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Comprehensive omics studies of p53 mutants in human cancer

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Abstract

The p53 is the master regulator of the cell known for regulating a large array of cellular processes. Inactivation of p53 by missense mutations is one of the leading causes of cancer. Some of these mutations endow p53 with selective oncogenic functions to promote tumor progression. Due to the vast array of mutations found in p53, the experimental studies showing the role of different mutant p53 as an oncogene are also expanding. In this review, we discuss the oncogenic roles of different p53 mutants at the cellular level identified by multi-omics tools. We discuss some of the therapeutic studies to tackle p53 mutants and their downstream targets identified by omics. We also highlight the future prospective and scope of further studies of downstream p53 targets by omics.

Keywords: p53; multi-omics; p53 mutations; tumor progression; cancer

Introduction

The Tumor Antigen p53 (TAp53) is one of the most extensively studied tumor suppressor proteins discovered in 1979 [1–6]. As the guardian of the genome, p53 is in charge of safeguarding the genome by regulating numerous cellular pathways such as DNA repair, cell cycle and senescence, cell stress, apoptosis, cell growth and development. The p53 (393 residues) comprises of five distinct functional domains: the N-terminal transactivation domain, a proline-rich domain, DNA-binding domain (DBD), tetramerization domain and C-terminal regulatory domain [7, 8]. In the absence of functional p53, cells lose their defense against mutagens, genotoxic agents and harmful epigenetic changes. The missense mutation(s), either somatic or germline, inactivates p53 leading to tumorigenesis and tumor progression in a diverse spectrum of tissues [9, 10]. In the past two decades, over 30 000 somatic mutations of p53 have been reported in various cancers [11, 12]. More than 3686 p53 mutations are reported in the COSMIC database [13, 14], scattered in over 250 codons in 1800 different variations of the 393 amino acid tumor suppressor [15–17]. In many cancers, the mutp53 inside the tumor's microenvironment is usually stabilized and protected from degradation by various oncogenic pathways [13, 18, 19]. Many mutant p53 acquire oncogenic function or gain of function in some cancers giving additional growth and survival advantages to the tumor cell. By far it is known that the presence of missense p53 mutants in the cell results in multi-drug resistance, tumor progression, metastasis and invasive phenotypes [20–27]. However, only a few studies have reported the oncogenic roles of p53 mutants in different tissue types [23, 28–31]; therefore, the involvement of different mutp53 displaying oncogenic properties in the tumor progression is still an underexplored area. For the targeted therapy, it is important to identify unique or similar downstream pathways of different p53 mutants for drug development. Interestingly, >87.56% of missense p53 mutations are prevalent in the exon 4–9 spanning 190 different codons confined to the p53 DBD [32, 33]. The mutations in the DBD are classified into two classes: the DNA contact mutants and the structural mutants. Although mutation in each amino acid residue of this master regulator is identified, but very little is known about the impact of these p53 mutations on tumor progression. Also, it is unknown whether a mutant p53 can exhibit unique or multiple oncogenic functions to

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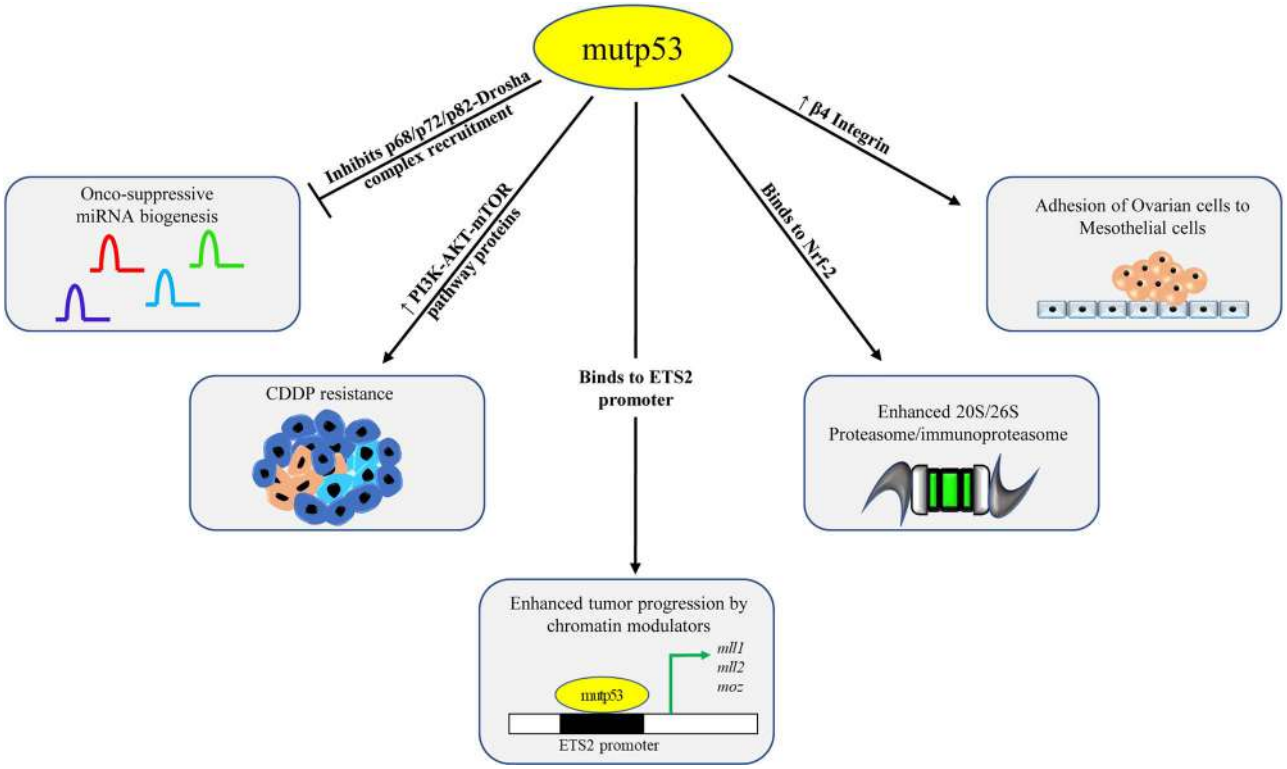

Figure 1. Multiple oncogenic functions performed by mutp53 to promote tumor progression.

assist tumor progression. The advancements of various high-throughput detection techniques have helped to generate an extensive library of data through omics, unveiling the mechanism of tumor progression. In this review, we try to decipher the role of oncogenic p53 mutants in tumor progression in different tissues/cell types through multi-omics studies (Figure 1).

