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The Role of the Mdm2/MdmX E3 Ligase System in Carcinogenesis, and Current Chemotherapeutic Interventions: A Literature Review

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Abstract

Introduction: E3 (ubiquitin) ligases play a major role in the ubiquitin-proteasome system (UPS), responsible for the ubiquitination and degradation of various proteins. The UPS has many roles, including regulation of the cell cycle. To mediate these functions, there are many different types of E3s, each with different substrates. A major E3 system involved in oncogenesis is the Mdm2/MdmX system, which acts as a heterodimer to degrade the tumour suppressor, p53, responsible for inducing cell cycle arrest and/or apoptosis in cancer cells, as needed. Upon overexpression/hyperactivation through mutation, the Mdm2/MdmX system can promote carcinogenesis through increasing degradation of p53, preventing necessary cell cycle arrest/apoptosis in cancer cells.

Methods: A literature review was conducted to synthesize and analyze research on Mdm2/MdmX E3 overexpression/ hyperactivation, and the treatment options available for cancers in which overexpression/hyperactivation plays a role.

Results: There are many types of mutations that may be present in cancer cells, however mutations leading to the inactivation of p53 are some of the most common. Inactivation of p53 can be achieved by direct gene mutation, or overexpression/hyperactivation of Mdm2/Mdmx. Current drugs target the expression of MdmX/Mdm2 or their binding interactions with p53. Inhibition of these interactions triggers apoptosis in cancer cells due to increased p53 activity. Therapies that have been developed to target the Mdm2/MdmX system include small molecule inhibitors such as Nutlins and MI compounds, as well as peptide drugs.

Discussion: Although direct mutations of p53 are commonly found in cancer, mutated p53 is not a viable drug target, so instead many treatment options specifically target a dysregulated Mdm2/MdmX system. Future studies should investigate novel drug targets, minimization of side effects, and treatment in the presence of mutations to other DNA repair systems.

Conclusion: This literature review aids in establishing an interdisciplinary perspective on the types of oncogenic mutations in the Mdm2/MdmX pathway, combining biochemical and mechanistic research with clinical applications and pharmacology, as well as identifying future drug targets involved in this system.

Keywords: ubiquitin-proteasome system; E3 ligases; Mdm2; MdmX; p53; cancer; carcinogenesis; therapeutics; oncogene; cell cycle regulation; apoptosis

Introduction

E3 (ubiquitin) ligases are protein enzymes that play a significant role in the ubiquitin-proteasome system (UPS), responsible for ubiquitination and consequently, the degradation of various proteins as seen in Figure 1 [1]. The UPS is made up of a series of proteins responsible for mediating protein ubiquitination- the covalent attachment of ubiquitin (Ub), a small conformationally mobile 76-amino acid protein, to existing substrate proteins primarily at lysine residues [1]. The human genome consists of a plethora of genes, including those that encode various types of E3 ligases [1]. Consequently, a wide variety of proteins can be targeted for ubiquitination using the unique substrate-specificity provided by each type of E3 [1]. Proteins that are degraded include misfolded and denatured proteins, but also proteins that are present at a high concentration, proteins that are endocytosed into the cell, and proteins that are cyclically produced and degraded as a part of cell cycle progression and regulation [2]. For example, E3 ligases are required to regulate cell cycle events by targeting specific proteins for ubiquitination and proteasomal degradation [2]. In this way, cyclins can be degraded to inactivate cyclin-dependent kinases (CDKs) and cell cycle inhibitors can be degraded when cell-cycle checkpoints are passed to activate CDKs [2].

These proteins are selectively tagged and sent to the proteasome for degradation in a two-step process:

