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Review Article

Bioinformatics Assessment of p53 Interactions with Immunological Response-Related Proteins

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Abstract

The p53 protein is a classic tumor suppressor protein related to cancer and a series of other diseases such as endometriosis, atherosclerosis, and infertility. It regulates cell cycle progression and protects DNA against several types of damage. The p53 structure comprises three main domains, the transactivation domain, a DNA-binding core domain and a C-terminal domain related to down regulation of the DNA binding domain. The protein p53 is indirectly related to the immunological response of tumorigenesis. Irregular protein-protein interactions of p53 may interfere with the immune scenery within tumor environment leading to inflammation. The interactome of p53 contains more than one thousand protein interactors. Proteins such as MDM2, MDM4, BRCA1, TP53BP1 and PML interact with p53 in order to maintain DNA integrity and genomic stability. Moreover, p53 interacts with immunological response-related proteins. Inflammation influences the onset of cancer, thus p53 could play immunological roles in tumorigenesis through immune response. Irregular protein-protein interactions of p53 may interfere with the immune scenery within tumor environment leading to inflammation and p53 interact with immunological response-related proteins such as CREBBP, SIRT1 and TRAF6. Here, we analyzed the interface of interaction between p53 and three binding partners, MDM2, CREBBP and SIRT1. We identified hot spots that could be of importance for the conformational structure of those proteins, their function and pattern of interaction with their partners. We have also shown that some of the hot spot amino acid residues present at the interface of interaction are polymorphic, which could disrupt the binding of p53 and partners, thus, leading to a higher susceptibility to cancer. Future studies should be performed in order to design small molecules that could Future studies should be conducted in order to design small molecules that could modulate the interaction between p53 and MDM2, CREBBP and SIRT1 in order to efficiency in the interaction, avoid disturbances immunological microenvironment of cells and the maintenance of genomic stability.

INTRODUCTION

The p53 protein, coded by the *TP53* gene, is a classic tumor suppressor protein related to cancer [1] and a series of other diseases such as endometriosis [2], atherosclerosis [3], and infertility [4]. It regulates cell cycle progression and protects DNA against several types of damage [5]. TP53 is located in the locus at 17p13.1 and comprises highly conserved 11 exons. The protein has 393 amino acids and presents structural homology between among species, as it can be confirmed by sequence alignment performed by BLAST (https://www.ncbi.nlm.nih.gov). Amino acid sequence alignment of human p53 and *Castor canadensis*, for example, shows 81% of identity (Figure 1). The wild-type p53 has a tetrameric molecular structure [6] as shown in Figure 2A.

The p53 protein is recruited when DNA undergoes exogenous or endogenous damage caused by a great variety of agents such as reactive oxygen species [7], hypoxia [8-10], nutrient [11-13] and micronutrient deprivation [14,15] and DNA replication stress [16]. Damaged DNA induces overexpression of p53 [14,17] and consequently it interacts with other proteins in order to trigger pathways related to repair [18], apoptosis [19] or cell cycle arrest [19,20]. The p53 protein structure (Figure 2B) is intrinsically related to its function. The conserved DNA binding motif of p53 ranges from amino acid residues 95 to 288 and encompasses approximately 66% of the entire protein. Mutations at this region

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Query  1    MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMDDLMLSPDDIEQWFTEDPGP  60
Sbjct  1    ...S..EL.I..........F........L..TSS.PP....LF-..EVAN.LE---.Q  56

Query  61   DEAPRMPEAAP-----------RVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGF  109
Sbjct  57   ..TLQI-L...VSKAPAPEVPAPEV.V.EV.A......VT.....................  115

Query  110  RLGFLHSGTAKSVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHM  169
Sbjct  116  ..................S...L..............................K....  175

Query  170  TEVVRRCPHHERCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDC  229
Sbjct  176  ................................A.....TH...................  235

