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HER2 cytoplasmic staining as an independent risk factor for death in penile cancer

A.M.T. Silva[1], R.M. Rocha[1], I.W. Cunha[1], A. Cubilla[2], G.C. Guimarães[3], A. Lopes[3], F.A. Soares[1]. *[1]Hospital AC Camargo, Anatomia Patológica, São Paulo, Brazil; [2]Universidad Nacional de Asunción, Anatomia Patológica, Asunción, Paraguay; [3]Hospital AC Camargo, Cirurgia Pélvica, São Paulo, Brazil*

Background: Although rare in developed regions, penile carcinoma is a serious concern for undeveloped countries such as Brazil, where it can represent up to 10% of all malignancies. HER2 is a well-known growth factor membrane receptor that has its high protein expression levels usually associated with aggressive disease. Recently, some studies have shown that soluble fractions of HER2 intracellular domain are found in tumors cytoplasm and there they can still activate intracellular pathways related to cell proliferation and survival.
Material and Methods: Immunohistochemistry against HER2 was carried out in 195 penile carcinoma samples selected from the files of AC Camargo Hospital, Brazil, using the monoclonal CB11 antibody (Novocastra™), which recognizes specifically HER2 intracellular domain. Cases were classified as positive or negative according to membrane and to cytoplasmic staining. All statistical analyses were performed by the SPSS for Windows 18.0, SPSS Inc. Comparisons between category variables was performed by Pearson chi-square test or Fisher's exact test. Survival rates were calculated using the Kaplan-Meier method and the curves were compared by means of the log-rank test. In all statistical tests, the alpha error was set at 5%.
Results: None of the cases showed membrane staining for HER2. However, a clear and strong cytoplasm staining was observed in 28 cases (14.9%), as shown in figure 1. The staining was limited to the tumor cells and does not represent background or artifact. Univariate analyses showed that this expression pattern is associated with higher histologic grade ($p < 0.001$) and lower overall survival ($p = 0.007$). Multivariate analyses showed that HER2 in the cytoplasm is an independent risk factor for death (RR = 2.966; 95% CI [1.6−5.2]; $p < 0.001$).

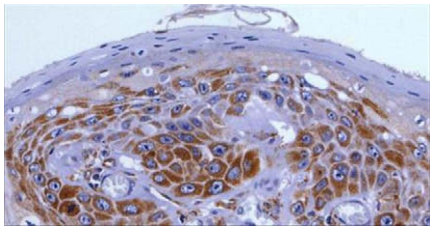

Figure 1 − Cytoplasmic staining of HER2 in penile carcinomas.

Conclusions: Corroborating with recent findings that cytoplasmic fragments of HER2 can be active kinases, the present study demonstrates that the presence of HER2 in tumor cytoplasm is a prognostic marker in penile carcinoma. We have also demonstrated that, although no membrane staining was seen, presence of HER2 in cytoplasm is an independent risk factor for death in this neoplasm.

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Biological correlation of the expression EGFR pathway in renal cell carcinoma with Hif1-a, VEGF, VEGFR-2(Flk-1), TGF-a, VHL in tumor tissue sample levels

M. Vanessa[1], G. Aparicio Gallego[1], I. Santamarina Caínzos[1], M. Quindós Varela[2], D. Dopico Vázquez[2], R. García Campelo[2], G. Alonso-Jaudenes Curbera[2], L. Valbuena Rubira[3], E. Grande Pulido[4], L.M. Antón Aparicio[5]. *[1]INIBIC (CHU A Coruña), Oncology, La Coruna, Spain; [2]CHU A Coruña, Medical Oncology, La Coruna, Spain; [3]CHU A Coruña, Pathology, La Coruna, Spain; [4]Ramón y Cajal Hospital, Oncology, Madrid, Spain; [5]University of A Coruña, Medical Department, A Coruña, Spain*