Decoding negative regulation of miRNA by mutant p53 in colon cancer using transcriptomics

MicroRNAs (miRNAs) are tiny (20–25 nucleotides), conserved single-stranded noncoding RNAs crucial for posttranscriptional modulation of gene expression [34–36]. Till now, around 2000 miRNA genes are known for regulating a pool of predicted human miRNA targets [37]. The miRNAs are generally transcribed from DNA as primary miRNAs (pri-miRNAs) by RNA polymerase II and get processed into a 70 nucleotide long intermediate pre-miRNAs (precursor) in the nucleus via the microprocessor complex containing Drosha (Nuclear RNase III), DiGeorge Syndrome Critical Region 8, p68 and p72/p82 (DDX17) [38]. These pri-miRNAs get transported by Exportin-5 to the cytoplasm and further processed into functional 20–25 nucleotide long mature miRNAs by Dicer and other RNase-related enzyme Transactivation response element RNA binding protein (TRBP) [34, 38, 39]. Generally, these mature miRNAs play a key role in the translational repression of certain specific genes by interacting with the 3′ UTR (untranslated regions) of their mRNA targets [39–43]. The downregulation of mature miRNAs is usually seen in vast human malignancies [44–49], especially colon cancer [39–43], triggered by epigenetic or genetic alterations and miRNA-processing impairments.

The TAp53 regulates a large number of miRNAs by forming interactions with miRNA processing machinery proteins like p68/p72 [50]. By transcriptomics, Suzuki *et al.* established the role of wtp53 in controlling tumors by regulating miRNA processing and the role of mutant p53 as an oncogene in tumor progression [40]. By RNA-chromatin immunoprecipitation, they found that with the doxorubicin-induced DNA damage in HCT116 (colon), WI-38 (skin fibroblast), TIG-3 (lung) and TOV21G (ovarian) cell lines (RNA-ChIP), the wtp53-mediated posttranscriptional processing of a large number of pre- and mature forms of miRNAs was identified. In response to DNA damage, wtp53 increases the posttranscriptional maturation of various miRNAs like miR-145, miR-16-1 and miR-143 (Figure 2). In a typical miRNA processing, the C-terminus of wtp53 DBD forms interactions with microprocessor co-factors p68 and helps miRNA processing. Upon mutation, an altered form of interactions is formed by the N-terminal domain of mutant p53 with the co-factors, p72/82 RNA helicase in the pri-miRNA stage thereby eliminating the formation of the Drosha complex for micro RNA biogenesis. This altered phenomenon is observed in the p53 mutants R273H, R175H, P309S and R280K [51, 52]. However, in the p53 knockout cell lines, both Pre- and mature miRNAs processing was completely abolished, establishing the key role of wtp53 in miRNA

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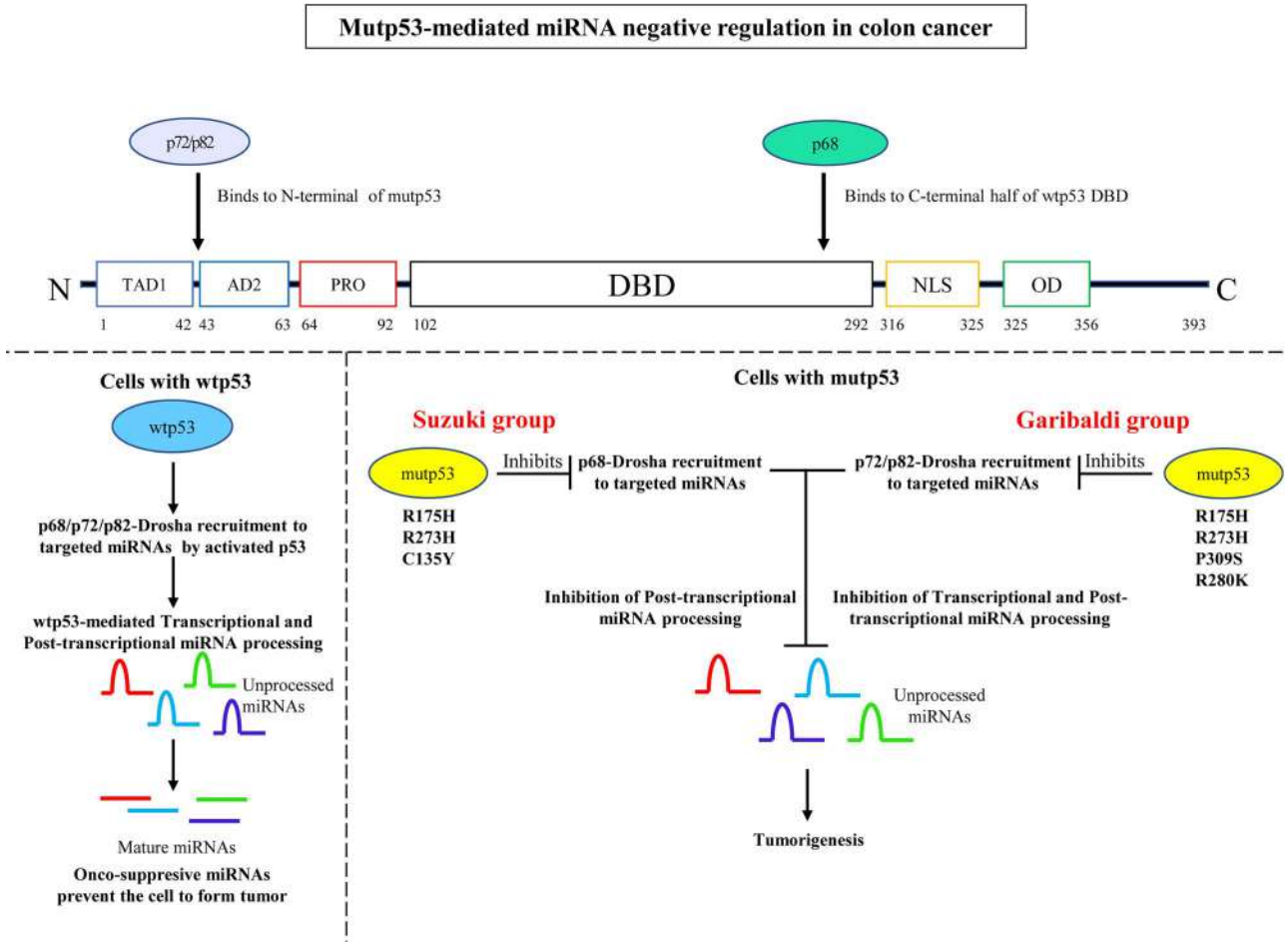

Figure 2. Schematic diagram of miRNA negative regulation mediated by mutp53 in colon cancer.

biogenesis. In p53 mutants R175H, R273H and C135Y, the Suzuki group also elucidated the oncogenic role of mutp53 in miRNA biogenesis. In p53 null colon HCT-116 cells, they found that the expression of mutp53 acquires an additional oncogenic role to suppress the levels of pre-and mature forms of miR-143, miR-206 and miR-16-1 (normally found to be elevated in the presence of wtp53). Hence, the miRNA biogenesis got abolished in these three different p53 mutants (Figure 2).

