

Metformin targets the GTPase Rac1 to inhibit prostate cancer cell migration

Béatrice Dirat, Isabelle Ader, Muriel Golzio, Amel Mettouchi, Kathiane Laurent, Frédéric Larbret, Bernard Malavaud, Mireille Cormont, Emmanuel Lemichez, Jean Tanti, et al.

► **To cite this version:**

Béatrice Dirat, Isabelle Ader, Muriel Golzio, Amel Mettouchi, Kathiane Laurent, et al.. Metformin targets the GTPase Rac1 to inhibit prostate cancer cell migration. *Cancer*

Metabolism, 2014, 2 (Suppl 1), pp.O24. <inserm-00997565>

HAL Id: inserm-00997565

<http://www.hal.inserm.fr/inserm-00997565>

Submitted on 28 May 2014

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.

ORAL PRESENTATION

Open Access

Metformin targets the GTPase Rac1 to inhibit prostate cancer cell migration

Béatrice Dirat^{1,2}, Isabelle Ader², Muriel Golzio², Amel Mettouchi^{1,2}, Kathiane Laurent^{1,2}, Frédéric Larbret², Bernard Malavaud^{3,2}, Mireille Cormont^{1,2}, Emmanuel Lemichez^{1,2}, Jean François Tanti^{1,2}, Frédéric Bost^{1,2*}

From Metabolism, Diet and Disease 2014: Cancer and metabolism
Washington DC, USA. 28-30 May 2014

Background

The anti-diabetic drug metformin has been shown to affect cancer cell metabolism [1,2] and to display anti-tumoral properties in numerous cancers [3,4], however, its role in the formation of metastases remains poorly documented. Cell migration is a critical step in the progression of prostate cancer to the metastatic state, the lethal form of the disease.

Results

We show here that metformin reduces the occurrence of metastases in an orthotopic metastatic prostate cancer cell model established in nude mice. As predicted, metformin hampers cell motility in PC3 and DU145 prostate cancer cells and triggers a radical reorganization of the cell cytoskeleton. The small GTPase Rac1 is a master regulator of cytoskeleton organization and cell migration. We report that metformin inhibits Rac1 GTPase activity by interfering with some of its multiple upstream signaling pathways, namely P-Rex1 (a Guanine nucleotide exchange factor and activator of Rac1), cyclic AMP and CXCL12/CXCR4, resulting in decreased migration of prostate cancer cells. Importantly, overexpression of a constitutively active form of Rac1 (Rac1-Q61L or Rac1-V12), or P-Rex1 as well as the inhibition of the adenylate cyclase were able to reverse the anti-migratory effects of metformin.

Conclusion

Our results establish a novel mechanism of action for metformin through Rac1 and highlight its potential anti-metastatic properties in prostate cancer.

Acknowledgement

This research was supported by The French National Institute for Cancer (INCa) and The foundation ARC.

Authors' details

¹INSERM U1065, C3M, Nice, France. ²CNRS U5089, IPBS, Toulouse, France. ³Rangueil Hospital, Toulouse, France.

Published: 28 May 2014

References

1. El-Mir MY, Nogueira V, Fontaine E, Averet N, Rigoulet M, Leverve X: Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. *J Biol Chem* 2000, **275**:223-8.
2. Ben Sahra I, Laurent K, Giuliano S, Larbret F, Ponzio G, Gounon P, et al: Targeting cancer cell metabolism: the combination of metformin and 2-deoxyglucose induces p53-dependent apoptosis in prostate cancer cells. *Cancer Res* 2010, **70**:2465-75.
3. Ben Sahra I, Laurent K, Loubat A, Giorgetti-Peraldi S, Colosetti P, Auburger P, et al: The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. *Oncogene* 2008, **27**:3576-86.
4. Zakikhani M, Dowling R, Fantus IG, Sonenberg N, Pollak M: Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. *Cancer Res* 2006, **66**:10269-73.

doi:10.1186/2049-3002-2-S1-O24

Cite this article as: Dirat et al.: Metformin targets the GTPase Rac1 to inhibit prostate cancer cell migration. *Cancer & Metabolism* 2014 **2**(Suppl 1):O24.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit



¹INSERM U1065, C3M, Nice, France
Full list of author information is available at the end of the article