ubiquitination followed by proteolysis [1]. First, a protein is tagged by the covalent attachment of Ub to a lysine residue within the polypeptide sequence of the protein that needs to be degraded. In this process, E1 (Ubiquitin-activating enzyme) activates Ub via ATP hydrolysis, and transfers it to E2 (Ubiquitin-conjugating enzyme) [1]. E2 holds the activated Ub via a thioester bond between an E2 cysteine residue and the Ub C-Terminal Domain (CTD), and finally E3 (ubiquitin ligase) interacts with both the loaded E2 and the substrate to promote Ub transfer (via formation of an iso-peptide bond between the Ub CTD and ε-amino group of lysine residues, present in the substrate) [1]. It has also been shown that in some proteins, E3s can ubiquitinate the N-terminal amine, allowing proteasomal degradation of proteins not containing any lysine residues [3]. The proteolytic machinery of the cell is then able to recognize the ubiquitin tag and begin to degrade the protein [1]. Specificity of proteins involved in the UPS is organized in a cascade-like fashion, in which E1 has the lowest specificity and can be acted on by many distinct E2s [1]. E2s are similarly less specific than E3s and are thus acted on by a variety of distinct E3s [4]. E3s must be the most specific, as they must be able bind to many unique protein substrates for Ub transfer [1]. This specificity cascade can be reflected in the number of identified proteins of each type: the human genome encodes only one major E1, over 40 distinct E2s, and over 600 distinct E3s [1, 4].

E3 ligases are a key component of this pathway, as they confer specificity to the ubiquitination interaction, and thus are responsible for direct recognition of the substrate to be ubiquitinated through protein degradation sequences (degrons), or recognition of specific protein motifs, depending on the E3 ligase [1]. Two major types of E3 ligases have emerged, marked by similar mechanisms, and catalytic domains: Really Interesting New Gene (RING), and Homologous to E6-AP Carboxyl Terminus (HECT) E3 ligases [1]. RING E3 ligases make up the largest family of E3 ligases and contain a U-box fold catalytic domain [1]. RING E3 ligases act by non-covalently interacting with the E2-Ub complex as a molecular scaffold stabilising Ub in a 'closed' conformation [1]. This is hypothesized to optimize the geometry of the E2–Ub thioester bond and its surrounding residues to favor the nucleophilic attack by the substrate lysine residue, in a process known as thioester aminolysis [1]. In contrast, HECT E3 ligases contain a C-terminal catalytic domain, and transfer Ub from the E2-Ub complex to the C-lobe of E3, forming a covalent thioester-linked E3 intermediate, in a process known as transthiolation [1]. Acting with a structural element found in the N-lobe, the C-lobe-Ub intermediate is thought to present the newly formed thioester bond to a lysine residue of the substrate, mediating nucleophilic attack [1]. It is also important to note that a third class of RING/HECT hybrid E3 ligases known as Ring Between Ring (RBR) E3 ligases, has been identified, and RBR E3 ligases act via a similar mechanism to HECT [1]. The difference between RING and HECT E3 ligases are highlighted in Figure 1.

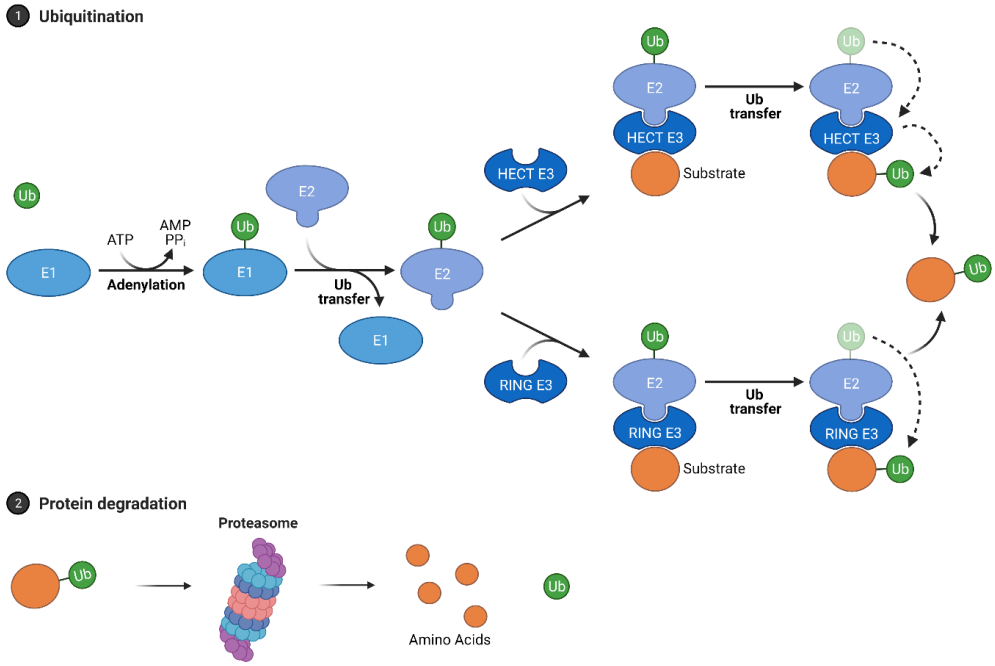

Figure 1. The ubiquitin-proteasome system (UPS). E1 activates Ub via ATP hydrolysis, and transfers it to E2 (Part 1: Ubiquitination). The E2-Ub complex is then acted on by an E3 to promote ubiquitination. The mechanistic differences between the RING and HECT E3 ligases are highlighted here. Once it is ubiquitinated, proteasomes are able to degrade the targeted substrate (Part 2: Protein degradation). This figure was created with BioRender.com.

