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Gene MDM2 as Biomarker Proliferation of Abnormal Cells: A Review Article

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1. Abstract

1.1. Introduction: Cancer begins due to the proliferation and differentiation of normal cells into abnormal cells. This process is a change in normal cells into cancer cells. This process begins with the process of initiation, promotion and progression from normal cells to cancer cells. Under normal conditions, cell division, proliferation and differentiation are well controlled. Non-lethal genetic defects are central to carcinogenesis. Genetic damage or mutation can occur due to environmental influences such as chemicals, radiation, viruses or inherited in germinativum cells. These genes inhibit growth by regulating cell cycle checkpoints, called gatekeepers, while guardians of gene stability, protecting the genome are called caretakers. Under normal circumstances the work of tumor suppressor genes is to inhibit cell proliferation with DNA damage, sometimes these genes are also called recessive oncogenes or anti-oncogenes. Several studies have shown that tumor suppressor gene products directly or indirectly interact with oncogenes, so that the function of these oncogenes is inhibited. However, when the oncogene gene is active, such as MDM2, it can inhibit tumor suppressor genes, resulting in abnormally high proliferation of abnormal cell. Aims of this article are to review gene MDM2 as biomarker proliferation of abnormal cell.

1.2. Discussion: The most studied mechanism is MDM2 p53 transcription mediated through the P2 promoter, whereas basal transcription starts from the P1 promoter. Additional transcription factors (such as NF-κB, Fli-ETS, IRF-8, SP1, and NFAT1) and the Ras-Raf-MEK-MAPK pathway can positively modulate MDM2 expression of one or both of the P1 and P2 promoters. On the other hand, the tumor suppressor PTEN decreased MDM2 expression, independent of p53. Several Micrornas (miRNAs) such as miR-143, miR-145, miR-29 (via the PI3K / Akt pathway) and miR-18b (upregulated p53) have been able to block mRNA

MDM2 regulation can result in post-translational modifications including phosphorylation of MDM2 protein by molecules such as ATM (reduces the stability of MDM2) and Akt (increases the translocation of MDM2 from the cytoplasm into the nucleus, allowing degradation of p53). Other enzymes, such as CK2 and DNA-PK, as well as members of the Ras-Raf-MEK-MAPK pathway, also regulate the phosphorylation of MDM2.

1.3. Conclusion : Gene MDM2 as biomarker proliferation of abnormal cell through this signal exists in MDM2 alternating between the cytoplasm and the nucleus and reduces p53 activity on amino acids 464-471 The MDM2 central domain is required for interaction with ribosomal L5 protein, and with p300 / CBP (CREAM Binding Protein). Recently, this domain was found to contribute to p53 degradation because the mutant MDM2 from this domain was able to degrade p53.

2. Introduction

Cancer begins due to the proliferation and differentiation of normal cells into abnormal cells. This process is a change in normal cells into cancer cells. This process begins with the process of initiation, promotion and progression from normal cells to cancer cells. Under normal conditions, cell division, proliferation and differentiation are well controlled. Non-lethal genetic defects are central to carcinogenesis. Genetic damage or mutation can occur due

to environmental influences such as chemicals, radiation, viruses or inherited in germinativum cells. At the molecular level, tumor development results from the accumulation of genetic lesions and some circumstances due to malfunctioning DNA repair. The main targets of DNA damage are several gene groups, namely [1].

First, proto-oncogenes, which are normal cell genes that can turn into active oncogenes due to mutations or overexpression, both inactive tumor suppressor genes, and repair genes. Oncogenes are genes that undergo differentiation from proto-oncogene genes that undergo mutations. Proto-oncogene genes are normal genes and are genes that code for proteins that play a role in regulating cell growth and division. Gene mutations that activate proto-oncogenes into oncogenes are located in structural genes that directly produce abnormal gene products (proteins), or in certain cases these mutations are present in the regulatory part of genes so that they produce excessive normal proteins. Both of these causes an increase in function and these binding results in a signal of continuous growth and abnormal proliferation [2, 3].

