



UNIVERSITY OF LEEDS

This is a repository copy of *Receptor Tyrosine Kinase Signalling in the Absence of Kinase Activity and Cancer of Non-Genetic Origin*.

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/151862/>

Version: Accepted Version

Proceedings Paper:

Ladbury, JE orcid.org/0000-0002-6328-7200 (2019) Receptor Tyrosine Kinase Signalling in the Absence of Kinase Activity and Cancer of Non-Genetic Origin. In: The Journal of Pathology. Leeds Pathology 2019. 12th Joint Meeting of the British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland, 02-04 Jul 2019, Leeds. Wiley , S8-S8.

<https://doi.org/10.1002/path.5345>

© 2019 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd. This is the peer reviewed version of the following article: Ladbury, JE (2019) Receptor Tyrosine Kinase Signalling in the Absence of Kinase Activity and Cancer of Non-Genetic Origin. In: The Journal of Pathology. Leeds Pathology 2019. 12th Joint Meeting of the British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland, 02-04 Jul 2019, Leeds. Wiley , S8-S8, which has been published in final form at <https://doi.org/10.1002/path.5345>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Receptor tyrosine kinase signalling in the absence of kinase activity and cancer of non-genetic origin

John E. Ladbury. School of Cellular and Molecular Biology, University of Leeds.

Cancer cells which express FGFR2 and have low concentrations of the adaptor protein Grb2 show high prevalence for metastatic outcome. In non-stimulated cells the SH3 domain (and not the SH2 domain(s)) of Plc γ 1 directly competes for a proline-rich binding site at the very C-terminus of FGFR2 with the C-terminal SH3 domain of Grb2. Reduction of Grb2 concentration permits access of Plc γ 1 to the receptor. Recruitment of Plc γ 1 in this way is sufficient to up-regulate phospholipase activity. This results in increased cell motility and promotion of cell invasive behavior in the absence of extracellular receptor stimulation. Therefore metastatic outcome can be dictated by the constitutive competition between Grb2 and Plc γ 1 for the phosphorylation-independent binding site on FGFR2. Since the majority of receptor tyrosine kinases have proline-rich sequences in their C-termini, the possibility of a second tier of signal transduction in the absence of growth factor stimulation, or kinase-activating mutations emerges – leading to cancer of non-genetic origin.