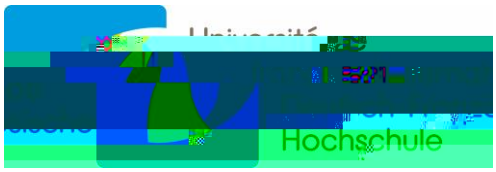

Abstract

The receptor tyrosine kinase MET and its ligand the hepatocyte growth factor/scatter factor (HGF) control vital cellular processes such as survival, proliferation, differentiation and motility. HGF-induced MET signaling is critical in embryonic development and tissue regeneration at the adult stage. A dysregulation of HGF/MET pathway can drive tumorigenesis and metastasis. Ligand-mediated MET activation is dependent on CD44v6 isoforms, which are members of the CD44 family. The transmembrane CD44v6 protein has two functions: its extracellular part regulates the phosphorylation of MET and its cytoplasmic domain is involved in MET internalization and downstream signaling. MET has another ligand called Internalin B (InlB), found on *Listeria Monocytogenes*. In Listeriosis, InlB induces MET activation to infect host cells and this process also requires CD44v6.

Indirect binding studies between MET, CD44v6 and ligands HGF or InlB revealed the formation of a trimeric complex in tumors and several cell lines. In addition, HGF was found to only bind to cells expressing CD44v6 and a physical association was evidenced between them

the role of lipid domains in the activation process of MET in HeLa cells. In this aim, we targeted the major components of lipid domains such as cholesterol and sphingomyelin and assessed the phosphorylation of MET and downstream targets. None of the targeting strategies affected MET or ERK phosphorylation. This led us to hypothesize that MET activation is likely independent of lipid domains.

In conclusion, our data are in line with a model where CD44v6 would be recruited out of confined lipid domains to dimerize and bind to HGF or InlB. This complex would then present the ligands to MET proteins to form an oligomeric active complex for signaling.