Murine double minute 2 (Mdm2) and Murine double minute X (MdmX) are RING E3 ligases that are responsible for the regulation of transcription factor p53 [5]. p53 is a tumor-suppressive transcription factor that is essential in inducing apoptosis in response to DNA damage and cellular stress, and thus preventing aberrant cell cycle progression [5]. After translation, p53 is unstable and is immediately polyubiquitinated at lysine residues located near the C-terminal domain [6]. In response to DNA damage, nuclear p53 is stabilized via phosphorylation, so that many genes, including cell-cycle inhibitors (e.g., p21) and DNA repair genes, can be expressed [7]. The goal of cell cycle arrest is to allow the cell time and resources to fix the damage. However, if the DNA damage cannot be repaired, the cell will undergo apoptosis. Thus, the activation of p53 will also induce the expression of apoptotic genes and cause cell death to remove the damaged cells [7].

The exact mechanism of Mdm2/MdmX function is not fully understood, however, it has been found that they act together as a heterodimer to augment the degradation of p53, via the UPS as seen in Figure 2 [5]. Ubiquitination of p53 blocks persistent activation of DNA damage responses, by targeting it for translocation out of the nucleus (monoubiquitination), and then marking it for protein degradation by the UPS (polyubiquitination) [8]. Both Mdm2 and MdmX possess p53 binding domains, and RING E3 domains, however it has been shown that MdmX binds to known E2 ligases very poorly and is unable to ubiquitinate p53 on its own [9]. There is, however, a large body of evidence to suggest that Mdm2 and MdmX act together as a heterodimer (via RING-RING interactions), with Mdm2 responsible for ubiquitinating p53, and MdmX responsible for regulating Mdm2 - a common mechanism in E3 ligase function [5]. It is important to note that Mdm2 can form a homodimer, however it has been shown that heterodimer formation is stoichiometrically favored, and the heterodimer has a significantly higher p53 binding affinity [10]. Mdm2/MdmX heterodimers undergo autoubiquitination, with Mdm2 ubiquitinating MdmX, but not itself [11]. The purpose of autoubiquitination has been widely debated, originally thought to cause enhanced UPS degradation of Mdm2/MdmX heterodimers, however recent studies suggest that autoubiquitination is an activating event leading to enhanced recruitment of activated substrate E2s [11].

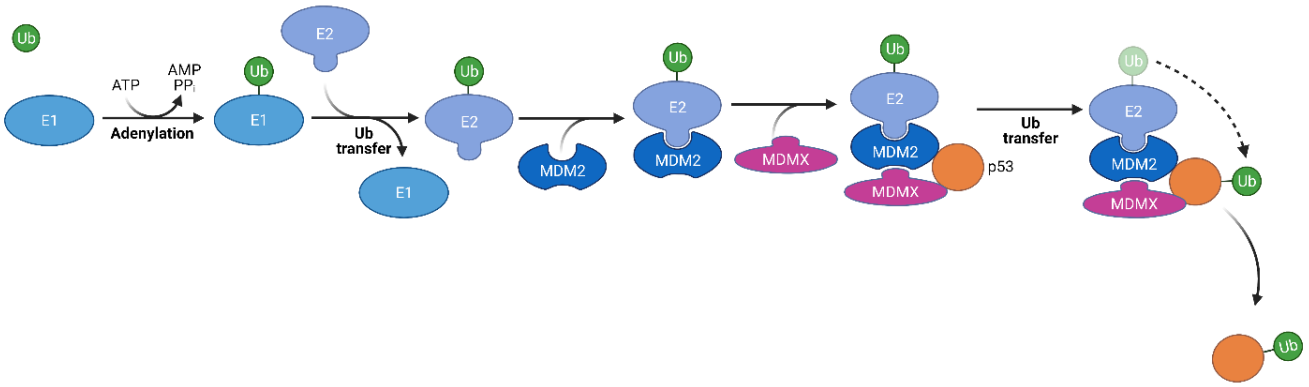

Figure 2. The ubiquitination process of p53 via the MDM2-MDMX pathway. Degradation of p53 is not shown (refer to Figure 1, Part 2: Protein degradation) This figure was created with BioRender.com.

