

Co-activation of the invasion and survival contributes to transformation induced by exon 14 splicing of MET receptor in lung cancer

Marie Fernandes, Sonia Paget, Zoulika Kherrouche, Anne Chotteau-Lelièvre, Luca Grumolato, Alexis Benjamin Cortot, David Tulasne

▶ To cite this version:

Marie Fernandes, Sonia Paget, Zoulika Kherrouche, Anne Chotteau-Lelièvre, Luca Grumolato, et al.. Co-activation of the invasion and survival contributes to transformation induced by exon 14 splicing of MET receptor in lung cancer. 3rd International Symposium Research on Healthy Ageing, Dec 2019, Lille, France. hal-04559723

HAL Id: hal-04559723 https://hal.science/hal-04559723

Submitted on 25 Apr 2024 $\,$

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Co-activation of invasion and survival contributes to transformation induced by exon 14 skipping of MET receptor in lung cancer

Marie Fernandes¹, Sonia Paget¹, Zoulika Kherrouche¹, Anne Chotteau-Lelievre¹, Luca Grumolato², Alexis Cortot^{1,3} et David Tulasne¹

¹ Univ. Lille, CNRS, Institut Pasteur de Lille, UMR8161 – M3T – Mechanisms of Tumorigenesis and Targeted Therapies, F-59000 Lille, France

² Normandie Univ, UNIROUEN, INSERM, DC2N, Rouen, France; Institute for Research and Innovation in Biomedicine, Rouen, France

³ Thoracic Oncology Department, CHU Lille, Univ. Lille, Lille, France

Introduction

MET is a tyrosine kinase receptor (RTK) expressed predominantly in epithelial cells and activated by HGF (Hepatocyte Growth Factor). Like other RTKs, its deregulation is associated to tumorigenesis in several cancers. Although the majority of RTK mutations affect the kinase domain, those affecting the MET receptor in lung cancer cause exon 14 sskipping (MET $\Delta 14$). This alteration can lead to the aberrant activation of MET and which make these patients eligible for MET targeted therapies. The in frame skipping of exon 14 induces the loss of the juxtamembrane domain. This domain contains at least three negative regulation sites. Among them, phosphorylation of residues S985 and Y1003 respectively leads to inhibition of kinase activity and degradation of MET in response to its ligand HGF. Moreover, the ESVD1002 motif is a caspase cleavage site involved in pro-apoptotic activity in the absence of ligand.

MET receptor & signaling pathways

Exon 14 skipping of MET

Juxtamembrane domain regulatory sites







Results



Figure 3: A. Expression and phosphorylation of MET, AKT and ERK were determined by Western Blot with protein extracts from T47D MET WT or mutants treated or not by HGF at 10 or 30 ng/ml for 30 min. B. Scattering assay by microscopy (40X magnification) of T47D, T47D MET WT or mutants fixed and stained Eosine-Carazzi after 48h of HGF stimulation (30 ng/ml). C. Wound healing assay of T47D MET WT or mutant. After cells seeding, injury was performed and cells were stimulated or not by HGF at 30 ng/ml during several days. Wound healing was tracked by videomicroscopy and quantified by IncuCyte software. D. Unsupervised analysis of transcriptional responses on Affymetrix microarray from total RNAs extracted from T47D MET WT or mutants treated by HGF at 30 ng/ml during 24h (biological triplicates).



End-point measure of tumor volume from 16HBE lines





Figure 5 : 16HBE MET WT and $\triangle 14$ cells (2.10⁶ cells) were xenografted in the flank of SCID-HGF^{hu} mice and they were monitored until the tumor was excised (9 weeks after injection).

 \rightarrow Next step : injection of 16HBE MET WT, \triangle 14, Y1003F and V1001A + Y1003F

Conclusion

We demonstrate that HGF stimulation of MET Δ 14 receptor induces sustained and stronger activation of the main signaling pathways associated with an increase of migration. Moreover, in absence of HGF, MET Δ 14 cells are more resistant to apoptosis. Therefore transforming capacities of MET exon 14 skipping can be the result of the loss of at least two regulatory sites. We are currently confirming these results in a normal pulmonary epithelial cell line (16HBE) and we will evaluate the consequence of MET exon 14 skipping in animal model of tumorigenesis. This original mechanism of loss of several regulatory processes calls into question the efficacy of therapies offered to MET $\Delta 14$ patients. Indeed, these patients can be treated by tyrosine kinase inhibitors targeting MET or with pro-apoptotic chemotherapies. Thus, the use of TKIs seems relevant since we demonstrated stronger HGF-induced signaling in MET Δ 14 cells. Nevertheless, the resistance to apoptosis observed could lead to of therapeutic failure in the context of pro-apoptotic chemotherapies.