Modeling the level of Bcr-Abl oncoprotein in K562 cells by inhibiting USP1 deubiquitinase

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Introduction

Statement of the Problem: The development of chronic myeloid leukemia (CML) is caused by oncoprotein Bcr-Abl. The use of existing tyrosine kinase inhibitors is ineffective for almost one-third of patients, so there is an urgent need to develop new approaches that will allow modeling oncogenicity in CML cells. The aim of this study was to determine the effects of the interaction of Bcr-Abl with USP1 deubiquitinase on the level of oncoprotein in CML cells. Methodology & Theoretical Orientation: K562 cells were selected for the experiment. Protein complexes were studied by coimmunoprecipitation, pull-down analysis, immunofluorescence, confocal microscopy. Expression level of Bcr-Abl was studied by Western blot analysis. The results were analyzed quantitatively and statistically. Findings: We found the interaction and colocalization of Bcr-Abl with USP1 deubiquitinase in nucleus of CML cells. Protein interaction between USP1 and PH domain of Bcr-Abl was revealed. It has been shown that the main site of localization of recombinant PH domain protein in K562 cells is the nucleus, and nuclear structures have been detected where it is localized with the USP1. Inhibition of USP1 by ML323 has been shown to disrupt the formation of Bcr-Abl/USP1 protein complex and to reduce the level of oncoprotein in K562 cells. Conclusion & Significance: It has been determined that the formation of Bcr-Abl/USP1 nuclear complex depends on presence of PH domain in the oncoprotein. We believe that the consequence of the formation of Bcr-Abl/USP1 protein complex is the deubiquitination of the oncoprotein, which leads to disruption of its proteasomal degradation. It has been shown that a decrease of the level of Bcr-Abl in CML cells can be achieved by inhibiting the deubiquitination activity of USP1. Thus, USP1 is a promising therapeutic target for the development of a new treatment strategy by modeling the level of oncoprotein in CML cells.

Conclusion

USP1 protein has been identified as a new protein partner of Bcr-Abl oncoprotein in chronic myeloid leukemia. The relationship between the functional activity of USP1 protein and the level of Bcr-Abl oncoprotein has been demonstrated, suggesting that the targeted inhibition of USP1 activity could be a challenging approach for reducing Bcr-Abl expression.

Keywords

BCL-XL, BCR-ABL, K562, Small interference RNA, STAT5

Biography

Antonenko Svetlana has experience in studying the molecular mechanisms of the pathogenesis of chronic myeloid leukemia. Svetlana is working on a new approach to CML therapy that will allow modeling the level of cancer proteins in cells using deubiquinating proteins and will be insensitive to mutational variability in the kinase domain, which is a major problem in developing resistance to kinase inhibitors.

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