When cells fail to respond to apoptotic signals, there is a net increase in cell number instead of an equilibrium of cell growth and cell death, which can result in the development of cancer [12]. This is especially problematic when there is a great deal of genetic damage and dysregulated cell division, which results in unregulated cell proliferation and the formation of benign or malignant tumours [12]. When the Mdm2/MdmX pathway is dysregulated or Mdm2/MdmX are overproduced through mutation, enhanced p53 degradation can act to promote carcinogenesis. As a result of p53's anti-carcinogenic properties, and the role of the Mdm2/MdmX system in carcinogenesis, the Mdm2/MdmX system is a promising target in the treatment of cancers [5]. Thus, the reduction of Mdm2/MdmX levels, and/or inhibition of interactions between these proteins and p53 are promising pharmacological targets for the treatment of cancers. A class of drugs known as Nutlins, is commonly used to attenuate this pathway [5]. Nutlins can down-regulate MdmX and occupy the hydrophobic p53-binding pocket of Mdm2, inhibiting Mdm2/p53 binding interactions [5]. In this review, we study how disruption of the Mdm2/MdmX system through mutation, can cause cancer and how the system can thus be targeted to treat cancer.

Methods

A literature review was conducted to synthesize and analyze carcinogenic, mutated forms of Mdm2/MdmX, and current therapeutics used in treating these mutations in cancer. We did multiple searches using keywords on various databases and generated a list of articles that were

relevant to our search terms. The list was narrowed down by answering the following questions:

1. *Is the title relevant to the topic?* The title must match with at least some of the Boolean operators that are defined in Table 1.
2. *Does the abstract contain content that is relevant to the topic?* The abstract must match with the Boolean operators that are defined in Table 1.
3. *Does the main body of the literature contain new information that could be used for the review?*

In addition to this list, other sources were drawn directly from the literature we obtained, as needed. From these sources, we synthesized current literature surrounding carcinogenic mutations of Mdm2/MdmX and cancer therapies targeting these mutations. Finally, new sources were identified via Google Scholar as a part of the peer review process, as areas to expand on were identified by reviewers.

Table 1 summarizes our search terms and the search results that were utilized in our analysis.

Table 1. Summary of literature search results. From the initial search (first row), 11 results were extracted. One of the 11 results was a review article (third row), and three sources were used from the review article. The rest of the results from the next search (second row) were further examined, and six results were used from the refined search. Additional sources were identified in the process of reading relevant review articles, and through peer review.

Database/Source	**Search Terms**	**Number of Search Results**	**Number of Results Used**
Web of Science	TS=((MDM2 mutations OR MDMX mutations) AND cancer) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.	1729	11
Web of Science	(TS=((MDM2 mutations OR MDMX mutations) AND cancer)) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article) Refined by: ESI Top Papers: (Highly Cited in Field) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.	10	6
Review Article: 'Targeting Mdm2 and Mdmx in cancer therapy: better living through medicinal chemistry?' [5]	-	111 (total number of review references)	7
Google Scholar (following peer review)	N-Terminal Ubiquitination E2 superfamily AND Ubiquitin-Conjugating Enzyme Mdm2 Amplification AND MdmX Amplification AND p53 siRNA AND Mdm2 AND oncogene expression Mdm2 Inhibitor AND p53 pathway AND drug development	-	5

Results

Cancerous Mutations within the MdmX/Mdm2 Pathway

Mutations of the MdmX/Mdm2 pathway are found in many cancers, including ovarian cancer, liposarcoma, lung cancer, and breast cancer [13]. It was found that the tumour suppressive function of p53 can be lost by genetic mutation or deletion [13]. p53 mutations are found in most cancers but are especially common in ovarian cancers [14]. For example, in high-grade pelvic serous carcinoma, missense mutations typically occur in the early stages of cancer within the exons of the p53 gene [14].