Tumor suppressor genes are normal genes and are involved in various biological processes, including cell cycle control, DNA replication, DNA recombination, signal transduction, DNA repair, tissue differentiation, apoptosis and the aging process, these genes also function as adhesion control between cells. Metastatic inhibitors and as a component of cell lines. Tumor suppressor genes are located on autosomal chromosomes. These genes inhibit growth by regulating cell cycle checkpoints, called gatekeepers, while guardians of gene stability, protecting the genome are called caretakers [4] (Figure 1).

Under normal circumstances the work of tumor suppressor genes is to inhibit cell proliferation with DNA damage, sometimes these genes are also called recessive oncogenes or anti-oncogenes. Several studies have shown that tumor suppressor gene products directly or indirectly interact with oncogenes, so that the function of these oncogenes is inhibited. However, when the oncogene gene is active, such as MDM2, it can inhibit tumor suppressor genes, resulting in abnormally high proliferation of abnormal cell5. Aims of this article are to review gene MDM2 as biomarker proliferation of abnormal cell.

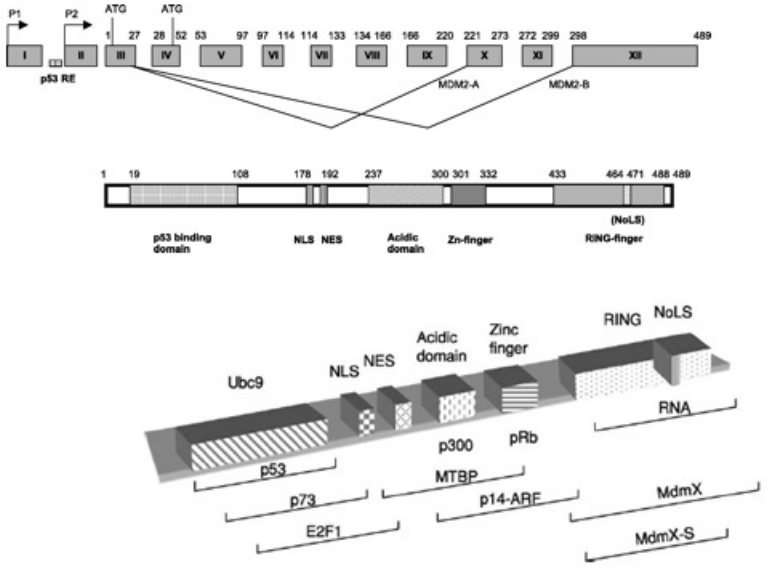

Figure1: Structure of MDM2 [5]

3. Discussion

3.1. Identification and Structure of MDM2: The murine double minute 2 (MDM2) gene was initially identified as one of the three genes (MDM1, 2, and 3) that were expressed more than 50-fold by amplification in BALB / c cells in mouse cells that changed spontaneously (3T3-DM). MDM genes are located in small, extra chromosomal astrometric nuclear bodies, called double minutes, which are retained in cells only if they provide a growth advantage. The gene product of the MDM2 gene was then shown to be the one responsible for cell transformation when expressed [5].

The MDM2 gene was found to bind to tumor suppressor p53 and inhibit p53 transactivation. MDM2 gene amplification was observed in more than one-third of human sarcomas that maintained p53. Another study showed that MDM2 overexpression is another mechanism by which cells can deactivate p53 in the transformation process. Some tumors contain high levels of MDM2 and mutations in the p53 gene. Another study showed MDM2 had a tumor growth enhancement function [6] (Figure 2).

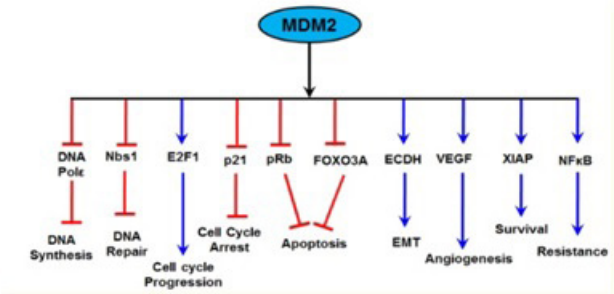

Figure 2: MDM2 Direct Mechanism [8]

MDM2 gene structure and protein. The MDM2 gene consists of 12 exons and two responsive p53 (p53 RE) elements in intron 1. The two promoters are. MD9 full-length p90 from the first ATG start codon in exon 3 and short form, p76 from the second ATG in exon 4. The two main variants in the human genes are MDM2-A and MDM2-B. The other structure is a protein, namely NLS, the nuclear signal; SEN, nuclear export signal; Zn-finger, zinc domain; NoLS, nucleolar localization signal; RING-spokes, ring-ringing domain. MDM2 also consists of 491 long amino acids, with a molecular weight of 56kDa and interacts via the N-terminal with α helic. In humans, this gene is located on chromosome 12q13-14, with a length of mRNA encode for 90KD protein [6].

