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Review Article

Role of MDM2 Regulator in Cancer: A Review Article

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Abstract

Introduction: Cancer cells themselves are formed due to the accumulation of genetic changes that contribute to tumorigenesis, tumor progression and resistance to chemotherapy and radiotherapy. Most of these genetic changes result in the regulation of the cell cycle in normal cells, to the balance between cell proliferation and cell death that is regulated through the cell cycle by cellular checkpoints. The existence of genes that play a role in the cell cycle has become the center of attention in relation to tumor growth, there are two classes of genes. The first group is genes for the triggering of tumors (oncogenes) such as MDM, and the second group is genes for the suppressor group of tumors (tumor suppressor genes), one of which is p53. In the development of cancer, protooncogens undergo mutations, DNA rearrangement (aneuploidy and chromosome translocation) or gene amplification to form oncogenes. Amplification and translocation of chromosomes can lead to increased gene products or the expression of new protein types caused by the fusion of regions encoding different genes. Point mutations (or deletions or insertions of multiple bases) can result from exposure to chemicals or radiation. These mutations can induce the formation of oncogenes or loss of tumor suppressor gene function or regulation, such as MDM2.

Discussion: The MDM2 gene (Murine Double Minute 2) is shown for transformation and differentiation of cells when expressed. The human MDM2 gene is 491 amino acids long and interacts with the terminal N domain in the p53 α helix transactivation. MDM2 is a gene that encodes a negative regulator of tumor suppressor p53. The MDM2 gene was initially identified as one of three genes (MDM 1, 2 and 3) which was expressed greater than 50-fold on spontaneous amplification in mice transformed into cancer cells. MDM2 is a p53 specific-E3 ring finger ubiquitin ligase which has negative regulatory properties for p53 activity. MDM2 is an oncoprotein that can regulate the stability of p53 by degrading p53. The amplification of the MDM2 gene caused the p53 protein levels to decrease due to overexpression of the MDM2 protein. MDM2 has also been shown to increase tumor growth so that cell growth is not controlled, resulting in malignancy. As a negative regulator of p53, it is predicted that MDM2 is a proto oncogene and overexpression of MDM2 will be oncogenic which prevents p53 activation. In humans MDM2 overexpression often occurs in various types of tumors. In some tumors, loss of p53 is a poor prognostic marker. Likewise, if MDM2 is excessive, it can be used as a prognostic determinant.

Conclusion: MDM2 is an oncogene that encodes a negative regulator of the tumor protein P53 either directly or via several factor proteins. Overexpression of the MDM2 gene can cause inactivation of TP53 and reduce its function as a tumor suppressor and has been shown to increase tumor growth. MDM2 overexpression in various tumors occurs by multiple mechanisms making it difficult to interpret the prognosis.

Keywords: MDM2; Regulator; Cancer

Introduction

Cancer is a health problem in the world that needs to be overcome. Cancer is a cause of death. Every year, there are more than 10 million cases of cancer found in the world. Based on the World Health Organization (WHO) in 2008 there were 12.7 million new cancer cases discovered and 7.6 million deaths due to cancer (Jacques., *et al*. 2008). In Indonesia, based on basic health research in 2007, cancer is the sixth cause of death from the national disease pattern. The prevalence rate of cancer in Indonesia in 2008 was 4.3 per 1000 population. Each year the cancer incidence rate (IR) in Indonesia is 100 per 100,000 population [1].

Cancer cells themselves are formed due to the accumulation of genetic changes that contribute to tumorigenesis, tumor progression and resistance to chemotherapy and radiotherapy. Most of these genetic changes result in the regulation of the cell cycle in normal cells, to the balance between cell proliferation and cell death that is regulated through the cell cycle by cellular checkpoints. The existence of genes that play a role in the cell cycle has become the center of attention in relation to tumor growth, there are two classes of genes. The first group is genes for the triggering of tumors (oncogenes) such as MDM, and the second group is genes for the suppressor group of tumors (tumor suppressor genes), one of which is p53 [2].

In the development of cancer, protooncogens undergo mutations, DNA rearrangement (aneuploidy and chromosome translocation) or gene amplification to form oncogenes. Amplification and translocation of chromosomes can lead to increased gene products or the expression of new protein types caused by the fusion of regions encoding different genes. Point mutations (or deletions or insertions of multiple bases) can result from exposure to chemicals or radiation. These mutations can induce the formation of oncogenes or loss of tumor suppressor gene function or regulation, such as MDM2 [3].