It was also found that Mdm2/MdmX overexpression/ hyperactivation is implicated in cancer formation, usually through genetic amplification of both proteins [13, 15]. Overexpression of Mdm2/MdmX via gene amplification occurs in many cancers, but it is most common in both well-differentiated and dedifferentiated liposarcoma [16]. For example, in cases where p53 dysfunction is detected, but p53 is not mutated, there are higher copy numbers of Mdm2/MdmX that have been observed in cases of both low-grade serous carcinoma and high-grade serous carcinoma [14]**.** Amplification of Mdm2/MdmX can also occur in conjunction with other mutations in patients, including the mesenchymal-to-epithelial transition factor (MET), an important tyrosine receptor kinase, involved in the growth and development of cells [17]. Although not as common, gene amplification of Mdm2 also occurs in metastatic breast cancer [18]. However, in triple-negative breast cancer, the basal-like 1 subtype was found to be unstable because numerous p53 mutations were found along with deletion of copy-numbers of the genes of various proteins involved in the pathways of p53, including Mdm2 [19]**.**

Current Cancer Therapies Targeting MdmX/Mdm2

As previously mentioned, Mdm2/MdmX is often overexpressed in cancers, functionally deactivating p53 and promoting oncogenesis [5]. As a result, two main therapeutic approaches addressing Mdm2/MdmX overexpression/hyperactivation have been developed, which are summarized in Figure 3. One possible approach is targeting the downregulation of MdmX or Mdm2. Given the role of these proteins in efficient degradation of p53, targeting Mdm2 or MdmX mRNA via RNA interference (RNAi), is one promising approach. Small interfering RNA (siRNA) and microRNA (miRNA) are short RNA sequences that are incorporated into an RNA-induced signalling complex (RISC), which is able to cleave the desired mRNA sequence [20]. Preclinical research indicates that Mdm2 or MdmX can be targeted in this way, however RNAi technology is still being perfected and faces issues with drug delivery [20, 21]. Another approach involves targeting activating pathways that promote Mdm2 or MdmX proteolysis, or inhibiting those that prevent Mdm2 or MdmX degradation [5]. For example, it is known that DNA-damage induced phosphorylation of MdmX promotes its degradation [22]. Interactions such as this could be targeted to decrease Mdm2 and/or MdmX levels in a cancerous system, however no such drug has been designed thus far [5, 22]. Transcription factors involved in Mdm2 or MdmX synthesis are another possible drug target, however this area has also been less explored, as it would likely lead to many off-target effects [5]. Another approach that has been better explored, is targeting of Mdm2-p53 and MdmX-p53 binding interactions. Preventing p53 from associating with Mdm2 and/or MdmX is another promising approach to treating a dysregulated Mdm2/MdmX system [5]. This is most often done with small molecule drugs, such as the *cis*-imdazoline Nutlins, and spiro-oxindole Mdm2 antagonists ('MI' compounds), which occupy the hydrophobic p53-binding pocket of Mdm2 and inhibit the Mdm2/p53 interaction, which stabilizes and activates p53 [5, 23]. However, it is important to note that these drugs cannot effectively antagonize MdmX-p53 interactions, likely due to the shallower p53 binding pocket [23]. MdmX levels have been shown to predict efficacy of Mdm2 antagonists, so more potent inhibitors of this interaction may still need to be developed [23]. However, both types of drugs may still be beneficial, and are currently in clinical testing phases [24]. Peptide drugs, such as PMI and pDI, which mimic the p53 binding site (amino acids F19, W23, and L26, the 'FWL' motif) have also been tested preclinically, however were found to be significantly less active than small molecule inhibitors, possibly due to failure to reach the cancer cells, and/or proteasomal degradation [25]. However, some peptide drugs, such as stapled α−helical peptides, have shown promise in appreciably inhibiting both Mdm2-p53 and MdmX-p53 interactions, and are thus still being explored as future therapies [26].

It is important to note that current therapies targeting the Mdm2/MdmX system have been found to be highly synergistic with other chemotherapeutic agents. Small molecule inhibitors of Mdm2-p53 and MdmX-p53 binding interactions were found to be more effective when used in conjunction with DNA damaging agents, such as topotecan, doxorubicin, and fludarabine in animal models [5, 27]. These drugs are hypothesized to potentiate the effects of small molecule inhibitors, by triggering down-regulation of MdmX, and increasing p53 activation via induction of cellular stress [5, 27]. However, while combination therapy is currently the most effective clinical approach, further work must be done, as these agents often lead to collateral DNA damage, which may cause undesired side effects [5].