Similarly, genome-wide expression studies conducted by Garibaldi *et al.* [52] on 376 mature miRNAs in SW480 (colon adenocarcinoma) cells harboring p53 R273H/P309S mutations showed the downregulation of four important miRNAs (miR-519e, miR-455-3p, miR-562, miR-412). These miRNAs play crucial roles in the cellular mechanisms such as cell cycle arrest, epithelial–mesenchymal transition (EMT) repression, migration inhibition and apoptosis. A similar observation was reported in other human HT29 colon cancer (R273H) and breast cancer SKBR3 (R175H) cell lines. Thus, indicating that p53-mediated miRNA regulation and processing is not restricted to just one cell type or one mutation. To cross-validate, their findings, a large data sets of next-generation sequencing data of breast cancer patients from The Cancer Genome Atlas (TCGA) was used and in most of the cases, the identified miRNA was downregulated. Together both these omics-based studies highlight the significance of p53 in miRNA processing in different cancers (especially colon cancer) (Figure 2). Both the studies also established the oncogenic role of mutp53 R273H in colon cancer cells. Therefore, the RNA-ChIP and the insights from next-generation sequencing can be used as a pathbreaking tool for understanding various mutp53 endowed oncogenic functions in the regulation of miRNA processing.

Deciphering the role of mutp53-mediated hyperactivation of the proteasome in breast cancer using proteomics and transcriptomics

The increased activity of the 20S/26S proteasome in cancer cells to degrade various tumor suppressors in a ubiquitin-dependent and -independent manner is a well-known phenomenon. [53, 54]. Targeting the ubiquitin proteasomal system with drugs like Bortezomib and Carfilzomib is a proven therapeutic strategy in cancer therapy [55–57] (Figure 3), but the acquired resistance against these drugs is the biggest hurdle in therapy, especially in breast cancer [56, 58]. In the majority of drug-resistant cases, p53 was reported to be mutated. Using various omics techniques like whole-cell proteomics,

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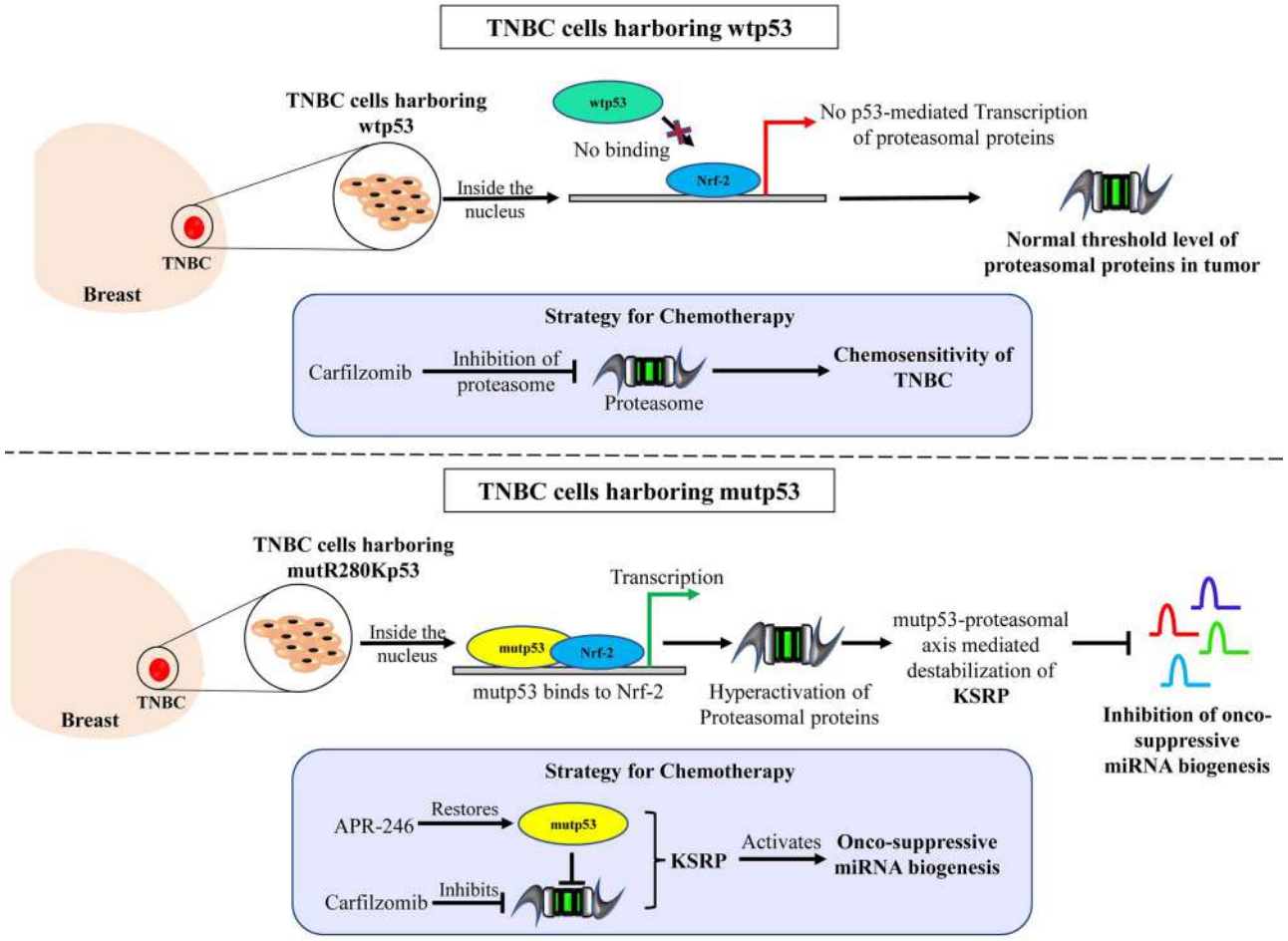

Figure 3. Illustration of Mutp53-mediated resistance to proteasome inhibition in TNBC.

