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## The therapeutic potential of the translation initiation factor $eIF2\alpha$ serine 51 phosphorylation for chronic myeloid leukemia

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The t (9; 22) chromosomal translocation present in almost all CML patients' results in the expression of a 210 kDa fusion protein known as Bcr-Abl. Bcr-Abl is a tyrosine kinase with potent oncogenic properties, which is the underlying cause of CML. Although Bcr-Abl has been an attractive target for therapeutic intervention, CML patients frequently develop resistance to pharmacological inhibitors of Bcr-Abl. Therefore, the identification of intracellular pathways that contribute to the oncogenic effects of Bcr-Abl and development of drug resistance has been an important goal of CML research. As a result of an international collaboration between Poland and Canada, we have identified a novel pathway of Bcr-Abl signaling, which is the phosphorylation of  $\alpha$  subunit of the translation initiation factor eIF2 at serine 51 (eIF2 $\alpha$ S51P). The eIF2 $\alpha$ S51P is a master regulator of stress and an important mechanism utilized by cells to adapt to various forms of environmental stress through the translational control of select mRNAs that can promote either cell survival or death. We found that Bcr-Abl induces eIF2 $\alpha$ S51P in CML cells in culture, CML patients and mouse xenograft tumor assays via the activation of the endoplasmic-reticulum (ER)-resident kinase PERK. Genetic inactivation of eIF2 $\alpha$ S51P impairs the oncogenic properties of Bcr-Abl and increases the sensitivity of CML cells to the anti-tumor drug imatinib in culture and mice. Our work demonstrates that pharmacological inhibition of eIF2 $\alpha$ S51P is likely to be a suitable approach to increase the sensitivity of anti-tumor drugs targeting Bcr-Abl as a means to combat CML disease.

## **Biography**

Katarzyna Piwocka has obtained her MSc degree in Microbiology from the Warsaw University in 1994 and PhD in Biology, specialization Biochemistry from the Nencki Institute in Warsaw, Poland in 2001. She has received Postdoctoral Training at the Bio-Sciences Institute, University College Cork, Ireland (2003-2004). In 2014, she has received Habilitation in Biological Sciences. Currently, she is an Associate Professor, Head of the Department of Biochemistry (since 2015) and Head of the Laboratory of Cytometry (since 2010) at the Nencki Institute in Warsaw, Poland. She has won several awards including a five-year ISAC Scholar Fellowship from the International Society for Advancement for Cytometry.

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