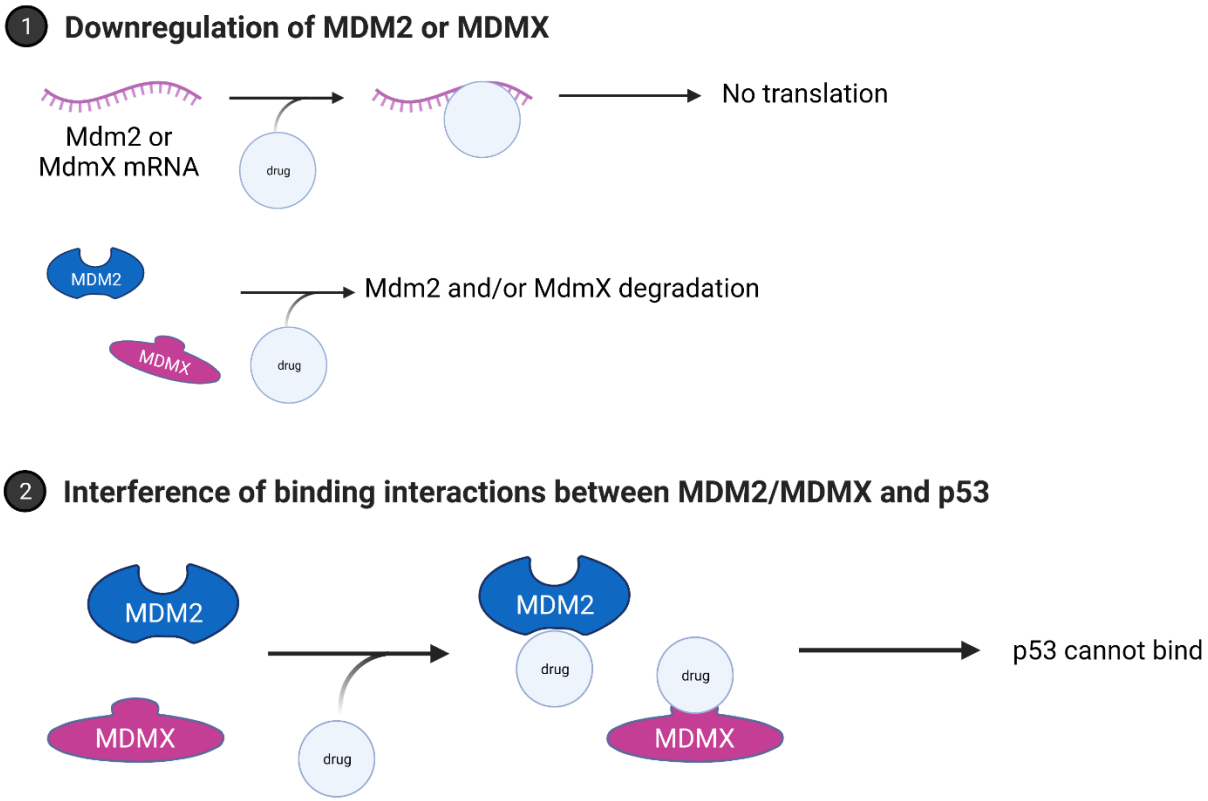

Figure 3. The two main approaches to therapeutically target the Mdm2/MdmX pathway. Mdm2 and/or MdmX can be downregulated, in several possible ways, including mRNA interference, or increasing the degradation of the proteins themselves (Part 1: Downregulation of Mdm2 or MdmX). Mdm2 and/or MdmX can also be targeted to prevent binding interactions with p53- a more common approach (Part 2: Interference of binding interactions between Mdm2/MdmX and p53). This figure was created with BioRender.com.

Discussion

Due to the large number of mutations that can lead to various types of cancer, only a select few were analyzed for the purpose of this review. However, one thing that these mutations had in common was the dysfunction of p53 via mutations of the p53 gene or overexpression of Mdm2/MdmX. This theoretically makes these good pathways to inhibit the growth of cancer cells. However, p53 mutations do not have a defined characteristic that can be used for the prognosis of cancer, as they can vary between individuals [13]. Thus, despite how common they may be, they cannot be easily targeted for cancer therapy [13]**.** Therefore, to treat cancer, it is best to either down-regulate the overexpression of Mdm2/MdmX or inhibit the binding interactions between p53 and Mdm2/MdmX.

