Molecular docking analysis of p53 with Toll-like receptors

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Abstract:
P53 is one of the most important proteins for its role in cellular signal transduction pathways. It regulates a wide variety of cellular processes, which includes apoptosis, senescence, cell cycle arrest, differentiation, and DNA repair and replication and cancer dynamics. It is a transcription factor for various cellular proteins. Recent report suggests that P53 is linked with transduction proteins involved in cellular immunity. Toll like receptors are needed for communication in cellular immunity. The interaction between p53 and toll like receptors is reported in various studies. Therefore, it is of interest to document the molecular docking analysis of p53 with Toll-like receptors for further consideration in therapeutic development. In the present paper we studied molecular interaction between p53 and toll like receptors using molecular docking approach. We used open-source tools for molecular docking and analyzing the data. Our molecular docking results suggest there is a promising interaction between p53 and toll like receptors. Our study will be a very useful for molecular therapeutics and drug design strategies. Further, molecular dynamics studies can be useful to determine of the stability of complex form by p53 and toll like receptors.

Key words: p53, Toll-like receptor, Interaction, Communication, Docking

Background:
P53 protein act as transcription factor for various cellular proteins such as MDM2, p21, Fas, Bax, p48, PTEN, B99, PAl, related to apoptosis, cell-cycle arrest, senescence, glycolysis, TCA cycle, differentiation, cell fate and suppression of cancer cells progression [1]. The concentration of p53 protein in cells also varies due to its response to a variety of cellular stress, such as, hypoxia, nucleotide depletion, nitric oxide, DNA damage [2]. Recently, role of p53 in cellular immunity have been reported [3]. It is evident that a highly activated form of the p53 protein leads to suppression of inflammation. It is suggested that it activates Toll-like receptors (TLRs) proteins [4]. Cellular immunity acts as defense systems against bacterial, viral and fungal infections [5-7]. Moreover, cells have specialized receptor proteins (such as PRRs (pattern recognition receptors)), which are responsible for recognizing antigens such as bacteria, virus, fungus etc, and activating the proteins which are directly and indirectly associated with cellular immunity. Further, PRRs are specialized in functions due to its recognition of repeating patterns of molecular structures of pathogen, known as PAMP (pathogen...
Complex | HADDOCK score | RMSD from the overall lowest-energy structure | Van der Waals energy | Electrostatic energy | Desolvation energy | Z-Score
---|---|---|---|---|---|---
P53-TLR1 | 249.635 | 11.403 | -82.928 | -406.638 | -3.65 | -1.9
P53-TLR2 | 160.730 | 0.705 | -1092.7 | -430.636 | 0.423 | 1.3
P53-TLR3 | 161.814 | 10.601 | -63.759 | -110.697 | -4.252 | 1.7
P53-TLR4 | 318.532 | 1.008 | -83.113 | -600.484 | 17.544 | 2.2
P53-TLR5 | 263.119 | 11.506 | -105.488 | -548.465 | -8.441 | 1.9
P53-TLR6 | 254.99 | 11.201 | -91.629 | -266.719 | -12.834 | 0
P53-TLR7 | 301.914 | 11.60 | -101.513 | -334.907 | 7.654 | 1.4
P53-TLR8 | 197.774 | 10.203 | -98.316 | -426.407 | -1.135 | -1.7
P53-TLR9 | 310.11 | 7.04 | -769.7 | -372.553 | -6.338 | -1.8
P53-TLR10 | 196.216 | 14.101 | -101.951 | -384.517 | -0.928 | -1.7

Table 3: Global Fold Score:

| Gene | TPAIR | ECOMB | ES3DC | ELOCAL | E3DC | E3D | ZPAIR | ZECOMB | ZES3DC | ZELOCAL | ZEDDC |
|---|---|---|---|---|---|---|---|---|---|---|---|
P53-TLR1 | -45.16 | -5210.93 | -73.97 | 3620.70 | -66.76 | 35680.90 | -5.58 | 3.30 | 3.18 | -2.82 | -7.19
P53-TLR2 | -20.83 | -4257.57 | -57.29 | 3349.50 | -63.28 | 33467.60 | -5.20 | 3.76 | 4.81 | -3.34 | -6.78
P53-TLR3 | -21.13 | -3253.20 | -19.22 | 1990.20 | -63.28 | 23090.90 | -3.26 | 2.55 | 3.43 | -2.13 | -6.01
P53-TLR4 | -103.56 | -16148.51 | -73.60 | 69910.50 | -717.20 | 85268.20 | -9.89 | 2.53 | 7.75 | -1.68 | -7.92
P53-TLR5 | -82.13 | -15551.21 | -84.42 | 83571.70 | -625.98 | 98414.50 | -8.62 | 4.97 | 6.40 | -4.17 | -12.56
P53-TLR6 | -55.59 | -4850.50 | -75.56 | 30377.60 | -29.53 | 35077.50 | -6.70 | 3.63 | 5.94 | -3.15 | -6.85
P53-TLR7 | -147.22 | -28641.69 | -152.60 | 87646.90 | -901.99 | 107423.90 | -11.52 | 3.80 | 10.06 | -3.12 | -9.36
P53-TLR8 | -107.67 | -19154.50 | -125.96 | 87646.90 | -761.24 | 103869.70 | -10.30 | 3.75 | 9.25 | -2.98 | -9.79
P53-TLR9 | -207.68 | -18212.90 | -152.77 | 86413.50 | -715.53 | 103758.10 | -11.18 | 3.29 | 9.69 | -2.63 | -8.33
P53-TLR10 | -54.11 | -5359.40 | -66.50 | 29382.00 | -70.80 | 34604.10 | -6.36 | 3.92 | 4.49 | -3.39 | -8.07