Query  230  TTIHYNYMCNSSCMGGMNRRPILTIITLEDSSGNLLGRNSFEVHVCACPGRDRRTEEENL  289
Sbjct  236  ......F.......................N...........R..............F  295

Query  290  RKKGEPHHELPPGSTKRALSNNTSSSPQPKKKPLDGEYFTLQIRGRERFEMFRELNEALE  349
Sbjct  296  ......CP.P.L.G......SG..............D....K...........M......  355

Query  350  LKDAQAGKEPGGSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD  393
Sbjct  356  F..N.NE....E......Y..........H.......R......  399
```

Figure 1 The *Homo sapiens* and *Castor Canadensis* p53 amino acid sequence alignment performed by NCBI BLAST. The protein p53 is highly conserved across species. The query sequence corresponds to *H. sapiens* p53 and the subject sequence, in red, corresponds to the *C. Canadensis* p53. The dots in the graphic indicate identical amino acids at the same position within both sequences.

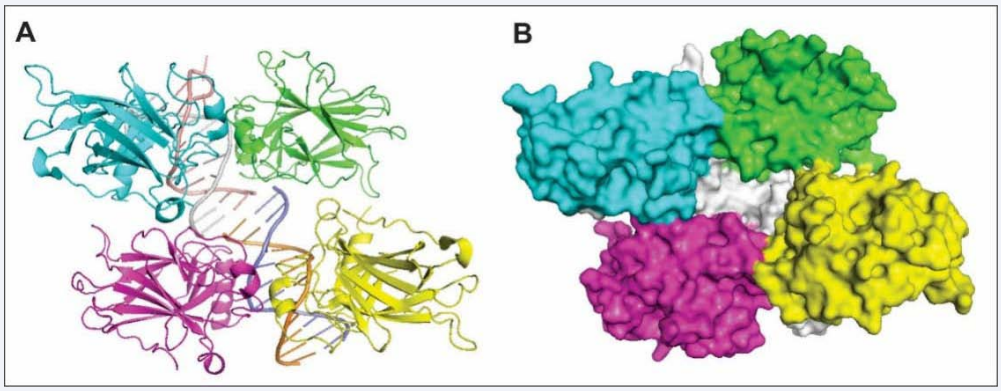

Figure 2 The *H. sapiens* p53 protein 3-D structure.
A) The p53 protein is a tetrameric molecular structure. Each color in the figure represents an identical monomer that undergoes tetramerization in order to assemble the p53 whole structure. The figure shows the region of the protein that interacts with DNA.
B) The surface of the p53 protein. The 3-D structures of p53 were retrieved from the PDB (protein data bank) and the images were constructed using the PyMol program.a

are rather common and may increase cancer and other diseases susceptibility considerably [21].

Mutations in *TP53* gene are generally of the missense type and lead to a reduced or total loss of p53 functions [22,23], altering its ability to bind to other proteins and fulfill its function. It has been suggested that *TP53* mutations and consequently p53 protein structure anomalies drive tumor related inflammation and affect immunological aspects of several types of cancer onset. Impairment of p53 within tumor environment correlates to immunosuppression and immune evasion of cells with mitotic dysfunctions [24-26]. The p53 pathway in tumorous cells is highly dynamic and might be related to an immunological design to alleviate immunosuppression or immunosenescence besides improving antitumor immunity aspects.

DNA damage and genomic instability are closely related top53 dysfunction and the immunological response of tumorigenesis [27]. It is well known that inflammation influences the onset of cancer [28], thus p53 could play immunological roles in tumorigenesis through immune response. Irregular protein-protein interactions of p53 may interfere with the immune scenery within tumor environment leading to inflammation [29].

Tumor suppression mediated by p53 takes place by autonomous or non-cell autonomous mechanisms. The former features p53 normal DNA damage response towards repair, apoptosis or growth arrest while the latter is related to the advancement of inflammation [30]. Tumorous cells formation and cancer progression along with metastases are driven by molecular and cellular components present in within tumor environment [31]. Immunological components of cancerous cell environment comprise extracellular matrix, cytokines, chemokines and immunosuppressive constituents that guarantee a landscape of inflammation in order protect cancer from immune surveillance and elimination [32-34].

