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**Title:** The metallopeptidase neprilysin is a hypoxia-induced prognostic factor in lung adenocarcinoma

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**Body:** Identification of hypoxia-induced pathways might lead to novel therapeutic targets in solid cancers. A comparative expression profiling study was performed in hypoxic and normoxic ex vivo cultured lung cancer fragments with preserved tumor stroma and 3D-structure. A considerable overlap was found between hypoxia-regulated genes from the ex vivo lung cancer model and published hypoxia-signatures. The stem cell marker neprilysin (membrane metallo-endopeptidase, MME, CD10), which was consistently up-regulated by hypoxia in the histological subtypes in our study, has not been reported so far to be hypoxia-induced in cancer. Neprilysin has been shown to be expressed by stroma cells, e.g. cancer-associated fibroblasts. Immunohistochemistry for neprilysin in fresh NSCLC specimens and normoxic or hypoxic fragments revealed a localization in both, stroma cells and neoplastic tumor cells. To assess a possible role of neprilysin in lung cancer progression we analyzed the association of neprilysin expression and overall survival in NSCLC patients from public microarray datasets. High expression of neprilysin was significantly associated with poor overall survival in 182 adenocarcinoma patients in a multivariate meta-analysis (P=0.000012) and in adenocarcinoma patients from two individual datasets. As a conclusion, neprilysin is a hypoxia-induced, independent adverse prognostic factor in surgically treated lung adenocarcinoma patients. The results of this study suggest an important role of stroma-derived

hypoxia-induced factors for lung cancer progression.