RNA sequencing and ChIP-sequencing, Walerynch *et al.* established the mechanism for the proteasome resistance in the triple-negative breast cancer cell (TNBC) lines harboring p53R280K mutation [59].

By gene silencing of p53R280K mutant in the MDA-MB-231 cell line, they found 72 genes dysregulated by both proteomics, RNA and ChIP-sequencing. The majority of these genes were part of the ubiquitin-proteasomal pathway (Figure 3). Furthermore, to understand the oncogenic role of p53R280K, Walerynch *et al.* performed a comparative mRNA transcriptomics profile of mutp53R280K MDA-MB-231 cell lines with four other TNBC cell lines harboring different missense mutations [HCC1395 (p53R175H); SUM149PT (p53M237I); BT-549 (p53R249S); MDA-MB-468 (p53R273H)]. After p53 gene silencing in all these cell lines, a total of 205 common genes were found to be dysregulated. The data showed that most of these (37 genes) genes are involved in the 26S subunit-based ubiquitin-proteasomal pathways and immunoproteasomes. All these genes are either direct p53-dependent or independent transcriptional targets. The transcriptomics data of all five different p53 mutants showed common ubiquitin-proteasomal pathway genes. Furthermore, the genes were cross-validated with other datasets pancreas, head and neck, colon, bladder, liver, stomach and brain cancers, thereby confirming the mutp53-dependent elevation of the proteasomal pathway as a typical signature. By the ChIP-sequencing method, the possible mutp53 promoter binding sites of the transcription factors Nrf1, Nrf2, NF-κB, NF-YA and STAT3 were identified indicating the regulation of these genes by p53 (Figure 3). Interestingly, all these promoters sites do not fall under the classical p53-consensus binding site. Remarkably, upon p53 knockout in these TNBC cell lines harboring R175H and R280K mutations, the dependency of Nrf2 transcription factors with mutp53 was established as it forms direct interactions inside the nucleus. In addition, the proteomics study reflects the mutp53-proteasome axis-mediated KSRP protein destabilization, which is usually required for tumor-suppressive miRNA maintenance and was found to be pivotal cause of aggressive phenotype in TNBC [60, 61]. The study also established the involvement of mutp53 in Nrf-2-mediated upregulation of proteasomal targets. Upon restoration of mutp53 function to wild type using APR-246, a loss of resistance against proteasomal inhibitor Carfilzomib was decreased in the TNBC cell lines [62–64]. Hence, by both transcriptomics and proteomics studies of the TNBC cell lines, Walerynch *et al.* estab-

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lished the possible mechanism of the mutp53-mediated drug-resistant against proteasomal inhibitors and also identified a new oncogenic role of mutp53 in TNBC (Figure 3).

Unveiling the dysregulation of chromatin pathways by mutp53 in breast cancer via transcriptomics

The role of mutp53 in chromatin pathways in tumor growth and progression is not well understood [65, 66]. It is known that many chromatin pathways are dysregulated in tumor harboring mutp53, but the changes in the genome and transcriptome are not well understood [14, 65–68]. A study by Zhu *et al.* using ChIP-sequencing data tried to establish the role of mutant p53 in the chromatin dysregulation in the TNBC cell lines harboring p53 mutation [69, 70]. A comparative study of wtp53 in the TNBC cell lines (MCF7 and MDA-MB-175VII) with the TNBC p53 mutants cell lines (HCC70 (R248Q), BT-549 (R249S) and MDA-MB-468 (R273H) showed the interaction of both wtp53 and mutants with the gene proximal regions that lie under the vicinity of 10 kb of TSS (transcription start site). The study showed that both the wtp53 cell lines have different binding patterns compared with all three mutp53 cells. The binding pattern of all these three mutants was similar to each other [71]. The TSS-proximal peak motif analysis for the R273H mutant data showed that ETS2 (E26 Transformation Specific) has more binding affinity toward mutp53 as compared with the wtp53 by utilizing the ENCODE protect ChIP-seq datasets [72, 73]. Based on the gene ontology report of TSS-proximal peaks, the cell lines with wtp53 showed activation of DNA response pathways compared with p53R273H mutant, where the ribosomal synthesis and translation pathway genes were abundantly found aiding rapid growth. By analyzing 600 chromatin regulators, Zhu's group identified histone acetyltransferase monocytic leukemia zinc finger protein (MOZ) (also known as KAT6A or K (lysine)-acetyltransferase 6A) as an interacting target of p53mut, indicating the oncogenic function of mutp53 in the cell lines containing R249S, R248Q and R273H mutation. The levels of histone modifiers are solely dependent on the levels of mutp53, which requires ETS2 for mediating the tumor progression. Interestingly, the reduction in mutp53 leads to a decrease in the MOZ-mediated Lys9 acetylation of the histone H3 (H3K9ac). However, the levels of mixed lineage leukemia (MLL) (also known as Lysine [K]-specific methyltransferase 2A or KMT2A, which mediate H3K4 methylation), was not decreased by mutp53 knockdown, indicating the involvement of other methyltransferases [74, 75]. The mutp53 executes the oncogenic function by post-translation modification in H3K9ac and H3K4me3 histones by regulating MLL and MOZ. By using RNA-seq, ChIP-seq and other experiments, they validated that mutp53 is responsible for the elevated levels of hox genes and H3K4me3 [76–78].

By knocking out mutp53 results in a reduction of tumor cell growth [79, 80], which is directly related to the reduction of oncogenic activity of mutant p53, and the decreased levels of MLL1 and MLL2 result in the loss of cell growth. Zhu *et al.* showed that by reducing the MLL1 level in mutp53 R249S and R273H cancer cell line, the colony formation can be halted with no effect on the wtp53 cell line. The targeted inhibition of the N-terminal menin binding site of the MLL1 [81–83] using the menin antagonist MI-2-2 [84, 85] showed reduced oncogenic function of mutp53 leading to loss of tumor growth and proliferation. The OICR-9429 (WDR5 antagonist) disrupts the interaction of MLL1 (hyperactivated by oncogenic mutp53) with its binding partner WDR5 [86] thereby inhibiting the oncogenic mutp53 function (Figure 4).