It contains 90 N terminal amino acids and is associated with binding to p53. Analysis of the crystal structure of the 109-residue amino domain, MDM2 terminal is bound to peptide 15 residue p53 transactivation domains, this shows that MDM2 has hydrophobic properties and the peptide p53 binds as an amphiphatic alpha helix [7].

MDM2 also contains a central acid domain (residual 230-300) and is important for regulating MD2 function. This domain as mentioned above contains the nuclear export and import signals which are very important for nuclear-cytoplasmic exchange in MDM2. This domain can also interact with ribosomal proteins. This shows a function in ribosome biosynthesis or in the translation process. Another fairly distinctive structure is the presence of a terminal ring which has been shown to specifically bind RNA. This demonstrates the role of MDM2 in cell translation regulation [4].

Recently demonstrated that the ring region is very important for MDM2 in degrading P53. This ring is a C-terminal RING (amino acid 430-480), which contains a Cis3-His2-Cis3 consensus coordinating two zinc molecules. These residues are required for zinc binding, which is essential for proper folding of the RING domain. The RING domain of MDM2 was used for ubiquitin E3 ligase activity and sufficient for E3 ligase activity. The RING domain of Mdm2 is unique in that it combines the characteristics of the Walker A or P-loop used by nucleotide binding proteins, as well as the sequence of nuclear localization [7] (Figure 3).

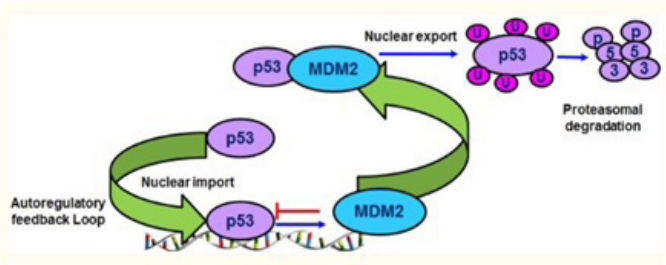

Figure 3: MDM2-P53 Feedback Loop Auto regulator [6]

Biochemically, MDM2 functions as an ubiquitin E3 ligase which is responsible for ubiquitination and p53 degradation. Protein biquitination occurs via a complex series of steps involving the E1, E2, and E3 proteins. Enzyme E1 binds to ubiquitin, a 76-amino acid protein, activating ubiquitin for further processing. The E2 conjugate enzyme accepts the activated ubiquitin from E1 and transfers it to the E3 enzyme, a ligase which covalently binds ubiquitin to the substrate. MDM2 functions as E3 ligase to ubiquitinate p53 on some lysine residues. MDM2 also has the ability to propagate on its own [6].

In humans, MDM2-A and MDM2-B are the main splice variants that remove exons 4–9 and 4–11, respectively. MDM2-B, also named MDM2-ALT1, interacts with MDM2 and functions in the cytoplasm. Thus, this short MDM2 protein can function as a dominant negative that inhibits complete MDM2 function and thereby amplifies p53 activity [7]. The p53 interaction domain is also encoded by the amino terminal 100 amino acid MDM2. This domain binds to the p53 amino terminal transactivation domain. If MDM2 is unable to degrade p53, it impairs p53's ability to interact with the transcription process. Other functions are the nuclear localization signal and the nuclear export signal [8].

3.2. MMD2 Mechanism and Abnormal Cell Proliferation

3.2.1. Direct MMD2 Mechanism: The most studied mechanism is MDM2 p53 transcription mediated through the P2 promoter, whereas basal transcription starts from the P1 promoter. Additional transcription factors (such as NF-κB, Fli-ETS, IRF-8, SP1, and NFAT1) and the Ras-Raf-MEK-MAPK pathway can positively modulate MDM2 expression of one or both of the P1 and P2 promoters. On the other hand, the tumor suppressor PTEN decreased MDM2 expression, independent of p53. Several Microns (miRNAs) such as miR-143, miR-145, miR-29 (via the PI3K / Akt pathway) and miR-18b (up regulated p53) have been able to block mRNA [6].

