Review Article
DOI: https://doi.org/10.70749/ijbr.v3i3.898

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Role of Lysine Methyl Transferase to p53 Dependent Apoptosis upon Myocardial Infarction

Raza Rehman[1], Muhammad Asyab Afzal[2], Zainab Rehman[2], Shiv Ram Ashraf[3], Saima Batool[4], Kashif Zia[5]

[1]CMH Medical College, Lahore, Pakistan.
[2]Department of Clinical Medicine (MBBS), Medical School of Hebei University of Engineering (HUE), China
[3]Department of Biochemistry and Biotechnology, University of Gujrat, Pakistan.
[4]Department of Biochemistry, Bahauddin Zakariya University, Multan, Pakistan.
[5]Department of Cardiac Surgery, Sindh Institute of Cardiovascular Diseases, Larkana, Pakistan.

ARTICLE INFO

Keywords
Lysine Methylation, P53, PKMT, Protein Lysine Methyl Transferase, Myocardial Infraction

Corresponding Author: Raza Rehman, CMH Medical College, Lahore, Pakistan
Email: razarehman152@gmail.com

Declaration
Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History
Received: 08-01-2025, Revised: 27-02-2025
Accepted: 11-03-2025, Published: 24-03-2025

ABSTRACT

The reversible protein methylation at lysine residues produces enhancements that boost the signal output of modified factors. The tumor suppressor and transcription factor p53, together with histones, show modified lysine residues through methylation, reflecting this modification acts as one common element for managing essential protein-protein connections and various vital signaling pathways. The research investigates lysine methylation modifications within the terminal region of p53 protein as well as their effects on functional activities. The enzymes which conduct protein post-translational modifications (PTMs) establish an essential regulatory pathway that controls cell processes inside organisms. Every cellular mechanism operates through this post-translational regulatory network as it is responsible for managing each cellular process. Cellular organisms reach biological maturity when different tissues exist in equilibrium while controlling the mechanisms of stem cell development along with cell specialization. Genetic-level cellular state regulation strongly depends on special histone post-translational modifications through lysine methylation processes. Protein substrates receive methyl groups from S-adenosyl-L-methionine through the enzymatic activity of lysine methyltransferases that perform lysine methylation.

INTRODUCTION

The human p53 tumor suppressor gene manifests genetic mutations within 50% of all human malignancies. The term 'guardian of the genome' correctly describes this gene, which researchers have studied extensively in molecular biology (Deb & Deb, 2016). Besides its critical role in cancer development, p53 remains active in various natural and disease processes, including ageing and differentiation, as well as fertility and neurodegenerative disease and diabetes and myocardial infarction (Tavernarakis, 2011). A funny scenario illustrates how p53 would explain its essential role to a psychologist in an important manner:

''I live under constant observation because everything I do receives thorough evaluation by others. I have regulations along with changes and physiological partners which I actively maintain.''

Tsvetkov and Dekel (Zwart, 2017).

Multiple metabolic pathways that guide p53 demand important investigation regarding how this single protein with vital activations correctly reaches specific locations during the appropriate times. Multiple regulatory pathways exist to control the complex structure of the tumor suppressor protein (Mir, 2024).

The protein control mechanisms for p53 in normal conditions operate through ligases that enhance protein degradation (Boutou & Stürzbecher, 2018). The p53 protein levels rise when DNA damage and multiple cellular stressors exist, and this initiates p53-dependent pathways that manage DNA repair, cell cycle arrest, and apoptosis (Kruman, 2011). The key element in p53 regulation involves post-translational modification (PTM) since the protein undergoes modifications through phosphorylation, acetylation, methylation, and ubiquitination. The post-translational modifications of histones resemble the modifications on the p53 protein and play a vital role in controlling the protein's functionality. The analysis in this article explores lysine methylation as its primary subject matter (Mohamed, 2024).

Studies reveal the methylation process conducted by different protein lysine methyl transferases (PKMTs) on specific lysine found in four positions of p53's C-terminal regulatory region (Barbas, 2001) (Figure 1). Post-translational modifications which control p53 open up potential explanations about its function in different cellular processes. Several protein lysine methyl transferases work dynamically to create distinct p53 populations that become methylated on specific C-terminal lysine residues (Romani et al., 2014). The specific p53 variants that can serve various downstream functions are tethered to effector proteins due to their distinct ability to detect particular p53 modifications.