From the studies conducted by Suzuki and Garibaldi group, the p53R273H was found to be negatively regulating the miRNA processing to promote tumor progression in colon cancer (Figure 4), whereas the same p53 mutant in the breast cancer cells found to elucidate different oncogenic function by hyper activating histone methyltransferases and -acetyltransferase which were proved to be involved in the tumor progression. Thus, it can be concluded that a single p53 mutant can exhibit different oncogenic functions based on the tissue type.

Elucidating mutp53-mediated adhesion of ovarian cancer cells to mesothelial cells using transcriptomics as a tool

Metastasis is profoundly the key cause of ovarian cancer deaths starting with the adhesion of the ovarian cancer cells to the mesothelial layer at the confines of the peritoneal cavity. Although the molecular basis of the adhesion is not very well understood, interestingly 47.8% of cancer patients have somatic-mutated gene p53 [10]. The role of mutp53 in cancer progression by adhesion of ovarian cancer cells to the peritoneal mesothelial cells has never been examined. Using transcriptomics, Lee *et al.* investigated the role of mutant p53R248Q in the regulation of the peritoneal-mesothelial adhesion step of metastasis in ovarian cancer [87, 88]. In the cell lines Hec1A and OVCAR-3 harboring p53R248Q mutation, the mutant protein overexpressed in contrast to different ovarian cancer cell lines having wild-type p53. The adhesive nature of OVCAR-3 cancer cells (p53R248Q) to Met5A mesothelial cells is 24-fold higher compared with A2780 ovarian cancer cells harboring wtp53.

By Whole Genome Microarray analysis, Lee *et al.* performed the global transcript profiling of gene expression in SKOV-3R248 mutant and SKOV-3 (Empty vector control) to understand the role of mutp53 in adhesion. A total of 146 genes cell adhesion ontology groups were identified out of which 10 genes were significantly upregulated in mutp53 cell lines quantitatively validated by real-time PCR. All the genes form a common signaling network involving PI3K/Akt and FAK pathways. In ovarian cancer, it is known that over expression of beta 4 integrin (ITGB4 gene) leads to tumor aggression. ITGB4 is also known as one of the most hyperactivated integrin in ovarian can-

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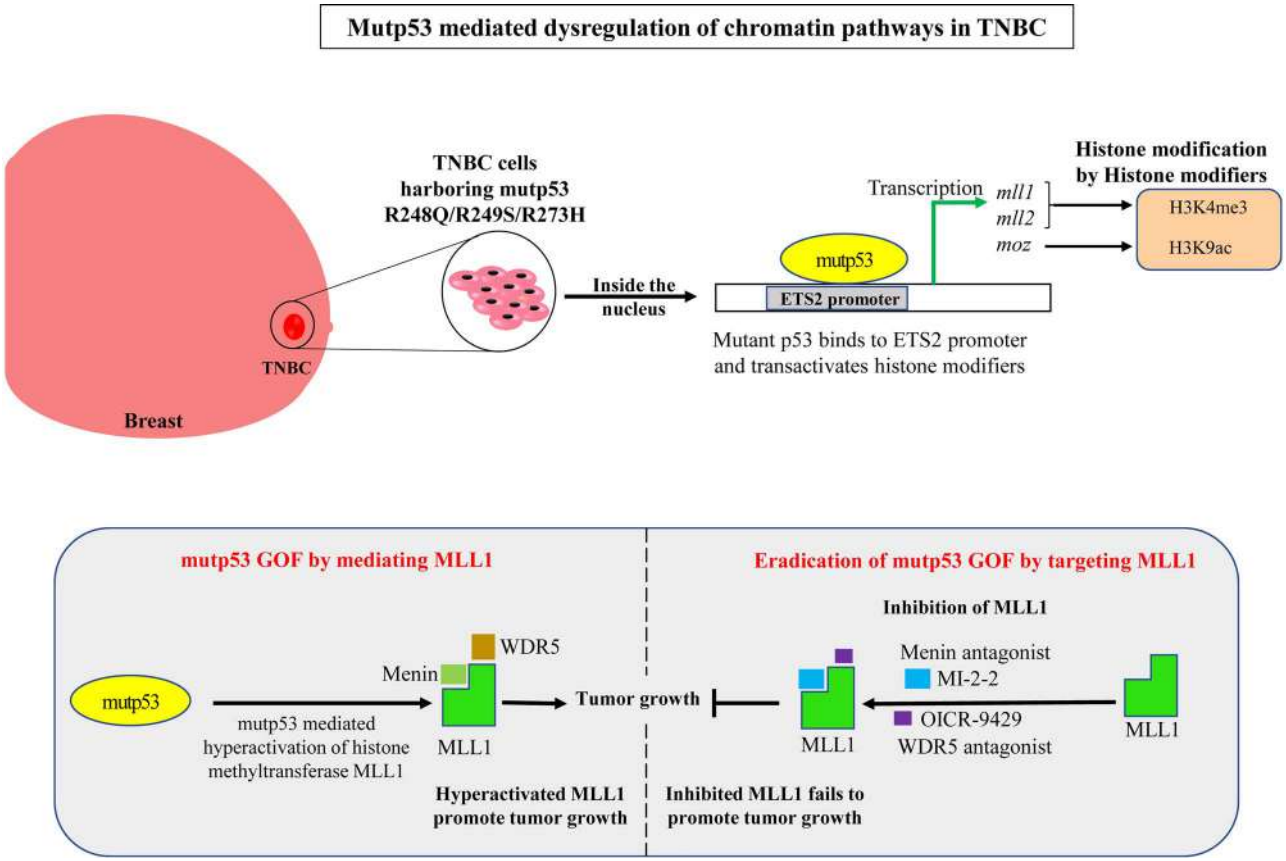

Figure 4. Scheme of Mutp53-mediated dysregulation of chromatin pathways in TNBC.

cer, which contributes to cell invasion, EMT, and many other cellular pathways [89–91]. By microarray network analysis and western blot of PTM specific antibody of focal adhesion kinase (FAK), PI3K/Akt showed upregulation of both pathways involving integrin-mediated signal transduction in ovarian cancer metastasis [92]. The expression level of $\beta 4$ integrin is directly dependent on the levels of p53 mutant indicating its role in facilitating the cancer-mesothelial cells adhesion by regulating the PI3K/Akt levels for tumor progression and metastasis (Figure 5).

