

Protein interactors of the cellular tumor antigen p53 with response to ionizing radiation

Silvia Vasquez^{1,3,4,*}, Roberto Pineda², Mohanalatha Chandrasekharan³, Prashanth Suravajhala^{3,4}

¹ Dirección de Investigación y Desarrollo, Centro Nuclear RACSO, Instituto Peruano de Energía Nuclear, Av. Canadá 1470, Lima 41, Perú

² Facultad de Ciencias Biológicas, Universidad Ricardo Palma, Av. Benavides 5440, Surco, Lima 33, Perú

³ Bioclues.org, IKP Knowledge Park, Secunderabad, 500009 AP, India

⁴ Bioinformatics Organization, Hudson, Massachusetts, United States of America

Abstract

TP53 interacts with the genes CDKN1A, CSNK1A1, CSNK1D, BAX, ATM, MDM2, HIF1A, SP1. This consensus network has many binding regions involved in phosphorylation. To find whether or not the interactions are involved in ionizing radiation (IR), we used protein interaction mining and visualization tools to decipher the network. We conclude that ATM, PCNA, TP53 and CDKN1A show protein interactions on cellular response to IR.

Resumen

TP53 interactúa con los genes CDKN1A, CSNK1A1, CSNK1D, BAX, ATM, MDM2, HIF1A y SP1. La red consensual mencionada presenta varias regiones de unión que intervienen durante la fosforilación. Para encontrar si estas interacciones participan o no en la respuesta a la radiación ionizante (IR) analizamos la minería de interacciones proteicas y las herramientas de visualización para descifrar la red. Concluimos que ATM, PCNA, TP53 y CDKN1A presentan interacciones proteicas en la respuesta celular a IR.

1. Introduction

The cellular tumor antigen p53[1] participates in the regulation of the cellular cycle and the tumor suppression as a cellular response. The gene TP53 is located on the chromosome 17 (17p13.1) in humans with the encoded protein for 393 amino acids and four units or domains where one domain activates the transcription factors while another recognizes specific DNA sequences. Together they are called the core domains and are responsible for the protein tetramerization recognizing the DNA damage. Earlier, we had explored the role of p53 in cardiovascular diseases CVD [2]. Our erstwhile approach, we believe has narrowed down the experimentation in finding better candidates for p53 in cardiovascular system. While MSH2 is known to be found in both mitochondria and cytoplasm (or nucleus), the subcellular location studies we had employed has given a validation that MSH2 might also play an important role in deciphering the role of these proteins linked to p53, towards CVD. We believe and envisage that the other

proteins could also be better candidates and it would be interesting to run pull down assays for these proteins to check for their candidacy in CVD. With TP53 interacting with host of genes, viz. CDKN1A, CSNK1A1, CSNK1D, BAX, ATM, MDM2, HIF1A, SP1, a consensus protein interaction networks of physical interactions need to be built which would allow us to find genes involved in phosphorylation of Thr-145 by Akt or of Ser-146. These impair binding to PCNA while phosphorylation at Ser-114 by GSK3-beta enhances ubiquitination by the DCX (DTL) complex. Phosphorylation of Thr-145 by PIM2 is known to enhance CDKN1A stability and inhibits cell proliferation. Whereas phosphorylation of Thr-145 by PIM1 results in the relocation of CDKN1A to the cytoplasm and enhanced CDKN1A protein stability, ubiquitination by MKRN1 leads to polyubiquitination and 26S proteasome-dependent degradation.

* Corresponding author: svasquez@ipen.gob.pe

2. Methods

Through this study, we exploited the protein interaction partners by showing evidence of interactions for ATM and CDKN1A, known to be involved in cellular response to IR [3]. We used protein interaction mining and visualization tools in the form of Genecards [4], Genemania [5] and String [6] to bring out the interactions and analyze them towards radiosensitivity studies. The methods discussed can be linked to our previous studies [2].

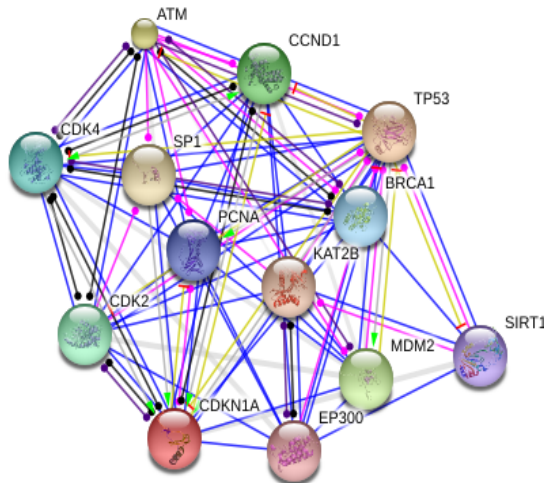


Figure 1. ATM, PCNA, TP53 and CDKN1A in a cloud of interactome.

3. Results and Discussion

We reviewed that CDKN1A is an important intermediate by which p53 mediates its role as an inhibitor of cellular proliferation in response to DNA damage. Further, it binds to and inhibits cyclin-dependent kinase activity, preventing phosphorylation of critical cyclin-dependent kinase substrates and blocking cell cycle progression while ataxia telangiectasia mutated (ATM) is a serine/threonine protein kinase involved in activation of checkpoint signaling upon double strand breaks (DSBs), apoptosis and genotoxic stresses (Figure 1). This allows the gene act as a DNA damage sensor. Further, it recognizes the substrate consensus sequence [ST]-Q phosphorylates 'Ser-139' of histone variant H2AX/H2AFX at

double strand breaks (DSBs) thereby regulating DNA damage response mechanism. Also known to be involved in signal transduction and cell cycle control, the gene plays a very important role as a tumor suppressor.

4. Conclusion

There is a lacunae of PPI studies involving cardiovascular diseased genes. We aimed to delve into these PPI studies as a whole allow to find the interacting genes involved in participation of cellular repertoire after the IR. Our analysis found ATM, PCNA, TP53 and CDKN1A as evident interactors related to IR. We now aim to identify genes and proteins participating at different levels of the cellular systems and validate the approaches in the wet lab.

5. References

- [1] PO4637 (Reviewed entry), UniProtKB /Swiss-Prot. Database. *UniProtKB*, Last modified May 29; 2013. Versión 209. Access date Jun. 10. 2013.
<http://www.uniprot.org/uniprot/P04637>
- [2] Chandrasekharan M, Vasquez S, Galimudi RK, Suravajhala P. Toward understanding the role of p53 in cardiovascular diseases. *J. Biomedical Science and Engineering*. 2013; 6:209-212.
- [3] Pernot E, Hall J, *et al.* Ionizing radiation biomarkers for potential use in epidemiological studies. *Mutation Research*. 2012; 751:258-286.
- [4] The GeneCards human gene database, *Genecards*, Last modified Apr 28; 2013. Versión 3.10, Access date Jun. 15. 2013.
<http://www.genecards.org>
- [5] GeneMANIA networks, *GeneMANIA*, Last modified Jul 19; 2012. Version 3.1.2, Access date Jun.15. 2013.
<http://www.genemania.org>
- [6] Franceschini A, Szklarczyk D, Frankild S, Kuhn M, Simonovic M, Roth A, Lin J, Minguez P, Bork P, von Mering C, Jensen LJ. STRING v9.1: protein-protein interaction networks, with increased coverage and integration. *Nucleic Acids Res*. 2013 Jan; 41(Database issue):D808-15.