The protein p53 connects to different cellular functions according to diverse stimuli in the body. The research methodology examines PKMTs, which modulate p53 activity by defining all known effector proteins that recognize methylated p53 species together with the mechanisms behind the consequences of p53 lysine methylation on subsequent p53 biological processes (Mir, 2024b).

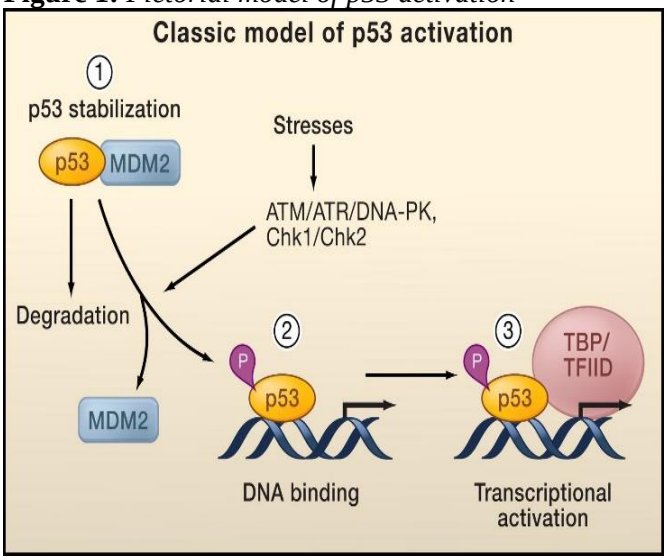
Lysine Methylation Signaling: Modulation of Histones and P53

Histone proteins show the most studies regarding lysine methylation. Lysine residues can lysine residue can accept three methyl groups to generate mono-methylated and then di-methylated, and finally, tri-methylated derivatives (Wu & Allis, 2012). The three distinct methylation activities (specifically labeled me1, me2, and me3) occur frequently among these three instances (me1, me2, and me3).

The enzymatic activities are linked to the exact methylation level installed on lysine residues. Most Enzymes that perform this covalent reaction (PKMTs) maintain a catalytically important preserved fragment motif called the SET domain (Cravatt et al., 2019). The removal of lysine methyl marks requires the activity of protein lysine demethylases (PKDMs). The modification of methylation states takes place through a dynamic switching mechanism. These modifications manage essential nuclear operations and precisely control gene expression mechanisms. On histones, most histone methylation reactions take place on the unstructured N-terminal tail regions of H3 and H4 (Kesharwani & Thakur, 2024). A similar pattern exists between the unstructured p53 C-terminal lysine that can be modified and those histone N-terminal tails which similarly harbor lysine modification (Figure 1) (Nardin & Schlaad, 2021). Scientific reports do not indicate that lysine methylation affects substrate proteins' structural properties. Structure-altering modification effects by lysine methylation are not observed in this process; thus, evidence indicates it acts by modifying the surface architectures of substrates (Gul, 2024). A mark is left on the substrate surface architecture through methylation events determining whether modular protein binding occurs infinitively or primitively binding by effector protein(s) (Uchiumi, 2018).

Lysine methylation is vital in chromatin biology because it allows multiple modification patterns. The potential effects of methylation on histone substrates become noticeable (Ganai, 2020). Each different methyl state at a single residue produces dissimilar outcomes that lead to divergent functional outcomes. The scientific data reveals H4K20me1 as a factor associated with condensed chromatin structure (Choo, 1997). Research indicates that H4K20me1 commonly appears with condensed chromatin structures, and it's binding with chromatin compaction factor L3MBTL1 leads to gene repression (E, 1861). The genetic repression activity of compaction factor L3MBTL1 starts after it interacts with chromatin (Meyers, 2012). Dimethylated H4K20 binds the two tandem Tudor domains of DNA damage response mediator 53BP1 bind specifically to DNA (Renaud, 2020). The modification H4K20me3 sustains constitutive heterochromatin structure and helps maintain its organization of constitutive heterochromatin (Zhang et al., 2016)

Figure 1: *Pictorial model of p53 activation*



Each methyl state is a multifunctional element that permits different functional outputs when binding multiple regulatory factors. Chromatin readers are regulatory factors that selectively identify distinct histone modifications (Chopra & Kaul, 2021). The predominantly promoter-associated binding site for H3K4me3 marks active genes. Users of this modification site lead to various functional results from gene activation through gene repression and V (D) J recombination (Abbas & Ansari, 2022). The following discussion details enzymes and readers that work below DNA helicases and topoisomerases to regulate the expression of target genes. Enzymes, along with sensory proteins and the signaling factors that lay down histone methyl marks, currently function as histone readers (Gupta & Gupta, 2021). Multiple research studies

indicate that p53 and the enzymes and readers controlling histone modifications may also manage transcription factor p53. In some cases, the relationship between histone and non-histone methylation activities creates reasonable outcomes. The targeting of histone and no histone entities by methylation produces synergistic effects, including the combination of chromatin condensation (Vijayaraghavalu, 2025). The processes of gene silencing link with chromatin relaxation and gene activation.

