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REVIEW

Gene Regulation by p53 in Human Cancer System

Supratit Ghosh[1], Meghna Bhattacharjee[1], Nandan Kumar Jana[2]

[1]Department of Life science and Biotechnology; Jadavpur University, Kolkata-700032, WB, India. [2]Department of Biotechnology, Heritage Institute of Technology, Kolkata-700107, WB, India.

Abstract

TP53 proto-oncogene constitutes tumor induction in more than 50% of human cancers as it is mutated frequently in a wide range of cell lines. The transcription of *TP53* is postulated to be autoregulated via either binding with TBP and CBF or via direct interaction of p53 protein with *TP53* promoter, though further investigation is needed to acknowledge it. Alteration in pathways, regulated through wild type, by mutant p53 (Mutp53) give rise to immortality through interaction with other transcription factors or inducing receptor tyrosine kinases and other signal components. The missense mutation is more frequent constituting more than 60% among all mainly because of the high rate of G>A or C>T transitions in *TP53*, giving rise to mutation hotspots in R248, R273, etc. In addition to the loss of function, mutations in the *TP53* gene also confers oncogenic functions that are not found in wild type p53, referred to as Gain of Function (GOF). GOF mutp53 has been found to promote metastasis, cell proliferation, cell stemness, metabolic reprogramming as well as chemoresistance. Mutp53 also inhibits the wild type effect that is referred to as the Dominant negative effect (DNE). Understanding the mechanisms behind GOF activities, how they promote chemoresistance, and targeting mutp53 will help in improving the treatment of many human cancers with *TP53* mutations.

Keywords: p53 Transcription autoregulation- mutation hotspots- Gain of Function- Dominant negative effect- Chemoresistance

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Introduction

In the early 1970s, cancer research was mostly concerned with the cancer-causing viruses that were evidenced to become oncogene. In 1979 the p53 was first discovered as a protein associated with SV40 large T antigen [1]. In 1989, it was first observed that the mutations in *TP53* lead to colorectal cancer [2]. It took almost 10 years to realize the wild type p53 as a tumor suppressor protein [2]. p53 acts as a hub node in regulating the normal cell life like DNA damage control, signal transduction, metabolism, cell cycle checkpoints as well as in apoptosis [3]. Wild type p53 binds DNA in a sequence-specific manner while mutant p53 fails to bind to the consensus sequence of wild type target [4,5]. Wide spectrums of genes associated with a range of typical functions performed in cells are somewhat directly or indirectly regulated by the p53 functional domain [6,7]. The genetic variations in *TP53*, located in chromosome 17p13.1 contribute to human cancers within which the major contributions are of somatic mutations. Germline mutations also to some extent confer on mutant p53 network that affects inheritable mutability through *TP53* mutations accumulation. Mutations of p53 in specific regions give rise to cancers in different cell types and not only so, but it also regulates the typical phenotypic expressions of cancer cells to a large extent [8-10]. These conventional, as well as altered networks for both wild type and mutant p53 respectively, make it an interesting gene to study in the realm of molecular oncology.

p53 Domain Structure

The Full-length p53 (FLp53) consists of a total of 393 amino acid residues with distinct functional domains. Functional p53 is a dimer of dimers that are oligomerized to be p53 tetramer through the hydrophobic interactions between Leucine 344 and 348 in the oligomerization domain [11,12]

Structurally p53 has five distinct domains, as __ N-terminal transactivation domain (TAD), proline-rich

Corresponding Author:
Dr. Nandan Kumar Jana
Department of Biotechnology, Heritage Institute of Technology, Kolkata-700107, WB, India.
Email: nandankumar.jana@heritageit.edu