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A Mini Review on an Enigma of Mutant P53

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Abstract

There are many genes that have been explored in relation with cancer. But 50 percent of cancers occur due to mutation in P53. In the beginning, there was a thought that P53 act as an oncogenic protein instead of suppressing cancers. Now we have reached on conclusion that mutant P53 instead of wild type, act as an oncogenic protein. Through research carried out in the past, it has been concluded that gain of function mutation in the P53 has early onset of cancer as compared to mutant P53 with loss of function. A number of hotspots for mutation in P53 such as R175, G245, R248, R249, R273 and R282 have been identified in the past. Mutant P53 interact and inhibit proteins normal functioning such as p63, MRE11, Rad51-NSB complex, p73 and Sp-1. Mutant P53 also lead to enhance functioning of protein such as SREBP, NF-Y, VDR, ETS2 and NRF2. For proper folding of wild type P53 Zn^{+2} is necessary. There are microRNAs which are under the control of mutant P53. Mostly, PRIMA-1 analog has been used to reactivate the mutant P53 to wild type.

Keywords: Mutation • P53 • DNA • Oncogenic protein

Introduction

P53 is one of the most studied tumor suppressor proteins. Mutations in P53 have been detected in many different types of tumors. For the first 10 years of discovery, P53 was considered to be an oncogene. This mistake in the initial classification of P53 was due to the fact that P53 gene that had been cloned and used in the initial experiments encoded a mutant version of the wild-type P53 gene. After 30 years of P53 discovery, we have come to conclusion that mutant versions of P53 act as oncogenic proteins. P53 is the most commonly mutated gene in human cancers [1]. Missense mutations in the DNA binding domain of P53 lead to tumors of different types. In some cases nonsense or frame shift mutations occurs which leads to suppression of P53 expression [2].

The powerful transcription factor p53 activates hundreds of genes, many of which are tissue- and cell-specific, by binding to two repeats of a particular DNA sequence (50-RRRCWWGYYY-30) as a tetramer. This sequence often appears within 10 kb of the promoter, while it can also appear at enhancers farther away. Numerous cellular cues, which frequently detect DNA damage, stress, and incorrect oncogene activation, cause p53 to be stabilised and activated. These p53-regulated genes serve a variety of purposes, including cell death (Puma, Noxa, Bax), cell cycle arrest (p21, Btg2, Ptprv), cell senescence (p21, Pml, Pai-1), and modifying metabolic status for cell survival (TIGAR, Soc-2, DRAM). What causes p53 to turn on so many genes? And how does it choose which genes to turn on at what time? These questions still have no clear solutions. Similar to the majority of transcription factors, p53 is often a highly transient protein (it has a 10-20 min half-life). Two important inhibitors, Mdm2 and Mdm4, keep p53 levels in healthy cells at extremely low levels. To target p53 for polyubiquitination and proteasomal destruction, Mdm2 encodes an E3 ubiquitin ligase. On the other hand, Mdm4 possesses a RING domain that isn't an E3 ligase but nevertheless joins forces with Mdm2 to stop p53 activity. Mdm4 probably acts as an E4 ligase to increase Mdm2's processivity.

Literature Review

Effect of mutations in P53

Mutant P53 shows novel gain of functions. Induction of mutant P53 in to P53 null mice gives rise to new phenotypes [3]. It has been shown that gain of function P53 mutants have higher and early onset of cancer as compared to mutant that lead to loss of P53 expression [4,5]. Consistently, *in vivo* studies have shown that mice expressing mutant P53 display a tumor profile that is more aggressive and metastatic than P53 null or P53 wild-type mice [6,7-9]. In both *in vitro* and xenograft models mutant P53s lead to enhance invasion and motility. Mutant P53 lead to enhance

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signaling through receptors such as Transforming Growth Factor b (TGF-b) receptor, epidermal growth factor receptor, and Hepatocyte growth factor receptor [10-14].

Mutation P53 interaction with DNA

P53 act as transcriptional factor and interact with DNA. P53 interact with the DNA by using DNA binding domain (p53-DBD) and C-terminal domain of p53 (p53-CTD) [15]. The interaction between p53 and target DNA through CTD and DBD depend on sequence. On the other hand mutant p53 interact with DNA through its core domain and C-terminal domain. Mutant p53 can bind with local DNA structure, non B-DNA and quadruplex DNA. Mutant p53 binds with local DNA structure with high affinity. The interaction between local DNA and mutant p53 does not depend on the sequence. The interaction between local DNA and mutant p53 depends on the structure of DNA. Mutant p53 can bind to non B-DNA structure in sequence independent manner. Moreover mutant p53 can bind to quadruplex DNA [16].