Monomethylation of Lysine 372 at SET7/9 Stabilizes p53

The activity and stability promotion appear to be the primary genetic function of SET7/9 activity and the stability of its substrates. The research findings from this activity demonstrate identical patterns to SET7/9 activity on p53, as described below.

Research in lysine methylation signaling reached its critical point through the identification of p53 as SET7/9 works on a substrate which this study designates as SET9 (Cravatt et al., 2019b). In this paper, the authors showed that DNA damage leads to SET9 mono-methylation of p53 at the lysine 372 position (Blumenthal & Cheng, 1999). The presence of p53K372me1 in the nucleus (Figure 1) achieves p53 stability while bound to chromatin. The research team reported an increased p53 promoter occupancy when p53K372me1 levels became elevated. SET9-associated regulation of p53, the acetylation of specific lysine residues near the p53 C-terminus appears to begin after SET9 promotes mono-methylation at p53K372 residues of p53 (Romani et al., 2014b). P53K372 experiences a continuous chain reaction for methylation in the nucleus, promoting p53 binding to DNA.

After DNA damage, SET9 uses p53 acetylation to activate methylation at p53 for installation (Miller, 2017). The levels of p53K372me1 rise after DNA damage to promote acetylation through SET9 mechanisms. One possible p53, the p300 acetyl-transferase, sustains a special preference for acetylating tetrameric p53 bound to DNA and post-lysine-methylation versus unmodified, unbound p53 as a substrate. In addition to modifying p53, when p300 installs itself at p53-target gene locations, it also acetylates the neighboring histone H4. H4 (Piccaluga & Paolini, 2024). SET9 performs gene activation by directly modifying p53 present in chromatin with an indirect mechanism that enhances the levels of acetylated H4. Interestingly, the DNA experiment revealed that DNA damage elevated p53 methylation while leaving H3K4 unmodified, indicating that environmental factors can direct SET9 activity (Chinnadurai, 2011). Research at the DNA molecular level needs to investigate how damage to DNA activates SET9, specifically, potentiates SET9 activity on p53 but not on H3K4 or other SET9 targets.

Experimental evidence from SET9-null mouse generation establishes that SET9 functions as a p53 activation factor that regulates p53. Cells derived from SET9-knockout mouse embryonic fibroblasts showed diminished p53 target gene expression activity after DNA damage exposure. The expression levels of p53 downstream effectors p21 and PUMA decrease after DNA damage exposure in cells lacking the SET9 gene. Wild-type cells reveal a higher susceptibility to transformation with HrasV12 or E1a oncogene introduction than the mutant SET9 cells (Williams & Gorelick, 2021).

The activation mechanism of p53 by p53 K372 monomethylation occurs on a molecular level. The additional acetylation at the same residues in the identical minus position of p53 competes against ubiquitin-related modifications, explaining how p53K372me1 alters p53 stabilization. However, a recent study indicates that the p53K372R mutant remains sensitive to SET9 activation. The researchers explored different routes through which SET9 activates p53 independent of K372 (Villers & Fougere, 2013). The authors demonstrate in this research that SET9 suppresses the activity of p53 de-acetylation by SIRT1. Under these conditions, SET9 can target alternative lysine residues instead of its preferred substrate. SET9 shows flexibility as an enzyme by transferring a methyl group to an adjacent lysine (Massoud & Rezaei, 2013). In addition, as lysine, the central role of lysine methylation affects downstream functions by recruiting methyl lysine-binding proteins to target locations. Researchers think an unidentified protein can recreate the K372me1 modification of p53, but this has yet to be discovered (Shah, 2023). Due to remaining unknown factors, scientists can explain how SET9 cons p53 functions. In this context, The PKMT Smyd2 also engages in methylation p53 through an adjacent p53 C-terminal lysine 370. The modifying relationship between different marks may influence SET9- activity based on the findings at lysine 370. Through p53K372me1 activity, SET9 facilitates stabilized p53 by blocking inhibitory methylation reactions in the p53 protein event at lysine 370 (Coppola, 2010).

