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Review

Structural and sequential context of p53: A review of experimental and theoretical evidence

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ABSTRACT

Approximately 27 million people are suffering from cancer that contains either an inactivating missense mutation of *TP53* gene or partially abrogated p53 signaling pathway. Concerted action of folded and intrinsically disordered domains accounts for multi-faceted role of p53. The intricacy of dynamic p53 structure is believed to shed light on its cellular activity for developing new cancer therapies. In this review, insights into structural details of p53, diverse single point mutations affecting its core domain, thermodynamic understanding and therapeutic strategies for pharmacological rescue of p53 function has been illustrated. An effort has been made here to bridge the structural and sequential evidence of p53 from experimental to computational studies. First, we focused on the individual domains and the crucial protein–protein or DNA–protein contacts that determine conformation and dynamic behavior of p53. Next, the oncogenic mutations associated with cancer and its contribution to thermodynamic fluctuation has been discussed. Thus the emerging anti-cancer strategies include targeting of destabilized cancer mutants with selective inhibition of its negative regulators. Recent advances in development of small molecule inhibitors and peptides exploiting p53–MDM2 interaction has been included. In a nutshell, this review attempts to describe structural biology of p53 which provide new openings for structure-guided rescue.

Contents

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1. Introduction

Spatio-temporal information of diverse proteins correlating their function in the tumor milieu is emerging as an important aspect of studying protein function in cancer microenvironment. The major factor responsible for cancer is the cumulative dynamic changes associated at the genomic level (Hanahan and Weinberg, 2000). This information alone is not considered to be sufficient to explain the equally intricate complexity in function of protein over time and space. Understanding how diverse proteins come together spatially as well as temporally and the translation of their unambiguous interactions into specific cellular response is therefore crucial. Linking structural changes of protein in the course of mutation with its altered cellular localization is therefore far more important to illustrate its function with respect to uncontrolled cellular proliferation. Thus the recent approach for studying molecular events in cancer is focusing more on the regulation of spatio-temporal distribution of proteins and their activity which can coordinate sequence–structure–function relationship with the progression of the disease. Tumorigenesis can be explained by a process of acquiring successive genetic mutations that transforms a normal cell into a malignant one. These genetic errors give rise to sustained proliferative signaling, enabling replicative immortality, evasion of growth suppression signals, resistance to cell death and tumor angiogenesis. This accelerates event like tumor cell invasion and metastasis. It is the deregulated expression of transcription factors, during tumorigenesis which promote proliferation and differentiation of the neoplastic population (Libermann and Zerbini, 2006). The relative expression of these proteins is found to be altered in cancer compared to that of the normal cells. The tumor suppressor protein p53 acts as a cell cycle regulator, involved in maintaining the genetic integrity and is popularly known as guardian of the genome. Control over the cell cycle machinery, apoptosis and DNA repair (Levine, 1997), are the critical activities of the tumor suppressor that elicits an anti-cancer response. Activation of p53 is triggered by events like DNA damage, hypoxia, heat shock and various other stress signals. Depending on the nature of the stress it decides the specific cellular outcome in an order to restrict any anomaly at the genetic level. Once activated, the confirmation of p53 undergoes modifications at both N- and C-terminal regions (Jenkins et al., 2012). Mutations affecting the three-dimensional structure of p53 have been reported to cause aberrant nucleo-cytoplasmic shuttling, cytoplasmic retention or mis-localization, thereby resulting in loss of its tumor suppressor functions.

The p53 family of transcription factors comprises the gene products of TP53, TP63, and TP73 genes. These proteins share a high-degree of homology in structure as they have evolved from the common ancestor in course of evolution (Belyi et al., 2010). p53 mutation develop variety of cancers including breast carcinomas, sarcomas, brain tumors, adrenal cortical carcinomas, defining the Li-Fraumeni and Li-Fraumeni-like syndromes (Olivier et al., 2003).

