and RET. LRIG1 is down-regulated in various neoplasms, including cervical and renal cell carcinoma. We also identified two human LRIG1 paralogs, LRIG2 and LRIG3. The LRIG proteins show differential subcellular localization in normal and pathological tissues, which seems to have clinical implications. Perinuclear LRIG protein localization is associated with good survival of astrocytoma patients, whereas, cytoplasmic LRIG2 expression was associated with poor survival of oligodendroglioma patients. LRIG1 is subject to proteolytic processing and the resulting fragments seemed to have biological activities. Taken together, the LRIG proteins seem to be important regulators of growth factor signaling with implications for patient survival in various malignancies.

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A MOUSE MODEL OF NEUROFIBROMATOSIS-1 OPTIC GLIOMA: A PRECLINICAL TOOL FOR ANTI-ANGIOGENESIS RESEARCH?

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Individuals affected with the neurofibromatosis 1 (NF1) are prone to develop tumors of the nervous system, including optic pathway gliomas (OPG). These tumors are classified as grade I pilocytic astrocytomas, characterized by low cellularity and rare mitotic figures. Despite their benign behavior in general, these gliomas often exhibit increased angiogenesis. Importantly, the development of prechiasmatic and chiasmatic optic gliomas has been observed in a genetically engineered mouse (GEM) model with inactivation of the neurofibromatosis-1 (*Nf1*) tumor suppressor gene in glial cells. Interestingly, the natural history and morphology of these GEM tumors was similar to their human counterparts. Furthermore, increased angiogenesis has been found during OPG development as evidenced by an increased blood vessel density. We validated this Nf1 optic glioma model using conventional chemotherapy (temozolomide) currently used for children with low-grade glioma and showed that treatment resulted in reduced proliferation and increased apoptosis of tumor cells *in vivo* as well as reduced tumor volume. Collectively, these findings indicate that this unique Nf1 GEM optic glioma model might be a potent tool for preclinical assessment of novel anti-angiogenic therapies.

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ROLE OF HYALURONAN-CD44 COMPLEXES IN REGULATION OF GROWTH FACTOR RECEPTOR ACTIVITY AND IN TUMOR PROGRESSION

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Introduction: The interactions between cells and the host microenviroment influences cellular behavior. Hyaluronan levels are determined by synthesizing (HAS) and degrading (HYAL) enzymes in response to growth factors. The hyaluronan receptor CD44 affects cell–cell and cell–matrix interactions. *Methods and Results:* HAS activity has been shown to be important for the maintenance of the malignant and invasive phenotype of the Hs578T breast cancer cells using specific siRNAs, we showed that HAS interacts with HYAL and the hyaluronan receptor CD44 to promote the aggressive character of breast cancer cells. Furthermore, using a 3D collagen matrix assay we studied in real-time the mechanisms by which CD44-hyaluronan interactions affect transendothelial migration; peritumoral hyaluronan is important for the early adhesion of tumor cells to endothelial cells. Recently, we investigated the downstream signaling pathways through which PDGF-BB stimulates hyaluronan synthesis using inhibitors of different signaling pathways, we showed that the Erk MAP kinase and PI3 kinase signaling pathways are necessary for the regulation of hyaluronan synthesis by PDGF-BB and that hyaluronan affects the mitogenic response to PDGF-BB. Recent data revealed that tissue hyaluronan content can be modulated through ubiquitinylation and possibly oligomerization of HAS enzymes. In another line of research, we demonstrated that CD44 forms a complex with both the PDGF β-receptor and TGFβ type I receptor; hyaluronan-activated CD44 suppressess the PDGF-BB-mediated activation of the PDGF β-receptor and TGFβ-mediated activation of Smad2. *Conclusion:* Hyaluronan favors the malignant phenotype in malignancies and modulates receptor tyrosine kinase activity.

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SINGLE OR COMBINATIONS OF TUMOR MARKERS IN CERVICAL CANCER – CORRELATION TO PROGNOSIS, SERUM PROGESTERONE AND ESTRADIOL, SMOKING AND ORAL CONTRACEPTIVE USE

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Background: Expression of a single tumor marker is rarely clinically useful in any cancer type. There is an increasing interest in using panels of tumor markers to increase prognosis prediction, differential diagnosis and choice of therapy. *Materials and Methods:* One hundred and thirty women with