It has been reported an increased elevated p53 activity in several tissues of patients affected by autoimmune diseases, which are governed by inflammation processes. The most common are rheumatoid arthritis [35], ulcerative inflammatory bowel diseases, Crohn's disease [36] and Sjögren's disease [37]. The protein p53 levels are considerably altered in those inflammatory diseases, which is an indication of its relation to inflammatory stress [38].

MATERIALS AND METHODS

The 3-D structures used in the analysis are available in the PDB (protein databank; https://www.rcsb.org/) and the p53 monomer were modeled by the I-TASSER server [39]. We used KBDOCK in order to find protein domains and possible interaction between protein domains [40]. The protein docking was performed by ClusPro [41]. We used PyMol (https://pymol.org) for the visualization of the interface of interaction and the visualization of hot spots and polymorphic residues. The hot spots in the proteins under study were identified by KFC2 [42]. The server offers an automated analysis of a protein complex interface. The server analyses the structural environment around amino acid residues and checks for already known hot spots environments determined experimentally. The hot spot prediction is based on characteristics regarding conformation specificity (K-FADE) and biochemical features such as hydrophobicity (K-CON. Finally, the polymorphic residues were identified through the dbSNP (data base of single nucleotide polymorphism; https://www.ncbi.nlm.nih.gov/SNP).

RESULTS AND DISCUSSION

The protein p53 conserved domains

The TP53 gene codes for a protein with 3 conserved domains. The first domain is the p53 transactivation motif or activation domain number 1, which binds to proteins with regulatory functions in order to activate p53 protein transcription by inducing the transcription factors. It is a very short motif with a single amphipathic alpha helix that extends from residues 6 to 9 [43]. The transactivation motif is formed by two complementary domains responsible for transcriptional activation. The major one is at residues 1 to 42 and the other at residues 55 to 75. This domain is especially related to regulation of apoptotic genes [44].

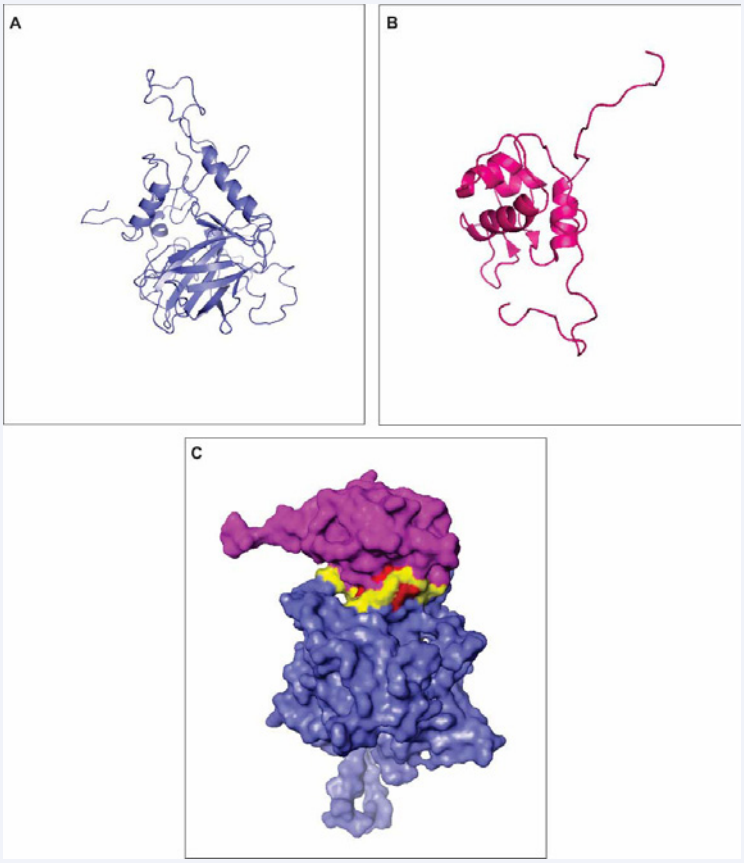

Figure 3 Hot spots prediction on the interface of interaction between p53 and MDM2.
A) p53 monomer. The p53 structure features intrinsically disordered domains responsible for the promiscuity pattern of interaction presented by the protein.
B) The MDM2 N-terminal domain. The structure features the prevalence of helical chains, which is directly linked to the regulatory role presented by MDM2.
C) The interface of interaction between p53 (blue) and MDM2 (pink). p53 is represented in blue and MDM2 in pink. The large interface of interaction between the proteins is represented in yellow. The red region represent hot spots predicted for the region of interaction and the one on p53 is the polymorphic hot spot residue related to disease susceptibility.

