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MET activation drives resistance to cetuximab in head and neck cancer

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Background: Innate and acquisition of resistance to cetuximab, an epithelial growth factor receptor (EGFR) blocker, is major problem in metastatic head and neck squamous cell carcinoma (HNSCC). Although cetuximab significantly prolongs the median overall survival in HNSCC patients, only 15% of the patients experience a partial response, which lasts only several months.

Objectives: Investigate the role of c-MET expression and localization in response to cetuximab, and elucidate the signaling pathway downstream of c-MET that is responsible for tumor cells survival and proliferation.

Methods: Genomic, transcriptomics, and proteomics profiling was done on cetuximab-sensitive ($Cetux^{Sen}$) and resistant tumor ($Cetux^{Res}$) lesions obtained from a patient who had an exceptionally good response to cetuximab monotherapy. Immunohistochemisty, FISH, and qPCR were applied to confirm MET localization, copy number, and expression, respectively. IHC staining and analysis of MET expression were done on 20-cetuximab treated patients. Biochemical studies *in vitro* were conducted to uncover the molecular mechanism of resistance.

Results: MET amplification and overexpression was observed in the $Cetux^{Res}$ tumor compared to the $Cetux^{Sen}$ tumor. This was accompanied by a change in localization of MET. In the $Cetux^{Sen}$ tumor MET was expressed mainly on the cell membrane, while in the $Cetux^{Res}$ MET was observed in the cytoplasm, indicating for its activity. *In vitro* studies verified that HGF/MET pathway activation is sufficient for conferring resistance to cetuximab mainly though reactivation of the MAPK pathway.

Conclusions: We show the first clinical evidence for MET-induced resistance to cetuximab in HNSCC. Evaluation of MET expression and localization may further improve decision making when treating with cetuximab.

Recent Publications

1. Toska E, Osmanbeyoglu HU, Castel P, et al. (2017) PI3K pathway regulates ER-dependent transcription in breast cancer through the epigenetic regulator KMT2D. Science 355(6331):1324-1330.
2. Shamay Y, Elkabets M, H Li, et al. (2016) P-selectin is a nanotherapeutic delivery target in cancer. Sci.Tras. Med 8 (345):345ra87-345ra87.
3. Elkabets M, Pazarentzos E, Juric D, et al. (2015) AXL mediates resistance to PI3Kα inhibition by activating the EGFR/PKC/mTOR axis in head and neck and esophageal squamous cell carcinomas. Cancer Cell 27(4):533-46.
4. Elkabets M, Vora S, Juric D, et al. (2013) mTORC1 inhibition is required for sensitivity to PI3K p110α inhibitors in PIK3CA-mutant breast cancer. Sci Transl Med 5(196):196ra99.
5. Elkabets M, Gifford A G, S Christina, et al. (2011) Human tumors instigate granulin-expressing hematopoietic cells that promote malignancy by activating stromal fibroblasts in mice. J Clin Invest. 121(2):784-99.

Biography

Moshe Elkabets is an Assistant Professor in the Department of Immunology, Micriobiology and Genetics at the Ben-Gurion University of the Negev (BGU). He completed his PhD at BGU in 2011. He has two Postdocs from Harvard Medical School under the supervision of Dr. Sandra Mcallister and Jose Baselga. Then, he moved with Dr. Balsega to Memorial Sloan Kettering Cancer Center in New York. He has published 22 pre-reviewed papers, and currently his lab focuses in therapy of head and neck cancer.

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