Discussion

Role of MDM2 as regulator

The MDM2 gene (Murine Double Minute 2) is shown for transformation and differentiation of cells when expressed. The human MDM2 gene is 491 amino acids long and interacts with the terminal N domain in the p53 α helix transactivation. MDM2 is a gene that encodes a negative regulator of tumor suppressor p53. The MDM2 gene was initially identified as one of three genes (MDM 1, 2 and 3) which was expressed greater than 50-fold on spontaneous amplification in mice transformed into cancer cells [4].

MDM2 is a p53 specific-E3 ring finger ubiquitin ligase which has negative regulatory properties for p53 activity. MDM2 is an oncoprotein that can regulate the stability of p53 by degrading p53. The amplification of the MDM2 gene caused the p53 protein levels to decrease due to overexpression of the MDM2 protein. Overexpression of this gene can cause inactivation of Tp53 and reduce its function as a tumor suppressor. MDM2 has also been shown to increase tumor growth so that cell growth is not controlled, resulting in malignancy [1].

Repeat MDM2-p53 feedback is essential for limiting p53 levels and activity during normal cell physiology and is regulated by several other factors. This other protein was identified to interact with MDM2 or p53 both at the beginning and at the end which is able to bind, localize, express and modulate MDM2 E3 ligase activity against itself, p53 and other substrates. Its function is to regulate a variety of different cellular processes [5].

MDMX or MDM4, a variant of MDM2, has a high level of homology for MDM2, especially in the N-terminal p53 binding domain and both proteins are believed to have a role in maintaining low p53 levels in normal cells. MDMX also directly binds to the p53 transactivation domain and inhibits p53 activity but does not cause p53 degradation. MDMX is expressed in several cancers and heterodimerizes to MDM2 via the RING finger domain in C-terminus, thereby modulating its E3 ligase activity. MDM2 and MDMX have been shown to form complexes to inhibit p53 transactivation or increase it. The interaction of the two can directly form ubiquitinate and reduce MDMX so that it damages DNA [2].

One of the other proteins found to interact with MDM2 is ARF. ARF is an alternative protein that is expressed from the INK4a locus. ARF interaction with MDM2 blocks MDM2 back and forth between the nucleus and cytoplasm through the nucleoli. The export of nuclear p53 by MDM2 is required for efficient degradation. Absorption of MDM2 in the nucleoli results in activation of p53. Mutations in human ARF exon 2 interfere with nucleolar localization and impair their ability to block nuclear export of MDM2 and p53. This deregulation results in an increase in the level of nuclear MDM2 thereby decreasing p53 and leading to transformation [7].

Like ARF, the ribosomal protein L11 binds to MDM2 and can introduce it to the nucleolus, resulting in stabilization of p53 levels. The addition of the increased amount of L11 inhibited the degradation of p53 by MDM2. Functionally, the addition of L11 to U2OS cells led to an increase in G1 capture. Thus, both the level of L11 and localization in cells affect p53 activity through interactions with MDM2. Likewise, hypoxia-inducible factor 1α (HIF-1α) also

interacts with MDM2 and enhances p53 function. This interaction prevents nuclear p53 export, but provides another example of a protein that can physically prevent MDM2 from binding to p53 [8].

Several kinases have also been shown to phosphorylate MDM2. The ATM kinase phosphorylates MDM2 to serine 395 and impairs the degradation and export of p53 nuclei by MDM2. Phosphatidylinositol 3-OH-kinase (PI3-kinase) and Akt/PKB serine-threonine kinase, after mitogen-induced activation also binds and phosphorylates MDM2 on serine 166 and 186. Phosphorylation in this section is required for translocation of MDM2 from the cytoplasm into the nucleus. Active expression promotes MDM2 nuclear entry, reduces p53 cell levels, and reduces p53 transcription activity [4].