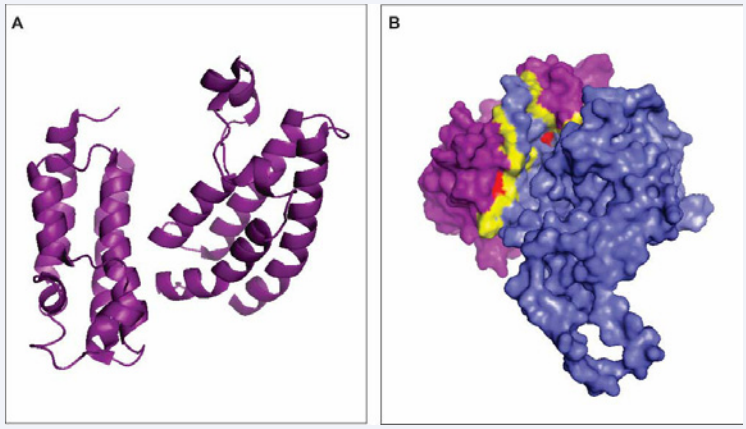

Figure 4 Hot spots prediction on the interface of interaction between p53 and CREBBP.
A) The CREBBPbromodomain.
B) The interface of interaction between p53 (blue) and CREBBPbromodomain (purple). The interface of interaction between the proteins is represented in yellow. Polymorphic hot spot residues are in the red regions and for this interaction, specifically, they are deep in within helices in the interaction interface.

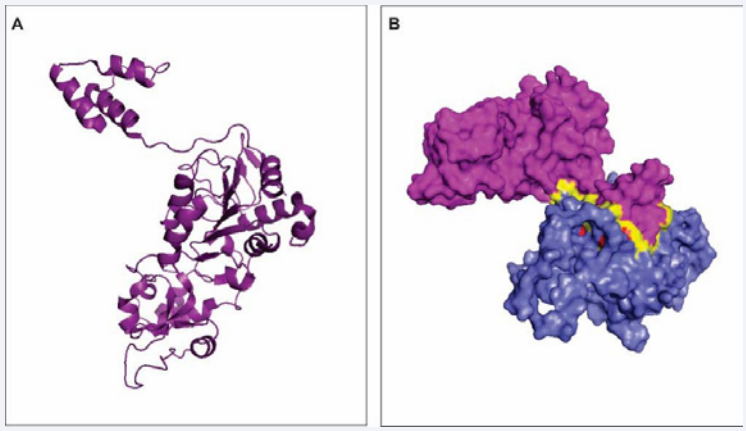

Figure 5 Hot spots prediction on the interface of interaction between p53 and SIRT1.
A) The SIRT1 conformational structure.
B) The interface of interaction between p53 (blue) and SIRT1 (purple). The interface of interaction between the proteins is represented in yellow. Polymorphic hot spot residues are seen red.

The p53 tetramerization motif is related to the protein oligomerization, which is essential for its DNA binding properties and consequently tumor suppression function [45]. It extends from residues 325 to 356. Oligomerization of p53 also plays important roles regarding its binding to other proteins belonging to DNA repair pathways, p53 turnover and post-translational modifications. The p53 DNA-binding domain attaches to damaged DNA and along with other proteins form a complex that stabilizes the DNA-protein complex (Figure 2A) [46]. The DNA binding motif is zinc dependent and rich in the amino acid arginine. It is the larger part of the protein and mutations, such as polymorphisms, are prone to disrupt p53 function and increase susceptibility to diseases [47].

Two domains are related to apoptosis, the activating domain number 2 and the proline-rich domain. The former span from residue 43 to 63 and the latter from residue 64 to 92. In addition, a nuclear localization signaling domain is located between residues 316 to 325. Finally, a C-terminal domain regulate the DNA binding feature of the activation domain 1, present at residues 356-393 [48].

Interactome of p53 and immunological response proteins

According to BioGRID database, *Homo sapiens* p53 interactome contains more than one thousand interactors. The large amount of proteins that interact with p53 shows how important it is for several biological processes. Some of the p53 protein partners are essential for the tumorigenesis suppression and maintenance of DNA homeostasis. Proteins such as MDM2 (proto-oncogene, E3 ubiquitin protein ligase) [49], MDM4 (p53 regulator) [50], BRCA1 (breast cancer 1, early onset)[51], TP53BP1 (tumor protein p53 binding protein 1) [52] and PML (promyelocytic leucemia) [53] interact with p53 in order to maintain DNA integrity.

MDM2 is a negative regulator of p53. MDM2 inhibits