The Monomethylation of Smyd2 at Lysine 370 Inhibits p53 Activity

The p53 transactivation activity became restricted due to Smyd2-induced monomethylation at K370 (p53K370me1) following the activating SET9-mediated methylation at K372 (Sahu, 2022). P53 binding to promoters of p21 and mdm2 target genes became weaker following Smyd2-mediated p53 modification by methylation at lysine 370. At the same time, the removal of Smyd2 resulted in more substantial p53-dependent apoptosis in response to various DNA damage agents.

Two closely positioned lysines, 370 and 372, create conditions for intermolecular communication between

the two adjacent methylation markers. In vitro and in vivo research demonstrates that K372 methylation by SET9 blocks K370 methylation by Smyd2. The flag-p53 and Smyd2 co-transfection with SET9 in H1299 cells disrupts p53-Smyd2 binding according to flag immune precipitation data, which shows SET9 acts to physically prevent Smyd2 from binding p53 (Zlatanova & Leuba, 2004). A portion of the beneficial effects SET9 methylation has on K372 become clear because it blocks Smyd2 from binding to p53.

Lysine Demethylase LSD1 Modulates p53

The enzyme responsible for K370 dimethylation on p53 remains unidentified, although it operates on this lysine residue. According to the research of Huang et al., p53K370me1 showcases different behavior than p53K370me2. The p53K370me2 form enhances p53 transcriptional activity by binding to protein 53BP1 through its Tudor domain. Research shows that the DNA damage response protein 53BP1 detects dimethylated p53K370 through the Tudor domain. The K370 dimethylation mark on p53 allows it to co-activate p53 target genes while interacting with the Tudor domain of 53BP1 protein (Miettinen, 2010). As discussed later, the Tudor DNA binding domain of 53BP1 shows minimal sequence preference when interacting with dimethylated lysines between different targets p53 dimethylated at lysine 382 (p53K382me2) and H4K20me2 (Frank, 2011) and in the case of DNA damage, signaling associates 53BP1 binding with p53K382me2 together with H4K20me2 biomolecules. The evaluation of molecular processes which determine 53BP1 recognition and functionality remains intriguing.

External factors influence various patterns of 53BP1 engagement while also determining its various functional consequences. The lysine demethylase LSD1 utilizes its enzyme activity to remove one methyl component from p53K370me2 moiety from p53K370me2 to generate p53K370me1 (Jurga & Barciszewski, 2019). This finding represents the first scientists to have identified for the first time that demethylation takes place on nonhistone proteins. Cells depleted of Maximal DNA damage exposure caused LSD1 to repress 53BP1 abundance. The dimethyl mark at p53K370me2 predominantly becomes a target of the activity of LSD1 in living cells based on in vivo examination (Jurga & Barciszewski, 2019). The enzyme maintains chromatin repression by performing histone demethylation activities. LSD1 suppresses p53 function through its ability to reduce mutant p53 dimethylated forms because of its demethylation functions (Faintuch & Faintuch, 2019). P53K370me2 experiences a reduction of the active dimethyl modification through the dynamic demethylation mechanism, which shifts the dimethyl species into inactive monomethyl species. Huang et al. indicated that when p53K370me1 loses its recognition pattern towards 53BP1, its coactivator duties fail. The ability of p53 to bind target gene promoters decreases because of this dysfunction. The identity of a gene-activating methyltransferase remains undiscovered, while conditions for gene expression enhance the population of p53K370me2. While studying the human cell population, the researchers supported the theory that p53K370me2 stabilization creates a strong executing bond with 53BP1. Target gene transcription proceeds because of this process (Félétou, 2011).

Monomethylation of lysine 382 by SET8 Inhibits p53 Activity

Science results 2007 proved the monomethylation of lysine 382 by SET8 in p53 as a third important physiological methylation event (Stillman & Laboratory, 1998). The enzyme SET8 functions as the protein lysine methyltransferase that creates the H4K20me1 modification, which promotes gene repression and compact chromatin states in mammalian cells, according to studies and existing research (Animesh et al., 2025). SET8 participates in multiple cellular functions, including moving cells through the S-phase, conducting mitosis and signaling DNA damage checkpoint signals. The regulatory aspects of p53 by SET8 combine elements from transcriptional repression with DNA-damage checkpoint signaling pathways.