C-abl is required for p53 accumulation in response to DNA damage. C-abl neutralized the inhibitory effect of MDM2 on p53 by phosphorylation of MDM2 on tyrosine 394. Mutation of MDM2 converting tyrosine 394 to phenylalanine increased MDM2's ability to degrade p53. Phosphatases also appear to play a role in regulating MDM2. Cyclin G is a regulatory component of the active holoenzyme PP2A, which binds and activates MDM2 through dephosphorylation [7].

MDM2 was identified as an RB-binding protein. RB is a powerful tumor suppressor in many types of cancer. MDM2 inhibits the ability of RB to inhibit E2F1 function, thereby inhibiting cell cycle capture in G 1. MDM2 also interacts with the transcription activator Sp1 *in vivo*. MDM2 binds to Sp1 thereby not allowing Sp1 interaction with its specific DNA binding sequence thus blocking transcription. The Sp1/MDM2 interaction is associated with the addition of RB, enabling control of Sp1 transcription. The transcription factor E2F1 functions as a heterodimer with DP1 to activate the genes required for the S phase. The interaction of MDM2 with E2F1 and DP1 produces a complex that can stimulate transcription. MDM2 also stimulates E2F1 growth enhancing activity and blocks E2F1 apoptotic activity [2].

The p300/CBP transcription coactivator not only interacts with MDM2 and acetylates p53. MDM2 inhibits the interaction of p53 with p300/CBP, thereby reducing p53 activity. Androgen receptors (AR) are transcription factors that are translocated to the nucleus upon binding to their ligands, androgens. AR can bind a region that includes the MDM2 RING domain. It phosphorylates AR and MDM2 and increases the efficiency of AR degradation by MDM2. Thus, AR can be another target of MDM2 E3 ligase. The ribosomal L5 protein is associated with the MDM2 and MDM2-p53 complexes, suggesting a role for MDM2 in ribosome biogenesis, ribosome transport to the nucleus, or translation regulation. MDM2 binds to ribosomal L5/5S ribonucleoprotein particles and can also bind to RNA sequences [8].

Promyelocytic leukemia protein (PML) mediates protein localization to the nucleus. PML is responsible for protecting p53 from MDM2-mediated ubiquitination by MDM2 sequestering in the nucleus. Casein kinase 1 (CK1) also plays a role in PML-mediated p53 protection by phosphorylating p53 in Thr18 in response to DNA damage and causing its localization to PML nuclear bodies, thus protecting it from MDM2-mediated degradation [4,5].

DNA damage activates several proteins, some of which are downstream target p53. The 14-3-3-σ protein is one of the p53 targets expressed after radiation exposure. This protein negatively regulates cell cycle progression through interactions with CDK2/4 and CDC2, preventing cyclin-CDK interactions and causing G2 phase cell cycle arrest. This protein can also decrease p53 degradation through increased MDM2 auto-ubiquitination and degradation, as well as by causing MDM2 translocation to the cytoplasm [7].

DNA damage also increases the accumulation of JMY, the co-transcription factor p53. As long as DNA impairs the p53-induced response, JMY forms a nucleus-dependent DNA damage complex with oncoprotein activator p300 and MDM2. JMY and p300 are formed into p53 in the protein complex after DNA damage and work together to enhance the p53 response. JMY was degraded following ubiquitination by the MDM2 RING domain [4].

Implications of MDM2 on cancer

As a negative regulator of p53, it is predicted that MDM2 is a protooncogen and overexpression of MDM2 will be oncogenic which prevents p53 activation. In humans MDM2 overexpression often occurs in various types of tumors. In some tumors, loss of p53 is a poor prognostic marker. Likewise, if MDM2 is excessive, it can be used as a prognostic determinant [9].

In each tumor there is a change in p53 so that the inactivation mechanism in the p53 tumor suppressor pathway will result in overexpression of MDM2. Here are some of the roles of MDM2 in various cancers so that in the future further research can be carried out and targeting MDM2 as a cancer therapy [10].

MDM2 and sarcomas

In sarcomas, a 24-sample cohort study showed that 8 tumors underwent a change in p53, whereas in 8 different tumors experienced amplification of the MDM2 gene with an increase in the number of nuclei, it could be seen by immunohistochemistry (CPI).