p53 transcription process by binding to the N-terminal transactivation domain and it also ubiquitinates p53 in order to maintain metabolic normal levels of the protein through a degradation pathway [54-57]. We propose an *in silico* model for the interaction of p53 and MDM2. Figure 3A shows the conformational structure of the p53 monomer and Figure 3B shows the N-terminal domain of MDM2, the latter comprises 119 amino acid residues and is basically formed by helical shape and a few residues on a β-strand. It has been experimentally shown that this domain of MDM2 interacts with p53 [58]. Figure 3C shows the lowest binding free energy of the complex formed by p53 and MDM2. We found only two hot spots within the interface of interaction of the complex (Figure 3C) and one of those hot spots is highly polymorphic (Table 1). The substitution of the hot spot residue by a different amino acid may reduce the efficiency of the interaction and increase the susceptibility to cancer and other disease [59-61].

The protein MDM4 is related to apoptosis pathways [62], it also negatively regulates p53 activity by binding to the transactivation domain and suppressing its function. It has been shown that p53 interacts with BRCA1 and mutated versions of those proteins may impair their interaction leading to genomic instability [51]. TP53BP1 is frequently down-regulated in patients with breast cancer. The protein is related to DNA double strand damage repair through homologous recombination [63].

It has been experimentally shown that p53 interacts with immunological response-related proteins [64]. CREBBP (cAMP response element binding protein) is virtually expressed in all tissues, participates in the transcriptional activation of several transcription factors [65]. CREBBP is a well-known protein that either activates or inhibits several cellular pathways such growth, differentiation, immune response, apoptosis and cell cycle arrest [66]. Interaction of p53 and CREBBP has been shown to play a role in DNA damage response [67-70], where CREBBP regulates p53 transactivation [68]. Figure 4A shows the conformational structure of CREBBP bromodomain, which if formed by 116 amino acid residues. More than 65% of the structure is found in helical form and this shape is related to the ability of the protein bind to partners. The interface of interaction between CREBBP and p53 is large and five hot spot residues were predicted for this region of interaction (Figure 4B). Interestingly, all of those hot spots residues are polymorphic (Table 1) and mutations on them increase the likelihood of cancer onset and immune deregulation of cells microenvironment [71-73], except on the Leu 93, which is normally a synonymous mutation.

The protein p53 also interacts with SIRT1 (Sirtuin 1 - NAD-dependent deacetylase sirtuin-1) [74]. SIRT1 epigenetically regulates p53 activity through deacetylation [75]. The relation of p53 and immunological response within tumor environment may relies on SIRT1 activities. SIRT1 inhibits NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) expression through deacetylation [76] and the latter belongs to the most important transcriptional regulator group of genes that leads to inflammation. In addition, SIRT1 also takes part in activation of T helper cells, influencing autoimmune diseases onset and progression [77]. Figure 5A shows the 3-D structure of SIRT1,

