MET Phosphorylation in Prostate Cancer Tissues: An Immunohistochemical Analysis

Introduction and Objective: Hepatocyte growth factor (HGF) is a multifunctional growth factor known to play an important role in cancer progression via its specific receptor tyrosine kinase MET, the *c-met* proto-oncogene product. Overexpression of MET in prostate cancer cells has been reported and several reports have suggested a strong relation between MET expression and metastasis or CRPC; however, it remains unclear whether overexpressed MET is activated or not. Here, we analyzed the phosphorylation of MET in prostate cancer specimens immunohistochemically using specific antibodies to major phosphorylation sites of MET and discussed the results with clinical data.
Materials and Methods: We examined a series of 62 primary prostate cancer specimens (needle biopsy) at the University of Miyazaki Hospital, Miyazaki, Japan, between 2006 and 2011. The prostate cancers were staged according to TNM classification. Immunohistochemical staining was carried out on formalin-fixed, paraffin-embedded tissue sections of biopsy specimens. Rabbit polyclonal phosphor-MET antibody (Tyr1235), which has been described previously (Inoue et al, Cancer Sci 2004), was used for this study. Antibodies to total MET and HGF-related proteins were purchased. Phosho-MET immunoreactivities were evaluated as either positive or negative, with a cut-off value of 5% positively stained cancer cells, according to the method described by Nakamura et al (Cancer Sci 2007). Associations between each parameter were determined statistically by univariate and multivariate analysis.
Results: Median patient age was 70 years (range 51 to 84 years). Nineteen patients had metastasis, including 15 cases of bone metastasis. Phospho-MET was positive in 35 of 62 cases (56%) overall. Apparent correlation between MET phosphorylation and metastasis, or Gleason score could not be detected; however, MET was highly phophorylated in high T-stage (greater than T3) patients (P=0.039). Morphologically, phosphorylated-MET were evident in 87.5% of cribriform structure (Gleason pattern 4), 100% of ill-defined glands (Gleason pattern 4) and 64.2% of solid architecture (Gleason pattern 5). Additional immunohistochemical analyses for other HGF-related molecules to prove the prognostic significance are currently underway.
Conclusions: MET phosphorylation was associated with clinical T stage. Pathologically, intense MET activation was observed in several specific architectures of the cancer.