

Gamma-Secretase, ErbB4 nuclear localization and neuregulin expression correlates with prostate cancer patient clinical outcomes

Authors: Ismaël Hervé Koumakpayi¹, Cécile Le Page¹, Pierre I. Karakiewicz², Jean-Simon Diallo¹, Laurent Lessard¹, Anne-Marie Mes-Masson^{1,3}, Fred Saad^{1,2}

¹CRCHUM – Hôpital Notre-Dame/Institut du cancer de Montréal, ²Department of Surgery/Urology and ³Department of Medecine Université de Montréal, Québec, Canada

Background: Membrane protein ErbB4 is a member of ErbB growth factor receptor family, which can be activated by neuregulins (NRG). Upon neuregulin activation, ErbB4 is cleaved within its transmembrane domain by presenilin γ -secretase (PSN) to release an intracellular domain that translocates into the nucleus. Although, ErbB4 ligand-dependant translocation of ErbB4 to the nucleus and its nuclear activity has been reported in breast cancer cell lines, there are few reports concerning ErbB4 nuclear localization and its clinical relevance. Here, we report for the first time the clinical relevance of ErbB4 nuclear localization, NRG, and PSN expression in prostate cancer tissues.

Methods: Immunostaining using anti-ErbB4, anti-PSN2 and anti-neuregulin antibodies was done on a set of tissue microarrays (TMA) from 140 patients. The TMAs contained, 92 cores of normal prostate tissue obtained from 46 autopsy specimens from young males, 373 tumor and normal adjacent cores from 63 hormone sensitive PCa (HSPCa) patients, and 146 cores from 31 hormone refractory PCa (HRPCa) patients.

Results: We found a statistically significant increase ($p < 0.01$) in the percentage of ErbB4 nuclear localization (68.7% vs 53.2%), NRG expression (2.06 vs 1.41) and PSN2 expression (2.14 vs 1.53) when comparing cancerous tissues to normal tissue adjacent to cancer. Interestingly, a similar statistically significant increase in nuclear ErbB4 and NRG expression was observed when comparing HRPCa to HSPCa ($p < 0.001$). In cancerous tissues, a strong correlation was found between nuclear ErbB4 nuclear and NRG expression ($r = 0.672$), between nuclear ErbB4 and PSN2 expression ($r = 0.51$), and between PSN2 and NRG expression ($r = 0.71$). Nuclear ErbB4 and PSN2 inversely correlated with tumor stage and lymph node invasion. Kaplan Meier analysis of nuclear ErbB4 ($p = 0.030$) and PSN2 expression ($p = 0.018$) showed an inverse association with biochemical recurrence (BCR) of PCa. In multivariate analyses including these three markers and clinical parameters, only nuclear ErbB4 retained an independent prognosis value.

Conclusion: Our results suggest that high nuclear ErbB4 along with increased PSN2 expression have a protective effect against prostate cancer progression and BCR.

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