MDM2 regulation can result in post-translational modifications including phosphorylation of MDM2 protein by molecules such as ATM (reduces the stability of MDM2) and Akt (increases the translocation of MDM2 from the cytoplasm into the nucleus, allowing degradation of p53). Other enzymes, such as CK2 and DNA-PK, as well as members of the Ras-Raf-MEK-MAPK pathway, also regulate the phosphorylation of MDM29.

Clinically and preclinical showed that MDM2 has an important role in cells, independent of p53. MDM2 is able to influence processes such as DNA synthesis and repair by interacting with DNA polymerase, DHFR, centrosome amplification and MRN DNA complexes containing Nbs1. MDM2 interacts with several proteins such as Rb / E2F-1, DNA methyltransferase DNMT3A, p107, MTBP, cyclin kinase inhibitor p21, independently, and promotes cell cycle development (in the S phase) [7].

MDM2 interacts with the E2F1 / Rb pathway to inhibit apoptosis.

The anti-apoptotic role of MDM2 also includes its interaction with apoptotic mediators such as p73 (MDM2 mediates p73 Neddylation and prevents transactivation of p53) and FOXO3a (MDM2 decreases the stability of the FOXO3a protein). MDM2 enhances the anti-apoptotic XIAP translation, thereby inactivating apoptosis. Therefore, MDM2 affects both pro-apoptotic and anti-apoptotic proteins. MDM2, apart from being a negative regulator of p53, also influences the function of other cellular proteins, which participate in pathways from DNA repair to apoptosis to cell motility and invasion so that abnormal cells can proliferate [9].

3.2.2. MDM2-P53 Feedback-Loop Auto Regulator: MDM2 is a potential inhibitor of p53. MMD2 binds to the p53 activation domain and inhibits p53's ability to regulate target genes and exert anti-proliferative effects. MDM2 expression is regulated by P53 in an auto regulatory feedback-loop mechanism. P53 stimulates MDM2 expression, while MDM2 inhibits p53 activity because it can block its transcription activity and stimulate degradation. If there are damaged cellular signals such as DNA damage or activation of oncogenes, it will induce p53 activation. DNA damage due to p53 phosphorylation, preventing contact with MDM2. The oncogenes activate the ARF protein, which prevents p53-mediated degradation of MDM2. Likewise, the inhibitor of the p53-MDM2 interaction activates tumor suppressors in tumor cells (which express the wild type of p53) [5].

MDM2 targets p53 for ubiquitination and degradation by proteasomes. MDM2 transports p53 out of the nucleus, prevents p53 from interacting with transcription activators, and produces a transcriptional counterpart of the repressor to p53. On the other hand, p53 regulates the expression of oncoprotein MDM2 by binding to its promoter. Increased MDM2 levels lead to binding to and inactivating p53 by directly blocking the p53 transactivation domain and by targeting the p53 protein for degradation by the proteasome. This auto regulation loop helps maintain low levels of p53 cells in normal cells so as not to increase abnormal cells [6].

MDM2-p53 interaction was initially thought of as mutual binding of MDM2 and p53 via the N-termininal domain. The new theory found that changes in the p53 C terminal such as deletion, mutation or acetylation can also influence MDM2-p53 interactions. In addition, the RING MDM2 C-terminal finger domain serves as a ubiquitin E3 ligase for p53 proteolysis and p53 ubiquitinates on some lysine residues. Lower levels of MDM2 activity induce mono-ubiquitination and export of p53 nuclear, whereas higher levels promote poly-ubiquitination and p53 nuclear degradation [8].

4. Conclusion

Gene MDM2 as biomarker proliferation of abnormal cell through this signal exists in MDM2 alternating between the cytoplasm and the nucleus and reduces p53 activity on amino acids 464-471 The MDM2 central domain is required for interaction with ribosomal L5 protein, and with p300 / CBP (CREAM binding protein). Recently, this domain was found to contribute to p53 degradation because the mutant MDM2 from this domain was able to degrade p53.

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