SET8-mediated monomethylation at the p53 lysine 382 position causes transcriptional repression during p53-mediated regulation. Evidence indicates that SET8 catalyzes methylation of p53 Lys382 using substrate recognition elements from both H4 K20 and the p53 C-terminal residues. When SET8 levels decrease, p53 can establish firmer control over the transcription of p21 and PUMA genes, representing direct p53 targets (Mir, 2024c). SET8 maintains p53 transactivation control through K382 monomethylation of dormant cells, which are present during regular conditions but suppressed during DNA damage. The normal cellular population remains available for DNA treatments during undamaged DNA conditions. SET8 protects healthy cells by blocking p53 activity through methylation processes. These traits are important because scientists have established that SET8 directly modifies p53 protein into methylation and excludes H4K20 methylation by SET8 as a separate possibility. The research design demonstrated these findings because manipulating SET8 expression levels or destroying specific target genes through p53 knockdown did not alter H4K20me1 levels and eliminated expression effects (Hanaoka & Sugasawa, 2016).

Revelations from SET8 monomethylation at lysine 382 demonstrate how lysine methylation helps substrates work with effector proteins. After U2OS cell treatment with neocarzinostatin, the overexpression of SET8 led to decreased K382 residue acetylation levels, which showed decreased detection with p53K382Ac antibody examinations. Researchers do not consider substrate-

binding inhibition caused by p53 transactivation as the primary mechanism of methylation because a p53K382R mutation demonstrated similar activation efficiency compared to wild-type p53 protein (Schlesinger & Hershko, 1988). The PKMT responsible for residue methylation was predicted by sequence similarity between p53 at K382 and H4 at K20, and later, proteins L3MBTL1 and 53BP1 were discovered.

The study found that the brain tumor protein L3MBTL1 operates as a p53K382me1 binding partner (Deeley & Deeley, 1974). L3MBTL1 recognizes H4K20me1 (and additional monomethylated histones) through its central MBT repeat to compact chromatin, dependent on histone lysine methylation (Renaud, 2020b). Laboratory findings indicate that L3MBTL1 links to p53 and RB through methylation-dependent mechanisms using MBT2 as the binding platform as it interacts with methylated histones (Devaux & Robinson, 2021). The p53 protein belongs to an expanding group of nonhistone substrates in which L3MBTL1 interacts alongside TEL and RB proteins, which use L3MBTL1 for their transcriptional repression activity at specific target promoters (Sonawane et al., 2020).

L3MBTL1 forms a bond with p53 in live tissues through p53 lysine 382 methylation due to SET8 activity. P53K382me1 is a boundary for attracting L3MBTL1 to bind with the p21 promoter area under standard regulatory conditions. Studies reveal that L3MBTL1 suppresses target genes without requiring the direction of transcription factors to chromatin. Both SET8-mediated H4K20me1 monomethylation and L3MBTL1 binding to promotors of RUNX1 and cyclin E1 appear sufficient for subsequent transcriptional silencing of these genes (Romani et al., 2014c).

L3MBTL1 protein is located at genes' promoters in p21, and PUMA targets through p53-positive HCT116 cells, yet it remains absent from the p53-null HCT116 cell population. Neocarzinostatin causes the decrease of SET8 protein levels, while the p53K382me1 modification simultaneously decreases in number after DNA damage. A p53 detachment from L3MBTL1 occurs, which reduces the promoter-binding capacity of L3MBTL1 at the p21 gene (Appasani, 2012). The binding of p53K382me1 with L3MBTL1 enables quiescent p53 to sit at promoters of high-sensitivity target genes, which prepares it for immediate activation upon DNA damage.

53BP1 Enhances the Stability of p53K382me2 in Response to DNA Damage

The tandem Tudor domains within the proteins of 53BP1 enable them to bind p53K382me2, which serves as a second dimethylated p53 residue (Barrangou & Van Der Oost, 2012). Together with L3MBTL1, 53BP1 represents the two protein effectors known to bind p53 K382 and histone H4 K20 dimethylation marks. At double-strand breaks, 53BP1 uses its two Tudor domains to connect with histone modification H4K20me2, which helps promote its accumulation (Kaneda & Tsukada, 2017). The exact two Tudor domains in 53BP1 detect augmented p53K382me2, which forms when cells encounter DNA damage. The complex between these proteins stabilizes p53 to increase p53 protein accumulation at double-strand break lesions (Hasan, 2024). Regarding the enzyme associated with p53K382, we lack information about how dimethylation occurs at the chemical level. A limited evaluation of interacting protein substances in both substrates suggests that the enzymes which execute H4K20me2, the enzymes Suv4–20h1/h2, show potential to perform dimethylation on p53 in addition to their known substrates. Screening studies with 30 lysine methyltransferases for p53K382 dimethylation activity did not identify Suv4–20/h1/h2 and other PKMT candidates among the contributors to this modification (Blumenthal & Cheng, 1999b). Research must identify specific proteins among the K370me2 and K386me2 dimethylation enzymes that assign these modifications since their responsible proteins remain elusive.

