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Pathophysiological Role of an Aberrant NRSF-mediated Transcriptional Regulation for the Tumor Specific Expression of Glycine Receptor α-1 Subunit in Small Cell Lung Cancer

(Charakterisierung der pathophysiologischen Bedeutung einer aberranten NRSF-vermittelten Transkriptionsregulation für die Tumorspezifische Expression von Glyzinrezeptor α-1 Untereinheit bei kleinzelligen Bronchialkarzinomen)

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Lung cancer is the most common fatal malignancy in the developed world and small□cell lung cancer (SCLC) comprises about 25% of these tumors. SCLC characteristically secrete a variety of neuropeptides such as adenocorticotrophin hormone (ACTH), gastrin□releasing peptide (GRP), gastrin, cholecystokinin, preprotachykinin and arginine vasopressin (AVP). This neuroendocrine phenotype distinguishes SCLC from the majority of other normal or neoplastic lung cell types and implies that SCLC transcriptional regulation may more closely resemble that of neuronal cells. The neuron-restrictive silencer factor (NRSF) is a transcriptional silencer involved in the deregulated expression of the argininine vasopressin and preprotachykinin genes in small cell lung cancer (SCLC). A novel NRSF-regulated gene that is upregulated specifically in SCLC is described here: the human glycine receptor alpha 1 subunit gene (GLRA-1). GLRA-1 mRNA is detectable in SCLC cell lines and in SCLC biopsies, but not in non-malignant or other malignant pulmonary lesions. NRSF-mediated silencing of a reporter construct containing the binding sequence of NRSF from the 5' UTR of the GLRA-1 gene (GLRA-1 NRSE) is impaired in three of four SCLC cell lines. Electrophoretic mobility shift assays and quantitative RT-PCR results revealed that the amount of the specific NRSF / GLRA-1 NRSE complex increases with transcriptional GLRA-1 repression. A splice variant of NRSF, sNRSF, had recently been reported to be specifically expressed in SCLC. sNRSF had been proposed to antagonize the repression of NRSE containing genes in SCLC via a dominant negative effect. Thus, the role of two human splice variants encoding truncated isoforms of NRSF/REST, hREST1 and hREST4/sNRSF was analyzed. In contrast to previously published data, a quantitative RT-PCR analysis demonstrated that neither of the variants is up-regulated in SCLC. In addition, it could be shown that in SCLC cells neither of the two human NRSF splice variants has a derepressor effect on GLRA-1 transcriptional activity. Reduced NRSF/REST transcript levels, however, strongly correlate with GLRA-1 expression in SCLC. The overexpression of NRSF/REST is able to reconstitute NRSE-GLRA-1 mediated silencing of the reporter gene. Moreover, preliminary results indicate that reconstitution of NRSF/REST-mediated silencing induces apoptosis in SCLC cells. Thus these results demonstrate that down-regulated expression of NRSF/REST may be a crucial step of clonal selection towards aggressive proliferation in the carcinogenesis of SCLC.