Background: Signal transduction triggers when cells respond to external stimuli. There is a not yet well understood intracellular crosstalk between different signal transduction pathways. The epidermal growth factor receptor (EGFR) pathway is one among the many pathways implicated in renal cell carcinoma (RCC) oncogenesis and leads to cell proliferation, motility, and survival. This work focuses on the signalling network formed by the interaction of the EGFR signalling pathway and those in which are involved: Hif1-α, VEGF, VEGFR-2, TGF-α and VHL tumor suppressor gene.
Material and Methods: For its purpose this study investigated the pattern of protein expression in RCC specimens using tissue-array (TA) technology. We retrospectively analyzed 80 paraffin-embedded RCC samples: 16 chromophobe RCC (cRCC), 4 papillary RCC (pRCC), 58 clear cell RCC (ccRCC) and 2 identified as unknown histological type (UNK). The immunohistochemical data of molecular factors were correlated by means of two non-parametric rank-based statistical tests: Pearson's correlation coefficient test and Spearman's rho test.
Results: EGFR reaction was detected in the membrane in 75% of cases. The remaining 25% presented a dual localization: membrane and cytoplasm. Cases that showed higher expression with were those falling within the ccRCC histological type ($p = 0.001$). We found that VEGFR-2 showed significant negative correlation with Hif1-α and EGFR ($r = -0.448$ and $r = -0.364$, sig. 0.01 respectively). Hif1-α presented a significant positive correlation with EGFR and VEGF ($r = 0.291$ and $r = 0.277$ with a sig. level of $p = 0.009$ and $p = 0.014$ respectively). Finally we found a significant positive correlation between TGF-α and EGFR (Spearman's rho = 0.222, sig. level 0.05).
Conclusions: The observation that ccRCC specimens exhibit EGFR at higher levels when compared histological subtypes may be helpful in diagnosis. HIF1-α and EGFR are key events during development and progression of RCC, which act in regulating tumor angiogenesis as well, and show intimate relationship with biological behaviour. Molecular findings need to be correlated with clinical features.

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Tissue array study in renal cell carcinoma: Hif1-a, CAIX and VEGF correlation

M. Vanessa[1], G. Aparicio Gallego[1], I. Santamarina Caínzos[1], M. Quindós Varela[2], D. Dopico Vázquez[2], R. García Campelo[2], M. Valladares-Ayerbes[2], L. Valbuena Rubira[3], E. Grande Pulido[4], L.M. Alonso-Jaudenes Curbera[5]. *[1]INIBIC (CHU A Coruña), Oncology, La Coruna, Spain; [2]CHU A Coruña, Medical Oncology, La Coruna, Spain; [3]CHU A Coruña, Pathology, La Coruna, Spain; [4]Ramón y Cajal Hospital, Medical Oncology, Madrid, Spain; [5]University of A Coruña, Medical Department, A Coruña, Spain*

Introduction: Recent progresses in the basic sciences have led to an increased understanding of the molecular pathways underlying the various renal cell carcinoma (RCC) subtypes. Hypoxia-inducible factor 1α plays a key role in RCC. Hif1-α regulates angiogenesis, tumor growth, progression, metastatic spread, and glucose metabolism by acting as a transcription factor for crucial proteins such as vascular endothelial growth factor (VEGF) and carbonic anhydrase IX (CAIX). The purpose of this work is evaluated the significance of these molecules in RCC.
Methodology: We retrospectively analyzed 80 paraffin-embedded RCC samples. We studied the pattern of protein expression by tissue-array (TA) technology. Immunohistochemical (IHC) reaction was visualized by the Dako En Vision system and diaminobenzidine. Immunoreaction was rated semiquantitatively by percentage of positive cells and staining intensity on immunohistological stainings. The expression levels were associated with pathological variables.
Results: A 46.3% of the samples showed a maximum score (+++ average expression cell/tissue from 80%) for Hif1-α. 27% of the samples showed a moderate positivity (++). We visualized cytoplasm localization in 100% of positive samplesHif1-α expression was greater in clear cell RCC (ccRCC) subtype (Kruskall-Wallis test $p < 0.001$), in those cases which presented renal pelvis invasion (Kruskall-Wallis test $p = 0.023$) and moreover its expression increased as the number of involved nodes (Kruskall-Wallis test $p < 0.001$). VEGF expression was characteristic for papillary RCC subtype, Fuhrman Grade III and when there were metastases in more than one regional lymph node (Kruskall-Wallis test $p = 0.009$, $p = 0.029$ and $p < 0.001$ respectively). For CAIX we could observe higher expression in ccRCC ($p < 0.001$). Regarding the correlations between the markers we can say that HIF1-α showed significant positive correlation with VEGF and CAIX (Spearman's rho = 0.391 sig. 0.01and Spearman's rho = 0.304 sig. 0.01 respectively).
Conclusions: These results suggest that these markers may be useful for diagnosis in RCC. Hif1-α and VEGF seems to appear as a markers of poor prognosis. Further studies are needed to clarify the role of these molecules in RCC.

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Discordant expression patterns of four different CD133 antibody clones in glioblastomas − possible implications for CD133 as a new therapeutic target

S.K. Hermansen[1], K.G. Christensen[1], S.S. Jensen[1], B.W. Kristensen[1]. *[1]University of Southern Denmark, Department of Pathology, Odense, Denmark*

Brain tumor stem cells are obvious new therapeutic targets because of their role in initiation and progression of brain tumors. As the putative