Dimethylation of lysine 373 by G9a and Glp Inactivates p53

The dimethylation of H3K9 in living cells requires the heteromeric lysine methyltransferase complex of G9a and Glp that operates as a high-order structure in vivo. However, both enzymes can perform independent H3K9 methylation in test tube conditions (Ganai, 2020b). H3K9 mono- and di-methylation performed by G9a/Glp acts as a key transcriptional repression element because it enables the HP1 protein to bind chromatin. Laboratory research shows that G9a and Glp form a heteromeric compound, enabling both enzymes to execute p53 dimethylation at lysine 373 (Cravatt et al., 2019c). Research shows dimethyl marks on H3K9 lysines 370 and 382 are produced by protein interactions with 53BP1, contrary to the activating results of dimethylation modification. Research confirms that p53K373me2 works as an inhibitory dimethyl modification, leading to effective p53 deactivation. Evidence shows that p53K373me2 fails to raise its levels during DNA damage treatment using Adriamycin or after silencing G9a or Glp proteins with siRNA. The experiment applied DNA damage treatment with Adriamycin and p53 protein knockdown using siRNA to test changes in activation levels after silencing G9a and Glp gene sequences (Cordani et al., 2021). Researchers need to identify the molecular processes that determine K373me2-based suppression.

CONCLUSION

The prior examples show how non-histone protein lysine methylation controls the multifunctional tumor suppressor p53. Studies indicate that the histone-based molecular processes which influence stability and

modify interactions and participation with methyl readers also regulate p53 transcription factors and additional factors. Concurrently with its work on histone substrates, a PKMT generally performs additional methylation modifications on both substrates to produce combined downstream effects such as chromatin condensation with gene silencing or chromatin relaxation with gene activation. The typical cell cycle pattern shows SET8 generating H4K20 monomethylation marks that become deposited at genomic regions with the replication fork because it operates during the S-phase and then follows the replication fork. SET8 methylate p53 protein at a single location produces p53K382me1 while simultaneously elevating its amount, resulting in p53 retention in its inactive state to block its tumor-suppressing functions, which could interrupt cell proliferation. Lysine methylation of p53 completes the existing post-translational modification signaling pathway found in histones so cells can respond appropriately to multiple intracellular situations.

The complete tumor-suppressing functions of p53 do not depend on any particular lysine methylation reaction. Research on mouse genes demonstrated that p53 mutants with all lysines in their C-terminal domain substituted by arginine display equivalent behavior to wild-type p53 for stability, transactivation, and apoptosis induction capabilities. Determining methylation's precise functions in mutational testing becomes complicated because mutating lysines to arginines simultaneously blocks all possible modifications, including methylation and ubiquitination on target lysines. Research through individual PKMT knockout could provide insights into p53 methylation but would be limited because PKMTs would have multiple targets. Different populations of p53 proteins emerge through lysine methylation processes to define how stimuli affect p53 sensitivity by enabling contact and movement between these populations, which activate or impede p53 function by interacting with distinct methyl reading proteins. The activities increase how sensitive and resilient p53 becomes through metastable equilibrium states while preserving standard systems homeostasis yet gaining promoter-specific gene-activated sensitivity when facing genotoxic stress.

Various nonhistone proteins besides p53 get methylated on their lysine residues. Scientists primarily lack understanding of the mechanisms and biological effects behind these situations. New applications of post-translational modification motifs discovered for p53 transcription factor control have recently allowed researchers to study control mechanisms of RB and RelA transcription factors. According to experimental findings, lysine methylation control presents a detailed system for managing nonhistone protein operations precisely.

Future Perspectives

Laboratory studies indicate that transcription factor p53 methylation and other proteins are dominant methods for building protein-protein interactions and signaling pathways. Unbiased candidate research approaches will result in substantial growth of lysine methylation detections on nuclear and cytoplasmic proteins in the upcoming years. Next-generation proteomic technologies and reagents will quickly discover different reader domains found on methylated proteins. Molecular signals from methylation help discover previously unknown cellular pathophysiological processes through their mechanisms, which alter protein structures at chromatin and other cellular locations.

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