Science Proceedings 2015; 2: e638. doi: 10.14800/sp.638; © 2015 by Alessandro Morotti
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RESEARCH HIGHLIGHT

The role of the tumor suppressor PTEN in chronic myeloid leukemia pathogenesis

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Received: February 12, 2015
Published online: March 11, 2015

The Phosphatase and Tensin homolog detected on chromosome Ten PTEN displays tumor suppressive functions within two different cellular compartments. In the cytoplasm/membrane, it controls cellular proliferation, survival and metabolisms, through the de-phosphorylation of the phosphatidylinositol (3,4,5) triphosphate (PIP3), therefore counteracting the PI3K-AKT pathway. In the nucleus, it regulates proliferation and genomic stability through phosphatase independent mechanisms. Chronic Myeloid Leukemia is a myeloproliferative disorder generated by the translocation t(9;22), which encodes for the chimeric protein BCR-ABL. PTEN was shown to play an essential role in CML pathogenesis in a murine model. We and others have demonstrated that PTEN is affected in human CML though non genomic loss of function mechanisms. Furthermore, we proposed strategies to reactivate PTEN in CML cells, with relevant therapeutic implications.

To cite this article: Alessandro Morotti. The role of the tumor suppressor PTEN in chronic myeloid leukemia pathogenesis. Sci Proc 2015; 2: e638. doi: 10.14800/sp.638.

Introduction

The Phosphatase and Tensin homolog detected on chromosome Ten PTEN is one the most important tumor suppressor, with mutation/deletion rates similar to those of p53 in all cancers [1]. Recently, the mechanism of tumor suppressor involvement in cancer has been completely revised [2,3]. Original observations by Knudson supported the model whereby a tumor suppressor plays a role in cancer pathogenesis when both alleles are genetically affected, generally one by point mutations and one by deletions. Observations in murine models and human cancers have suggested that even genetically wild-type tumor suppressors can be involved in cancer pathogenesis [4,5]. In particular, reduction of tumor suppressor protein levels, changes in protein compartmentalization or post-trasductional modifications can functionally inhibit tumor suppressor functions [6–8]. These observations could have tremendous implications from the therapeutic standpoint. The discovery of mechanisms that promote tumor suppressors inactivation could indeed be directly targeted to promote normalization of protein level, localization or protein status. These events could lead to a selective strong apoptosis induction in cancer cells without affecting normal cells [9]. Chronic Myeloid Leukemia is a challenging disease to test this model [10]. CML is a myeloproliferative disorder characterized by the translocation t(9;22) coding for the chimeric protein BCR-ABL [11]. CML is referred as an unique cancer, due to the fact that no tumor suppressors have been found mutated/deleted in the early stages of CML pathogenesis [12]. Furthermore, expression of BCR-ABL was considered sufficient to promote leukemogenesis [13], suggesting that BCR-ABL expression could somehow promote tumor suppressors inactivation. Notably, Peng and colleagues demonstrates that PTEN plays an important role in the pathogenesis of CML, in a murine model [14]. In human CML, PTEN was never shown mutated or deleted during the chronic phase of the disease [15]. Following these observations, we aimed to demonstrate that BCR-ABL functionally inactivates PTEN in CML.

Mechanisms of PTEN functional inactivation in CML

BCR-ABL promotes PTEN nuclear-exclusion in CML

Changes in the proper cellular compartmentalization of tumor suppressors have been reported to play an essential and druggable role among non genomic loss of function mechanisms that inactivate tumor suppressors [16]. In particular, PTEN, p53 and FoxOs have been shown to display different tumor suppressive functions accordingly to their cellular compartmentalization [16]. PTEN loss of nuclear pool was indeed associated with disruption of PTEN nuclear suppressive function [17–19]. In line with these considerations, while we were assessing PTEN cellular compartmentalization in CML, we discovered that CML progenitor cells and differentiated cells were characterized by PTEN nuclear exclusion [20,21]. We demonstrated that BCR-ABL regulates PTEN localization through a PML/HAUSP network. Strikingly, CML stem cells expressed physiological cytosol/nuclear diffuse PTEN localization, due to high levels of expression of the HAUSP regulator PML. These observations demonstrated that PTEN is functionally inactivated through the loss of nuclear pool in CML. Furthermore, we also showed that PML/HAUSP/PTEN network can be targeted by arsenic trioxide treatment, which in turn promotes CML stem cell exhaustion [20,22].

