c-MET SIGNALING AS A PROMISE OF TARGETED THERAPY IN GLIOBLASTOMA TUMOR

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Nuclear c-Met (nMET) refers to one of the receptor tyrosine kinases (RTKs), which plays key roles in cellular organization, proliferation, migration and invasion. Hepatocyte growth factor (HGF) is the only known ligand for c-Met binding and activation. Membranous c-Met is classically identified with its role in cancer metastases, while nMET is associated with a more invasive, aggressive and proliferative form of cancer. Full-length c-Met or N-terminal transmembrane domain cleaved c-Met can translocate into nucleus in a cell growth and pH dependent but ligand-dependent (full length c-Met) and -independent (cleaved c-Met) manner. We recently found that nuclear form of nMET may play greater essential roles in cancer recurrence than membranous c-Met. Our data suggest that nMET activates cancer cell reprogramming especially in recurrent cancer cells. nMET overexpression increases sphere formation of relapsed cancer cells and self-renewal of cancer stem–like cells. Mechanically, nMET activates SOX9/β-Catenin pathway in relapsed cancer. Emerging evidence suggests the possibility of nMET as a prognostic marker in relapsed cancer. It has been shown that full length c-Met promotes glioblastoma (GBM) cell reprogramming through Nanog and Sox2. Moreover, c-Met expression correlates with stem cell markers CD133, Sox2, and Nanog in glioblastoma patient samples. c-Met inhibitors have been entered into clinical trials. Thus targeting c-Met/nMET signaling would provide a novel avenue for treatment of recurrent glioblastoma by preventing GBM stem cell mediated relapse.