Mutant P53 as a protein

Mutant P53 has oncogenic effect in cell culture system in the absence of wild type P53. A number of hotspots (including R175, G245, R248, R249, R273 and R282) have been identified. Mutant P53 has been divided in 2 categories: 1. Structural mutants that can cause unfolding of the P53 protein. 2. DNA-contact mutants that change amino acids critical for DNA binding [17,18], It has been known that tumor derived P53 retain the N-terminal transcriptional transactivation domain. It has been found previously that tumor derived mutation in P53 may change, rather than abolish, the sequence specific DNA binding [19,20].

In most of the studies, it has been found that mutation in P53 occurs at codon 175,245,248,249,273 and 282. Almost every codon in DNA binding domain of P53 has been found to be mutated in cancer. Mutations have been found in the other domain of P53 but there significance in carcinogensis is unknown [21].

Mutant P53 interaction with other proteins

Mutant P53 has oncogenic function in the absence of wild type P53. Cancer due to mutant P53 shows increased metastasis and genomic instability. Several studies have shown that p63, a transcription factor; interact with mutant P53 instead of wild type P53. Mutant P53 inhibits the normal functioning of P63, MRE11, Rad51-NSB complex, p73 and Sp-1 which leads to genomic instability, chemoresistance, or proliferation. On the other hands, Mutant P53 can also promote the function of protein such as SREBP, NF-Y, VDR, ETS2 and NRF2 which leads to enhanced proliferation, cholesterol synthesis, accumulation of reactive oxygen species and enhanced cell survival [21].

Mutant P53 and its interaction with Zn^{+2} ion

Wild type P53 binds to Zn^{+2} ion so that it can fold properly. The R175H P53 mutant was shown to be impaired in Zn^{+2} ion binding. Loss of metallothioneins that chelate and store intracellular Zinc promotes a wild-type conformation of misfolded P53 [22]. On the other hand addition of Zinc to the conformational mutants of P53 such as G245C and G245D partially restored the wild-type conformation [23]. The use of Zn^{+2} to recover wild type conformation of P53 has been explored and it has been shown in the past that it increases the chemosenstivity to anticancer drugs. In addition, the thiosemicarbazone metal ion chelator NSC31926 was found to restore wild-type function, in a variety of different mutant P53-expressing cell lines, possibly through increasing the bioavailability of Zinc to mutant P53.

Mutant P53 and its interaction with microRNA

Mutant P53, besides regulating protein coding genes, also regulate many microRNAs and thereby alter the stability of various microRNA. There are many microRNAs which are found to be up regulated by mutant P53 such as miR-128-2, miR-155. On the other hand there are many microRNA which are down regulated by mutant P53 such as miR-223, miR-130b, miR-27a, let-7i, miR-205. Two recent studies have shown that mutant P53 regulate global miRNA biogenesis.

Discussion

Mutant P53 and its interaction with drugs

Mostly, PRIMA-1 analogs has been used to restore the activity of mutant P53 to wild type P53. PRIMA-1 is rapidly converted to other compounds, including MQ, which can bind to both mutant P53 and wild-type P53. Although mechanism that reactivate the mutant P53 to wild type remains still mystery. In some cases, unfolded P53 behave like mutant P53 which leads to invasion and metastasis. Functioning of unfolded wild-type P53, grown under hypoxia in tumor cell lines, can be restored by PRIMA-1 treatment. Cholesterol lowering drug statin has been found to induce degradation of misfolded P53 mutants with minimal effects on wild-type P53 and DNA contact mutants. Statin impairs the interaction between mutant P53 and DNAJA1, a Hsp40 family member. Knockdown of DNAJA1 leads to mutant P53 degradation; on the other hand over expression of DNAJA1 inhibit the degradation of mutant P53.

Conclusion and Future Prospect

Mutant p53 plays a major role in causing different type of tumors. In this review, we have briefly discussed some aspect of mutant p53 that have been described in the literature in the recent past. It is the need of hour to look at mutant p53 in detail especially its interaction with the DNA that will provide insight about cause of cancers. Secondly, we can look for anticancer drug which can directly inhibit Mutant p53 activity.

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