Results:

We have shown p53 and TLRs interaction obtained from HADDOCK docking in Figure 1. It is noticed that all the TLR protein interact with p53 protein. We observed hydrogen as well as electrostatic bond near the interface between p53 and each TLR as shown in Figure 1. It is found that among all interaction between protein-protein, TLR 4 interaction is stable as shown table 1 and table 2. The binding affinity between TLR4 and p53 was found to be ~1.8, which is comparatively higher among all interactions. Further, dissociation constant is also comparatively higher for p53 and TLR4 interaction. The higher is the stability constant (dissociation constant), higher is the stability of the complex. Molecular docking results using PyDOCK (online server for protein-protein docking) as shown in figure 2. It is noticed from results shown in figure 2 that there is comparatively strong interaction between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9.

We assessed the stability of the complex formation between p53 and various TLRs proteins using SPSERVER statistical tools as shown in Figure 3. We observed that all TLR proteins forms stable complex with p53. Moreover, it is also noticed that from results shown in Figure 3 that there is comparatively strong stability between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes. Heatmap plot, as shown in figure 4, further confirmed the interaction between p53 and TLRs are very prominent. Moreover, it is again noticed that there is comparatively strong stability between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes.
Figure 1: HADDOCK docking output between p53 and TLRs. (A). Docking between p53 (in blue colour) and TLR 1 (in yellow colour) (B). Docking between p53 (in blue colour) and TLR 2 (in yellow colour) (C). Docking between p53 (in blue colour) and TLR 3 (in yellow colour) (D). Docking between p53 (in blue colour) and TLR 4 (in yellow colour) (E). Docking between p53 (in blue colour) and TLR 5 (in yellow colour) (F). Docking between p53 (in blue colour) and TLR 6 (in yellow colour) (G). Docking between p53 (in blue colour) and TLR 7 (in yellow colour) (H). Docking between p53 (in blue colour) and TLR 8 (in yellow colour) (I). Docking between p53 (in blue colour) and TLR 9 (in yellow colour) (J). Docking between p53 (in blue colour) and TLR 10 (in yellow colour).
Figure 2: PyDOCK docking output between p53 and TLRs. (A). Docking between p53 (in magenta colour) and TLR 1 (in blue colour) (B). Docking between p53 (in magenta colour) and TLR 2 (in blue colour) (C). Docking between p53 (in magenta colour) and TLR 3 (in blue colour) (D). Docking between p53 (in blue colour) and TLR 4 (in magenta colour) (E). Docking between p53 (in blue colour) and TLR 5 (in magenta colour) (F). Docking between p53 (in magenta colour) and TLR 6 (in blue colour) (G). Docking between p53 (in blue colour) and TLR 7 (in magenta colour) (H). Docking between p53 (in blue colour) and TLR 8 (in magenta colour) (I). Docking between p53 (in magenta colour) and TLR 9 (in blue colour) (J). Docking between p53 (in magenta colour) and TLR 10 (in blue colour).

Figure 3: SPSERVER interaction output between p53 and TLRs. (A). Interaction between p53 (in red colour) and TLR 1 (in cyan colour) (B Interaction between p53 (in red colour) and TLR 2 (in cyan colour) (C). Interaction between p53 (in red colour) and TLR 3
(in cyan colour) (D). Interaction between p53 (in red colour) and TLR 4 (in cyan colour) (E). Interaction between p53 (in red colour) and TLR 5 (in cyan colour) (F). Interaction between p53 (in red colour) and TLR 6 (in cyan colour) (G). Interaction between p53 (in red colour) and TLR 7 (in cyan colour) (H). Interaction between p53 (in red colour) and TLR 8 (in cyan colour) (I). Interaction between p53 (in red colour) and TLR 9 (in cyan colour) (J). Interaction between p53 (in red colour) and TLR 10 (in cyan colour).

Discussion:
The role of p53 in apoptosis and cancer is reported in various research literatures [1,2,17,20, 21]. Moreover, the role of p53 in cellular immunity is still a challenging area of the research [3,4,22]. Similarly, the role of TLRs is very much studied in cellular immunity [23-27]. However, role of TLRs in apoptosis and cancer is still few reported [10,28-31]. Docking result suggests that there are strong possibilities of interaction between p53 and TLRs proteins. The HADDOCK docking results in figure 1, suggests that TLR1 to TLR10 proteins interacts with p53 protein. Again, the binding affinity and dissociation constant as shown in table 1 further support the docking results obtained from HADDOCK. The PRODIGY analysis suggests that comparatively strong interaction between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes. Moreover, PyDock server docking results further suggest that there are interactions between p53 and TLRs proteins as shown in figure 2. The statistical assessment of the stability of complexes between p53 and various TLRs proteins also suggests and support the docking results as shown in figure3. Moreover, statistical analysis results also suggest that there is comparatively strong stability between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 complexes. Finally, Heatmap plot as shown in figure 4, clarify the interactions between p53 and TLRs proteins. Heatmap plot also suggests that there is comparatively strong stable complex between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9.

Conclusions:
We document the Molecular docking analysis of p53 with Toll-like receptors. Moreover, the interaction between p53-TLR4, p53-TLR7, p53-TLR8 and p53-TLR9 is found to be stable for the understanding of their molecular mechanism. Our study will be a very useful for molecular therapeutics and drug design studies for cellular immunity and cancer. In future path, for more clarity, molecular dynamics studies can be useful to determine of the stability of complex form by p53 and toll like receptors.

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