Other avenues to target this pathway have also been hypothesized- namely, dimerization interactions between the RING domains of Mdm2 and MdmX [5]. However, development of a drug for this interaction is challenging as E3 RING domains are atypical active sites due to the non-covalent, scaffold-like nature of catalysis [1, 5]. Another promising approach would be the pursuit of drugs targeting regulatory pathways for Mdm2/MdmX, such as the natural DNA damage response induced phosphorylation event that leads to degradation of MdmX (as previously mentioned) [5, 22]. Targeting of E1s and E2s has also been considered, however, due to the low specificity of these proteins (as examined in introduction), this would likely lead to many off-target effects [1, 5]. The same is true for transcriptional regulation, as previously mentioned [5].

Drugs targeting a dysregulated Mdm2/MdmX system have the potential to exhibit synergy with other chemotherapeutic agents that activate p53 through induction of cellular stress/DNA damage [5]. As a result, development of combination therapies is an area with great potential in this line of research and will need to be further pursued with existing and future drugs targeting the Mdm2/MdmX system.

Conclusions

Mdm2/MdmX are E3 ligases that act as a heterodimer to degrade the tumour suppressor, p53, via ubiquitination, causing degradation by the UPS. Disrupting the function of

p53 by either gene mutation or overexpression/ hyperactivation of Mdm2/MdmX promotes carcinogenesis. Current drugs can treat cancers with these characteristics by either downregulating the expression of Mdm2/MdmX or binding to Mdm2/MdmX at their p53 binding sites, to block degradation, and to functionally activate p53. However, throughout this review, it was not apparent as to how to treat cancer in conjunction with mutations in other DNA repair systems. Thus, future research should explore how the Mdm2/MdmX system can interact with other DNA repair systems, how its conjugated mechanisms can cause cancer, and how it can be targeted to inhibit its overexpression/hyperactivation in cell growth and differentiation.

List of Abbreviations Used
UPS: ubiquitin-proteasome system
Ub: ubiquitin
E1: ubiquitin-activating enzyme
E2: ubiquitin-conjugating enzyme
E3: ubiquitin ligase
CTD: C-terminal domain
RING: really interesting new gene
HECT: homologous to E6-AP carboxyl terminus
RBR: ring between ring
CDK: cyclin-dependent kinase
Mdm2: murine double minute 2
MdmX: murine double minute X
RNAi: RNA interference
siRNA: small interfering RNA
miRNA: micro-RNA
RISC: RNA-induced signalling complex

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
This study did not require ethics approval and participant consent because no experiments were done, and no live participants were recruited for this literature review.

Authors' Contributions
RI: contributed to the design of the study, drafted the manuscript, critically appraised, and revised the manuscript, and gave approval of the final version to be published.
KMG: contributed to the design of the study, drafted the manuscript, critically appraised, and revised the manuscript, and gave approval of the final version to be published.