Table 1: Hot spots prediction and polymorphisms that are likely to take place within the interface of interaction.

Interface	Residues	Score A*	Score B*	Polymorphism
p53-MDM2				
p53	Phe 212	1.93	0.35	Ile
MDM2	Lys 94	1.67	0.14	-
p53-CREBBP				
p53	Leu 93	1.21	0.04	synonymous
p53	Phe 212	1.11	0.00	Ile
CREBBP	Glu 1149	0.81	0.06	Gln
CREBBP	Trp 1151	1.65	0.25	Arg, Cys
CREBBP	Gln 1152	1.27	0.25	Gly, Hys
p53-SIRT1				
p53	Tyr 163	0.94	0.34	Cys, Asn, Hys
p53	Gln 165	1.67	0.15	Nonsense
p53	Arg 248	1.06	0.08	Gln
p53	Arg 249	0.45	0.26	Lys, Thr, Met
p53	Arg 273	0.90	0.23	Cys, Ser, Arg
p53	Phe 328	0.76	0.00	Synonymous
p53	Met 332	1.22	0.33	-
p53	Met 340	1.32	0.32	-
SIRT1	Tyr 185	1.40	0.36	-
SIRT1	Phe 187	1.40	0.26	Synonymous
SIRT1	Gln 189	0.74	0.10	Arg
SIRT1	Gln 190	1.32	0.13	Synonymous
SIRT1	Met 193	1.27	0.23	Val, Thr, Ile
SIRT1	Ile 201	0.36	0.13	-

*Hot spot model based on structure characteristics.
**Hot spot model based on biochemical characteristics (intermolecular hydrogen bonds).

comprised by 356 residues and highly variable N- and C- terminal domains. The interface of interaction between p53 and SIRT1 (Figure 5B) has 14 hot spot amino acid residues and 10 residues are polymorphic, including one linked to a nonsense mutation (Table 1).

The protein TRAF6 (TNF receptor associated factor) activates signal transduction pathways for TNF (tumor necrosis factor) receptors as response to proinflammatory cytokines, interferon, interleukin and growth factors. TRAF6 interacts with p53 in mitochondria and interferes with its apoptosis and DNA damage response functions [78]. TRAF6 also regulates the p53translocation to mitochondria, thus participating in apoptosis processes through unrepaired DNA disruption. Down-regulation of TRAF6 and poor levels of TRAF6-p53 interaction induces ubiquitination of p53 in the cytoplasm and consequently low levels of p53 in the face of DNA damage increases cancer and other diseases susceptibility [78].

CONCLUDING REMARKS

Computational methods have made important tools available and have increased our knowledge about the complex multiprotein world. The identification of molecular and biochemical features of the interaction interface in protein-protein interactions (PPI) has driven the development of new ways of diagnose and treatment of diseases such as cancer. Here, we analyzed the interface of interaction between p53 and thee binding proteins. We proposed hot spots that could interfere with the conformational structure of the complex, its function and the efficiency of interaction with their binding partners. We compared the hot spot residues with polymorphic residues from the dbSNP database. Several hot spots involved in the PPIs were polymorphic, which could disrupt the interaction between p53 and its protein partners, leading to a higher susceptibility to cancer. Future studies should be conducted in order to design small molecules that could modulate the interaction between p53 and MDM2, CREBBP and SIRT1 in order to efficiency in the interaction, avoid disturbances immunological microenvironment of cells and the maintenance of genomic stability.

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