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Erk5 pathway is a new indirect target of sorafenib.

M. Ortega-Muelas[1], L. Muñoz-Martinez-Blanco[3], R. Pascual-Serra[1], O. Roche[1], D.M. Fernández-Aroca[1], R.Olivares-Martin[1], M.J. Ruiz-Hidalgo[1,2], B. Belandia[3], R. Sánchez-Prieto[1,3].

[1]Laboratorio de Oncología, Unidad de Medicina Molecular, Centro Regional de Investigaciones Biomédicas, UCLM, Unidad Asociada de Biomedicina CSIC-UCLM, Albacete, España.
[2]Área de Bioquímica y Biología Molecular, Dpto. de Química Inorgánica, Orgánica y Bioquímica, Facultad de Medicina de Albacete, UCLM.
[3]Departamento de Biología del Cáncer, Instituto de Investigaciones Biomédicas "Alberto Sols". CSIC-UAM, Madrid, España.

*Corresponding author:
Marta Ortega Muelas, Laboratorio de Oncología, Unidad de Medicina Molecular, Centro Regional de Investigaciones Biomédicas, UCLM, Unidad Asociada de Biomedicina CSIC-UCLM, Albacete, España. E-mail: mortega@iib.uam.es

Introduction: Sorafenib is a tyrosine kinase inhibitor that was developed as a B-RAF inhibitor. Afterwards it was discovered that Sorafenib could also inhibit other kinases like VEGF-R and PDEGF-R. The fundamental therapeutic mechanisms of Sorafenib are anti-angiogenesis and anti-cell proliferation. Its use has been approved in Renal Cell Carcinoma (RCC), Gastrointestinal Stromal Tumor (GIST), Thyroid Cancer and Hepatocellular Carcinoma.

Material and Methods: An experimental model of human epithelioid cervix cancer cells (Hela) was used to analyse how Sorafenib impacts on MEK5 function assessing the inhibition of the phosphorylation of its immediate downstream MAPK, ERK5. Moreover, cell viability by MTT assay**,** and migration of cancer cells by wound healing assay were also studied.

Results and Conclusion: In this study, we demonstrated that MEK5/ERK5 signaling pathway is a new target of Sorafenib. Thus, we showed that Sorafenib provokes a partial inhibition of MEK5 activity upon treatment with EGF or by expression of a constitutively active MEK5 mutant form. Furthermore, we have confirmed our observations by using specific shRNA against ERK5.

Therefore, our data indicate that part of the therapeutic effect of Sorafenib could be mediated through the inhibitory effect exerted onto ERK5 signalling pathway, discarding other MAPK as ERK1/2 or p38MAPK pathways. In sum, our data demonstrate that ERK5 pathway is an indirect target of Sorafenib, providing new therapeutic opportunities in the use of this novel tyrosine kinase inhibitor.

Keywords: Sorafenib, ERK5, MAPK.
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