Interestingly, the p53R248Q mutation in different tissues was found to activate different pathways leading to tumor progression. In breast cancer, it hyperactivates histone methyl, and acetyltransferase, whereas in ovarian cancer it increases the adhesive nature of cancer cells by regulating $\beta 4$ integrin pathways.

Revealing the mutp53-mediated CDDP resistance in squamous cell carcinoma of head and neck (SCCHN) using genomics and transcriptomics and proteomics

Mutations in p53 account for ~72% of all HPV$^-$ SCCHN (Human Papilloma Virus Negative Squamous Cell Carcinoma of the Head and Neck) being the sixth highest cancer cases reported in 2018 [93]. The platinum-based drug Cisplatin (CDDP, *cis*-diamminedichloroplatinum II) is a widely used standard chemotherapeutic agent in the treatment of SCCHN [93, 94]. However, resistance to CDDP is the major hindrance in the treatment of SCCHN, ovarian carcinoma [95], non-small cell lung cancer [96, 97] mediastinal and testicular germ cell tumors [98] often leading to the relapse of the tumor [99]. To solve the problem behind the CDDP resistance, Niehr *et al.* used omics to discover the role and involvement of mutant p53 in resistance to CDDP in SCCHN cells. A CDDP-resistant model cell lines FaDu (HPV$^-$ SCCHN) were generated by prolonged treatment with increasing doses of CDDP [100]. By targeted Next Generation Sequencing (tNGS) of CDDP-sensitive (CDDP-S) and CDDP-resistant cells (CDDP-R), a comparative single nucleotide variants (SNVs) analysis based on the allelic frequencies showed 294 (SNVs) in both the cell lines. By clustering SNVs of both CDDP-R and CDDP-S cells, large difference in allelic frequencies were found in six SNVs located on five genes including p53. The resistant cells with the missense mutation p53 R248L carried an allelic frequency (> 0.2) greater than sensitive cells. By FISH analysis, more than two copies of p53 genes were observed in resistant clones and showed aneuploidy in most of the resistant cells. The microarray transcriptomics data showed many genes transcriptionally regulated by p53 are upregulated in CDDP-R clones (20%) and also, 64% of these genes are already known to

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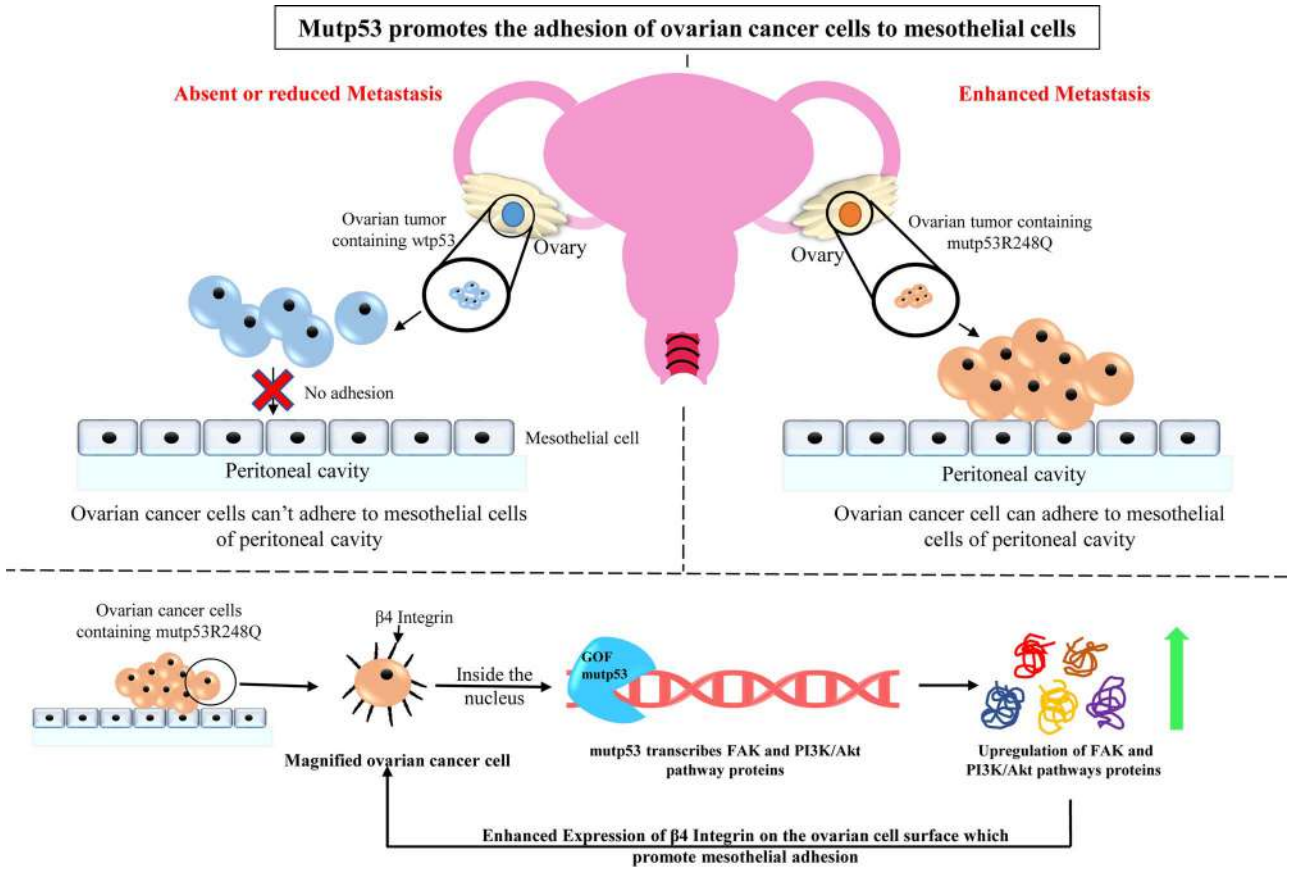

Figure 5. Schematic diagram showing Mutp53 promotes the adhesion of ovarian cancer cells to mesothelial cells.

interact with CDDP. On the other hand, the hyperactivation of the many genes in CDDP-S clones was found to be downregulated in mutp53 cell lines indicating the role of p53 in CDDP resistance. The genes forming interactions with CDDP are also regulated by p53, whereas on the other hand, the mutp53 with lost wild-type activity leads to decreased expression of transcription targets such as CDKN1A (p21) and GADD45A. The decreased expression of CDKN1A (p21) and GADD45A genes in CDDP-R clones confirmed the inability of mutant p53 in transcribing essential downstream cellular stress pathway targets.