The family members of p53 are not only found in vertebrates but also in many invertebrates including mollusks, insects, and worms (Yang et al., 2000). Within the higher vertebrates, p63 and p73 have taken on new functions in the development of tissues and organs, whereas p53 has become the guardian of the somatic genome and a tumor suppressor as well. Mutation in p63 gene show developmental disorder like cleft palate, skeletal abnormalities, skin pathologies, but they do not develop cancers at high rates (Yang et al., 1999). p73 is involved in the development of the central nervous system and immune system (Belyi and Levine, 2009). It is to note that p73 can act as a back-up for p53 in response to various stress signals and can initiate apoptosis (Yang et al., 2000).

In the present review, an attempt has been taken for understanding the sequence and structural architecture of p53 protein and its importance with respect to cancer biology. Along with the information detailing structure–function affairs of proteins elucidated with experimental techniques, it is of high value to consider the computational aspects for exploring important physiological functions of biologically relevant molecules like p53 (Lane et al., 2011). Adoption of ideology with appropriate techniques, such as homology modeling, molecular docking and molecular dynamics to account the dynamicity and conformational attributes, could be useful in addressing important biological questions. Similar concepts such as free energy evaluation, energy landscape and water dynamicity have been discussed here with reference to the reported literature in context to p53 family. Thus evidences of sequential and structural information of p53 using relevant experimental and computational methods have been reviewed in this article, which explains functional signature of p53 in the biology of cancer (Brown et al., 2009).

2. Structure and function

2.1. Individual p53 domains

The general understanding of the biological concept necessitates an integration of experimental as well as computational research. An overview of the reported experimental and computational studies has been discussed in context to structure and function of p53. The theoretical studies have either correlated or supplemented additional information in conjunction to the experimental approach. Such an attempt will not only present a detailed overview of p53, but will also motivate to develop robust way-out to explore the missing link from structure to drug-design.

TP53 gene that resides on chromosome 17p13.1 encodes the 393 amino acid long protein-p53, which is the most frequent target for mutation in human cancer (Olivier et al., 2010). The functional state of p53 is homo-tetramer, where each monomer consists of an intrinsically disordered N-terminal transactivation domain (Met1-Asp42), a proline-rich domain with multiple copies of PXXP sequence (Asp61-Ser94), a central DNA binding core domain (Thr102-Lys292) and a C-terminal domain (Pro301-Asp393) containing a tetramerization domain (Asp324-Ala355) (Fig. 1).

The N-terminal domain of p53 is required for making contacts with the transcriptional co-activators or co-repressors (Fig. 2A). Biochemical and biophysical studies have revealed that this region of helix with double β-turn, occupy many structural motifs. It is noteworthy to mention that the secondary structure of this region is transiently stable. This region is crucial for binding with MDM2; where upon binding, there is a change in secondary structure form random coil to helix (Thr18 to Leu26) (Dawson et al., 2003). Kussie et al. have deciphered a part of p53 N-terminal domain structure in complex state with MDM2 (Fig. 2A) (Kussie et al., 1996). Espinoza-Fonseca et al. have further explored the helical property of the N-terminal domain using molecular dynamics (MD) simulation (Espinoza-Fonseca and Trujillo-Ferrara, 2006). It is interesting to find that the region of p53 (Phe17 to Leu22), depicts a stable picture of helical conformation in the simulation studies. The aromatic stacking ($\pi-\pi$ interaction) between Phe19 and Trp23 is also believed to be crucial in perturbing the secondary structure. Mutational studies in conjunction to MD simulation also reveal these two amino acids to be critical for functional role and maintaining structural stability of p53 (Lee et al., 2000). It can be concluded from these studies that the short region (Phe19 to Leu22), have anchor role for interaction between p53 and MDM2. Considering the residue-wise energetics contribution, it is Phe19 (−6.6 kcal/mol), Leu22 (−2.5 kcal/mol), Trp23 (−5.5 kcal/mol) and Leu26 (−3.9 kcal/mol) of p53 which are the key amino-acids for its interaction with MDM2 (Joseph et al., 2010). Binding of MDM2

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