PTEN protein levels are reduced in primary CML cells

BCR-ABL expression was associated with PTEN protein down-regulation [23]. Recently, we and others have demonstrated that PTEN is under-expressed in primary CML samples [24,25]. Similarly to oncogenic Ras regulation of PTEN levels [26], we observed that BCR-ABL regulates PTEN expression through a Ras-MEK pathway [25]. Notably, treatment with MEK inhibitors was associated with restoration of PTEN levels in BCR-ABL-infected cells. Interestingly, BCR-ABL mediated cellular transformation was also associated with the expression of a long non coding RNA, which is able to regulate PTEN expression, suggesting a more complex mechanism of PTEN expression regulation in CML [27]. These data further highlight how mechanisms of regulation of PTEN expression could play an essential role in the pathogenesis of CML.

PTEN is inactivated in CML

Our observation that PTEN is delocalized into the cytosol of CML primary cells suggested that PTEN could affect PI3K-AKT pathway in CML. This hypothesis was in contrast with the observations that PI3K-AKT plays an essential signaling transduction role in BCR-ABL-mediated transformation [28,29]. To solve this controversy, one simple explanation could be that the reduction of PTEN levels in CML counter-acts the effects of delocalized PTEN toward PI3K. However, PTEN activity was also shown to be regulated by post-trasductional modifications [4,8]. In particular tail phosphorylation by Casein Kinase II was shown to inhibit PTEN activity [30]. In line with these considerations, we observed that PTEN is highly tail-phosphorylated on serine residues by Casein Kinase II, a BCR-ABL substrate. BCR-ABL/Casein Kinase II-mediated PTEN phosphorylation eventually results in PTEN inactivation [31]. These data are important from the therapeutic standpoint. Treatment with Casein Kinase II inhibitors is indeed able to promote PTEN de-phosphorylation and activation toward PI3K-AKT pathway, with apoptosis induction.

Conclusions

All together, these data demonstrate that CML is characterized by PTEN functional inactivation at different layers. BCR-ABL promotes PTEN delocalization through a PML/HAUSP network, PTEN under-expression, through Ras-MEK, and PTEN inactivation by Casein Kinase II mediated phosphorylation of PTEN tail. These phenomena likely coexist in the regulation of PTEN activity. Importantly, the BCR-ABL/PTEN network has important implications from the therapeutic standpoint. We indeed demonstrate that PTEN proper cellular compartmentalization could be restored by targeting PML, which is a physiological regulator of HAUSP, PTEN levels could be restored by MEK inhibitors and PTEN activity can be increased with Casein Kinase II inhibitors treatment. All these strategies are associated with CML growth arrest and apoptosis induction. Future efforts are require to better characterize the relevance of BCR-ABL/PTEN network in different CML cellular populations. Data regarding PTEN cellular compartmentalization have been indeed performed in sorted progenitors cells and stem cells, showing significant differences. Data regarding PTEN protein levels and activity are on the contrary observed in un-sorted cells. Therefore, due to the heterogeneity of CML cells, it could be that PTEN nuclear exclusion, PTEN down-regulation and PTEN inactivation are differentially regulated by BCR-ABL in CML. This situation could have important biological consequences and therapeutic implications.

Conflicting interests

Author has no financial conflict of interests.

Authorship contribution

The manuscript was written by A.M.

Acknowledgment

The author expresses his gratitude to Prof. G. Saglio and Prof. PP Pandolfi for their support while performing the experiments regarding PTEN in CML. Furthermore, these works were possible due to the help of Prof. A. Guerrasio, Dr. C. Panuzzo, Dr. S. Crivellaro, Dr. G. Carrà, Dr. A.H. Berger and Dr. K. Ito. My research is funded by the "Giovani ricercatori – Ricerca Finalizzata" Funding of the Italian Ministero della Salute, Grant GR-2010-2312984.

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