Furthermore, through phosphoproteomics studies, the phosphoprotein expression of both CDDP-S and CDDP-R clones showed enrichment of the kinases in the resistant clones. Along with the kinase enrichment, they also observed the activation of PI3K-AKT-mTOR pathway in the CDDP-R clone harboring mutp53R248L. Since the PI3K-AKT-mTOR pathway is crucial for survival during cellular stress [101], its activation suggests the role of mutant p53 in mediating CDDP resistance.

To understand the clinical relevance of p53 mutation in SCCHN cancer ,the Niehr group performed a pilot study of tNGS in patients with primary and recurrent tumors relapse after CDDP treatment. From a total of eight patients, 50% patients were identified with p53 mutation in the first diagnosis. A comparative allelic frequency analysis of p53 mutation in the tissue of primary and recurrent tumors showed increased CDDP resistance in tumors with a higher allelic frequency of p53 mutation. The tissue of patients with less frequency had reduced relapse. A correlation between the CDDP resistance and oncogenic activity of p53 was assessed using TCGA database of HPV$^-$ SCCHN cases with known p53 status and classified into two groups according to the mutational status of p53. The first group comprised of cases where p53 mutation is considered high risk and is associated with oncogenic function, whereas the other group comprised of remaining p53 mutations or wtp53. Kaplan–Meier analysis of the two groups finally confirmed the decrease in the overall survival rate due to mutant in p53.

Hence, the omics studies conducted by Niehr *et al.* helped in the identification of mutp53-mediated oncogenic functions as the key player involved in CDDP resistance and recurrence of SCCHN (Figure 6).

Discussion and future perspective

Based on these omics studies a concordant conclusion can be made about the oncogenic functions of mutant p53 in various cancers (Table 1) **(**Figure 1). The omics-based studies highlighted the significance of p53 in miRNA processing in colon cancers and established the oncogenic role of mutp53 R273H in colon cancer cells. Similarly, Walerych *et al.* by multi-omics study identified a novel oncogenic role of mutp53 and the underlying

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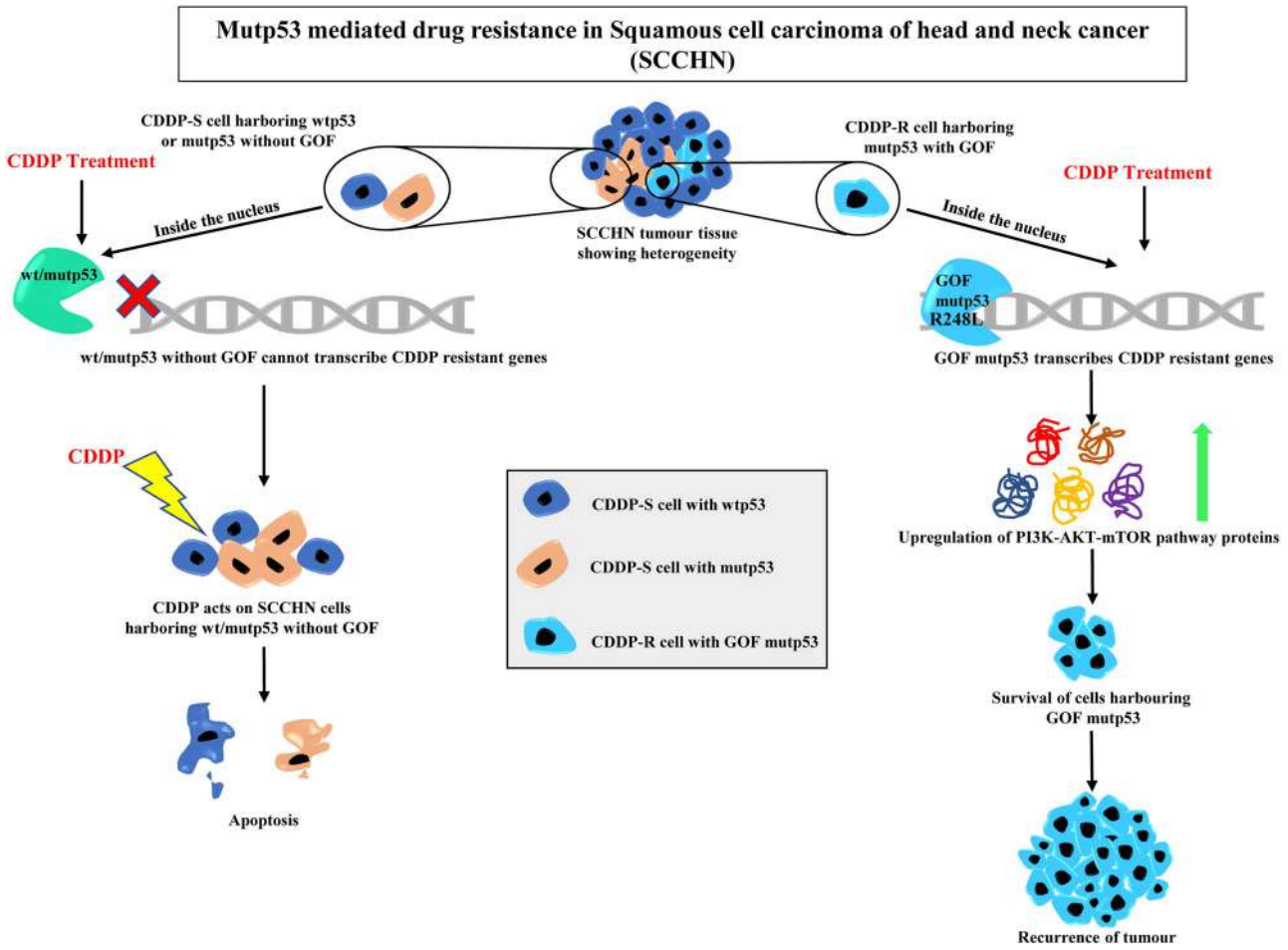

Figure 6. Illustration of Mutp53-mediated drug resistance in squamous cell carcinoma of head and neck cancer (SCCHN).

mechanism for the drug resistance in TNBC. From the studies conducted by Suzuki and Garibaldi group, the p53R273H was found to be negatively regulating the miRNA processing to promote tumor progression in colon cancer, whereas on the other hand, the same mutant was found to elucidate different oncogenic properties in the breast cancer cells by hyper activating histone methyltransferases and acetyltransferase to be involved in the tumor progression. Interestingly, the p53R248Q mutation in different tissues was found to activate different pathways leading to tumor progression. In breast cancer, it hyperactivates histone methyl, and acetyltransferase in ovarian cancer to increase the adhesive nature of cancer cells by regulating $\beta 4$ integrin pathways. The same was further confirmed by the loss of resistance against proteasomal inhibitor Carfilzomib upon restoring the mutp53 function to wild-type by APR-246 in the TNBC cell lines. Hence, the omics studies conducted by Niehr *et al.* helped in the identification of mutp53-mediated oncogenic functions as the key player involved in CDDP resistance and recurrence of SCCHN.

