Biological Differences between Normal and Tumoral Tissue Not Always an Increase of Expression is Indicator of Poor Prognosis

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Tumor markers (TM) can be cODssLﺖed into two main groups: a) Secretion TM, preferably dosed in blood and useful in monitoring patients for early detection of recurrence and/or metastasis, as well as better knowledge of the therapeutic eﺖcDc\- b) Tissue TM, including biochemical-molecular parameters, which, analyzed in the tissue itself, allow tumor characterization about their prognosis and therapy. An attractive possibility of study is to compare the behaviour of a possible TM in normal and tumoral tissues in order to ﺖnd conclusions of practical interest. In malignant lung disease, adhesion molecules are an attractive ﺖeOd of interest and within those, we can stand out CD44. CD44 is a surface adhesion molecule expressed in many normal tissues by cells of dLﻭ́erent origin and involved in some physiological processes. CD44 exists in a standard form (CD44s) and in multiple isoforms (CD44v) and related with dLﻭ́erent features of the tumor evolution. For instance CD44v6 regulates ras/mitogen-activated protein kinase (MAPK) signalling, playing an important role in the transition from normal to transformed phenotypes and some authors have described the value of CD44v6 expression as a parameter of poor survival patients with in non-small cell lung cancer Similarly, CD44 promotes Kras-dependent lung adenocarcinoma.

Hyaluronic acid (HA) is a linear unsulfated glycosaminoglycanubiquitously expressed, who plays a role in some physiological functions as cell adhesion, migration and dLﻭ́erentLDtLon It is a critical component of cancer microenvironment and increases progression and aggressiveness of tumors. Its elevated production can induce epithelial to mesenchymal-like transition, and therefore it can contribute to tumorigenesis, as well as, increase resistance to certain epidermal growth factor receptor inhibitors. Here are dLﻭ́erent receptors for HA, being CD44 the most important. Studying CD44s, CD44v5 and CD44v6 expression in cell surface membranes, using Enzyme Immuno Assay (EIA) in patients with nonsmall cell lung carcinomas (squamous and lung adenocarcinomas) and normal lung samples removed from a surrounding tissue region at Least 2 cm away from the tumors, and macroscopically free from neoplastic growth, we observe the following: In normal pulmonary tissue, we cannot ﺖnd dLﻭ́erences in the positive percentages of CD44s, CD44v5 and CD44v6 related to patient's tumor. However, when comparing dLﻭ́erent biological parameters between normal and tumoral tissues, we were able to ﺖnd two common and opposing facts:

1. Cytosolic concentrations of cathepsin D were always higher in the normal tissue than in the tumor, regardless of tumoral subtype.

2. HA cytosolic and membrane concentrations were always higher in tumoral than in normal samples. ﺢLs dLﻭ́erent behaviour can help to explain and understand the value of these parameters as tumor markers. So, and in relation to cathepsin D, we know that their high cytosolic levels were associated with good outcome squamous lung carcinomas and the same has been found when messenger RNA was analysed HDt is, it shows a dLﻭ́erent behaviour than might suspect a priori. About HA, we know that induce EMT through either TGF-1 and EGF. TGF-1 up-regulates the expression of Hyaluronan synthethase and promotes the expression of CD44, which interacts with EGFR, ensuing the activation of the downstream AKT and ERK pathways. ﺢose are the mechanisms of TGF-1 to induce epithelial-mesenchymal transition. Strong HA staining intensity is associated with cancer cells and a direct association was observed in tumors between high percentages of HA and elevated MicroVessel Density (MVD) in tumoral stroma. In lung tumors there was a sLJnLﺖcDnt association between better survival and low HA levels, and the same occurs in patients with gastric and colorectal cancer, whereas in invasive breast cancer, high HA cytosolic levels are associated with longer relapse-free survival time in patients with ductal subtype, as well as those without any type of systemic adjuvant treatment. Similar happens with malignant mesothelioma, where high eﻭusLon levels of HA are associated with a sLJnLﺖcDntO\ longer median survival than those with low levels [9]. ﺢLs dLﻭ́erent behaviour than expected also can be foundwith matrix metallo-proteases. In conclusion and summarizing all described above, the comparative study of dLﻭ́erent biological parameters between tumor and non-tumor tissues from the same patient, may be useful for understand the malignant transformation, and predict the value of some of them as candidate tumor markers. However, no always a biological behaviour is correlated with their clinical value.