This indicates that there are two occurrences of alternative mechanisms for inactivating the same pathway. In a larger cohort of 211, 76 out of 207 tumors overexpressed MDM2, and 56 of 211 had p53 overexpression (indicated accumulation of inactive mutant p53). These two proteins were overexpressed in 22 cases. Both groups have a poor prognosis, this indicates that p53 is independent of oncogenic properties to the MDM2 mechanism [11,12].

Another study with 86 clinical pathology studies, yielding data with p53 and MDM negative in tumors will have the best prognosis, followed by MDM2-/p53 +, then MDM2 +/p53-, and MDM2 +/p53 +. The results obtained in this study indicate that overexpression of MDM2 has a poor prognosis compared to overexpression of p53, possibly due to the role of p53 in activating MDM2 oncogenes [13].

MDM2 and glioma

Glioma malignancy represents another type of tumor that loses function of p53. This p53 mutation was determined in one-third of all glioblastomas. Approximately 10% of gliomas have MDM2 amplification, the rest are epidermal growth receptor factors. In gliomas, gene amplification is the main mechanism for overexpression of MDM2. The loss of p53 function and overexpression of MDM2 is due to the feedback loop autoregulator factor, the prognostic implications of p53 mutation and MDM2 overexpression are not the same (various) [10].

A case of 61 central nervous glioma patients found that having a high proliferation index was associated with poor prognosis, while expression on p53 and MDM2 was the second factor independent of the overall prognosis. In contrast, in another study with 107 advanced glioma patients, it was seen that overexpression of MDM2 was significantly associated with poor prognosis (short survival rate). Likewise, in a study with 75 glioblastoma patients where MDM2 amplification and p53 mutations were associated with survival. One-third of the tumors had the p53 mutation, while MDM2 was 13%. In this study, p53 mutations were significantly found in patients who were younger than those who experienced MDM2 overexpression [11].

MDM2 and cancer hematology

In contrast to sarcomas and gliomas, loss of p53 function is a very rare occurrence in acute lymphoblastic leukemia (ALL) in children, presumably because of another mechanism for functional inactivation of p53. In sarcomas, MDM2 overexpression occurs in 1: 3 of all cases. In a cohort test with 48 samples of children with leukemia, it did not detect any amplification of the MDM2 gene, on the other hand, overexpression of MDM2 mRNA was found in 53% of these samples, some of which had a nearly 50-fold increase found in normal bone marrow. In addition, MDM2 overexpression was dominated by leukemia with unfavorable chromosomal markers. In the larger group, 135 cases of leukemia, there were no cases of the p53 mutation, nor were there any cases of MDM2 amplified leukemia. However, in 9 cases of ALL where there was overexpression of mRNA in 3 cases, all of them were associated with poor response to therapy [12].

These data suggest that MDM2 protein overexpression is a marker of poor prognosis, supported by another study using the CPI in a population of children with acute lymphoblastic leukemia. Expression of p53 is rarely seen at the time of diagnosis. Expression of MDM2 was recorded at diagnosis in the cells of 4:30 children in the non-relapse group, but was found in 10 out of 15 children at the time of bone marrow transplantation. P53 expression was more common in the free/non-relapse group as an expression of MDM2 [14].

MDM2, melanoma and carcinoma

Melanoma is another type of tumor that has lost the p53 mutation. In the case of 172 patients with skin melanoma, MDM2 at different stages who underwent melanocyte transformation, there was overexpression of MDM2 in 50% of the sample due to depth of skin invasion as well as metastasis. MDM2 correlates with outcomes in a study in 134 patients conducted at an institution for more than 10 years, it was found that MDM2 overexpression was an independent predictor of survival [11].

In breast carcinoma, it was observed that overexpression of MDM2 mRNA was common in normal breast tissue, this was related to overexpression of protein with CPI in 24 of 33 tumors tested. Gene amplification was not observed, in some samples MDM2 mRNA was not found in normal breast tissue when identified, and its presence was associated with poor prognosis. MDM2 overexpression occurs only at estrogen receptor positive and associated with good prognosis [15].

Conclusion

MDM2 is an oncogene that encodes a negative regulator of the tumor protein P53 either directly or via several factor proteins. Overexpression of the MDM2 gene can cause inactivation of TP53 and reduce its function as a tumor suppressor and has been shown to increase tumor growth. MDM2 overexpression in various tumors occurs by multiple mechanisms making it difficult to interpret the prognosis.

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