The reported omics studies of p53 mutants showed promising results in identification of biomarkers, new target pathways, disease prediction and progression. The occurrence rate of mutations in p53 is very high in diverse cancer [102] (Table 2). By multi-omics, the effect of p53 mutation in the modulation of the molecular mechanism leads to miRNA modulation, drug resistance, epigenetic modifications and genome instability, which will help in solving the important questions in the process of clinical cancer treatment. The p53 multi-omics will shed light in establishing common disease pattern from different tissues with different mutants. The multi-omics will help in the identification of oncogenic role of mutant p53 to design targeted cancer therapy to improve the survival rate. To connect the diseases phenotype at different stages of cancer and for early prognosis in aggressive cancer like glioblastoma multiforme, pancreatic cancer, etc., the multi-omics will be of huge benefit. A comprehensive understanding of p53 mutations and its role in cancer progression can bring more transparency in the mechanism of mutp53-mediated tumor progression, which may contribute to novel biomarker identification and early prognosis. As an oncoprotein, mutant p53 controls large signaling pathways promoting tumor activities. Hence, still, a lot of research work is required on various mutants as a potential drug target and to establish a map for personalized cancer therapy. In the future, the multi-omics approaches could provide targeted

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Table 1. Oncogenic functions of mutp53 in different tissues

S.No.	Mutation	Mutation		Structural /Contact mutation	Role in tumor progression	Cell line/type	Type of technique used	Omics	Ref.
		Somatic	Germline						
1	C135Y	Yes	Not reported	Structural	• Inhibits miRNA processing in colon cancer.	• HCT-116 (Transient)	• RNA-ChIP	• Transcriptomics	[40]
2	R175H	Yes	Yes	Structural	• Inhibits miRNA processing in colon and breast cancer. • Provides resistance to proteasomal inhibition in triple-negative breast cancer. • Hyperactivates histone modifiers in breast cancer	• HCT-116 (Transient) and SKBR3 • HCC1395 • HEK293T (Transient), Patient	• RNA ChIP and GWAS • Microarray • Microarray, Exome seq and RNA seq	• Transcriptomics • Transcriptomics • Transcriptomics	[40, 52] [59] [69, 70]
3	M237I	Yes	Yes	Structural	• Provides resistance to proteasomal inhibition in triple-negative breast cancer.	• SUM146PT	• Microarray	• Transcriptomics	[59]
4	R248Q	Yes	Yes	Contact	• Provides adhesion to the ovarian cancer cells to the mesothelial cells. • Hyperactivates histone modifiers in triple-negative breast cancer	• Hec1A, OVCAR-3 • HCC70	• Microarray • Microarray, Exome seq and RNA seq	• Transcriptomics • Transcriptomics	[88] [69, 70]
5	R248L	Yes	Yes	Contact	• Offers CDDP resistance in squamous cell carcinoma of head and neck	• FaDu, Patient	• tNGS, Microarray, Phoshoproteomics	• Genomics, Transcriptomics, and Proteomics	[100]
6	R248W	Yes	Yes	Contact	• Hyperactivates histone modifiers in triple-negative breast cancer	• HEK293T (Transient), Patient	• Exome seq and RNA seq	• Transcriptomics	[69, 70]
7	R249S	Yes	Not reported	Structural	• Hyperactivates histone modifiers in triple-negative breast cancer • Provides resistance to proteasomal inhibition in triple-negative breast cancer.	• BT-549 • BT-549	• ChIP seq, Exome seq and RNA seq • Microarray	• Transcriptomics • Transcriptomics	[69, 70] [59]
8	R273H	Yes	Yes	Contact	• Inhibits miRNA processing in colon cancer. • Hyperactivates histone modifiers in triple-negative breast cancer • Provides resistance to proteasomal inhibition in triple negative breast cancer.	• HCT-116 (Transient), HT29, SW480 • MDA-MB-468 • MDA-MB-468	• RNA ChIP, GWAS, NGS • ChIP seq, Exome seq and RNA seq • Microarray	• Transcriptomics • Transcriptomics • Transcriptomics	[40, 52] [69, 70] [59]
9	R280K	Yes	Yes	Contact	• Provides resistance to proteasomal inhibition in breast cancer.	• MDA-MB-231	• LC/MS, RNA ChIP, RNA seq	• Transcriptomics and Proteomics	[59]
10	P309S	Not reported	Yes	Structural	• Inhibits miRNA processing in colon cancer.	• SW480	• GWAS, NGS	• Transcriptomics	[52]

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Table 2. Global cancer statistics 2020 with Tp53 mutation distribution in different cancers

Type of cancer	Reported cases	Reported death	Tp53 Mutation frequency distribution (%)
Colon and rectum cancer	1 930 000	916 000	**60**
Breast cancer	2 261 419	684 996	**20**
Ovarian cancer	313 959	207 252	**66.3**
SCCHN	550 000	300 000	**72**

therapeutic strategies to specific tumors harboring different p53 mutant variants.

Key Points

- Mutp53 represses miRNA processing by sequestering p72/p82 proteins from the microprocessor Drosha complex in colon cancer.
- Mutp53 provides Nrf-2-mediated proteasomal resistance in TNBC.
- Mutp53 hyperactivates methyl-transferases (*mll1* and *mll2*) and acetyl-transferase (*moz*) to drive cancer growth in TNBC.
- Mutp53 hyperactivates $\beta 4$ integrin in ovarian cancer cells to achieve mesothelial adhesion.
- Mutp53 hyperactivates PI3K-AKT-mTOR pathway proteins in SCCHN cancer to acquire cisplatin resistance.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Authors' contributions

LM is responsible for conceptualization, data collection, writing and editing, graphics generation, visualization, formal analysis. AS is responsible for writing, editing and graphics generations. PK is responsible for formal analysis and editing. ASE is responsible for formal analysis, data curation, original draft, writing, review and editing and visualization.

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