoxia also modulated cholesterol content and the number and size of lipid rafts, with migration of Notch3 from the non-raft into the raft compartment where the receptor co-localized with the γ-secretase complex. Moreover, expression of Notch3 positively correlated with HIF-1 alpha and Carbonic anhydrase IX expression and with Gleason score, in human PC biopsies.

Conclusion: Hypoxia triggers a change of lipid-raft composition with activation of Notch3 which seems to correlate to higher proliferation, in vitro, and higher Gleason score, in human tissues. Notch3 pathway may represent a promising target for adjuvant therapy in patients with PC.