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References
[1] Zheng N, Shabek N. Ubiquitin ligases: Structure, function, and regulation. Annual Review of Biochemistry. 2017 Jun 20;86(1):129–57. https://doi.org/10.1146/annurev-biochem-060815-014922
[2] Dang F, Nie L, Wei W. Ubiquitin signaling in cell cycle control and tumorigenesis. Cell Death & Differentiation. 2021 Feb;28(2):427–38. https://doi.org/10.1038/s41418-020-00648-0
[3] Ciechanover A, Ben-Saadon R. N-terminal ubiquitination: More protein substrates join in. Trends in Cell Biology. 2004 Mar 1;14(4):103-6. https://doi.org/10.1016/j.tcb.2004.01.004
[4] Valimberti I, Tiberti M, Lambrughi M, Sarcevic B, Papaleo E. E2 superfamily of ubiquitin-conjugating enzymes: Constitutively active or activated through phosphorylation in the catalytic cleft. Scientific Reports. 2015 Oct 14;5(1):1-3. https://doi.org/10.1038/srep14849
[5] Wade M, Wahl GM. Targeting Mdm2 and Mdmx in cancer therapy: Better living through medicinal chemistry? Molecular Cancer Research. 2009 Jan;7(1):1–11. https://doi.org/10.1158/1541-7786.mcr-08-0423
[6] Lavin MF, Gueven N. The complexity of p53 stabilization and activation. Cell Death & Differentiation. 2006 Jun;13(6):941–50. https://doi.org/10.1038/sj.cdd.4401925
[7] Lakin ND, Jackson SP. Regulation of p53 in response to DNA damage. Oncogene. 1999 Dec;18(53):7644–55. https://doi.org/10.1038/sj.onc.1203015
[8] Biderman L, Manley JL, Prives C. Mdm2 and MdmX as regulators of gene expression. Genes & Cancer. 2012 Mar 1;3(3–4):264–73. https://doi.org/10.1177/1947601912455331
[9] Linares LK, Hengstermann A, Ciechanover A, Muller S, Scheffner M. HdmX stimulates Hdm2-mediated ubiquitination and degradation of p53. Proceedings of the National Academy of Sciences of the United States of America. 2003 Oct 14;100(21):12009–14. https://doi.org/10.1073/pnas.2030930100
[10] Linares LK, Hengstermann A, Ciechanover A, Müller S, Scheffner M. HdmX stimulates Hdm2-mediated ubiquitination and degradation of p53. Proceedings of the National Academy of Sciences. 2003 Oct 14;100(21):12009-14. https://doi.org/10.1073/pnas.2030930100
[11] Ranaweera RS, Yang X. Auto-ubiquitination of Mdm2 enhances its substrate ubiquitin ligase activity. Journal of Biological Chemistry. 2013 Jun;288(26):18939–46. https://doi.org/10.1074/jbc.m113.454470
[12] Kastan MB, Bartek J. Cell-cycle checkpoints and cancer. Nature. 2004 Nov;432(7015):316–23. https://doi.org/10.1038/nature03097

[13] Wang S, Sun W, Zhao Y, McEachern D, Meaux I, Barrière C, et al. SAR405838: An optimized inhibitor of MDM2–p53 interaction that induces complete and durable tumor regression. Cancer Research. 2014 Oct 15;74(20):5855–65. https://doi.org/10.1158/0008-5472.can-14-0799

[14] Ahmed AA, Etemadmoghadam D, Temple J, Lynch AG, Riad M, Sharma R, et al. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. The Journal of Pathology. 2010;221(1):49–56. https://doi.org/10.1002/path.2696

[15] Riemenschneider MJ, Büschges R, Wolter M, Reifenberger J, Boström J, Kraus JA, Schlegel U, Reifenberger G. Amplification and overexpression of the MDM4 (MDMX) gene from 1q32 in a subset of malignant gliomas without TP53 mutation or MDM2 amplification. Cancer Research. 1999 Dec 15;59(24): 6091-6.

[16] Ray-Coquard I, Blay J-Y, Italiano A, Le Cesne A, Penel N, Zhi J, et al. Effect of the MDM2 antagonist RG7112 on the p53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: An exploratory proof-of-mechanism study. The Lancet Oncology. 2012 Nov 1;13(11):1133–40. https://doi.org/10.1016/s1470-2045(12)70474-6

[17] Schrock AB, Frampton GM, Suh J, Chalmers ZR, Rosenzweig M, Erlich RL, et al. Characterization of 298 patients with lung cancer harboring MET exon 14 skipping alterations. Journal of Thoracic Oncology. 2016 Sep 1;11(9):1493–502. https://doi.org/10.1016/j.jtho.2016.06.004

[18] André F, Bachelot T, Commo F, Campone M, Arnedos M, Dieras V, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: A multicentre, prospective trial (SAFIR01/UNICANCER). The Lancet Oncology. 2014 Mar 1;15(3):267–74. https://doi.org/10.1016/s1470-2045(13)70611-9

[19] Bareche Y, Venet D, Ignatiadis M, Aftimos P, Piccart M, Rothe F, et al. Unravelling triple-negative breast cancer molecular heterogeneity using an integrative multiomic analysis. Annals of Oncology. 2018 Apr 1;29(4):895–902. https://doi.org/10.1093/annonc/mdy024

[20] de Fougerolles A, Vornlocher HP, Maraganore J, Lieberman J. Interfering with disease: A progress report on siRNA-based therapeutics. Nature Reviews Drug Discovery. 2007 Jun;6(6):443-53. https://doi.org/10.1038/nrd2310

[21] Yin JQ, Gao J, Shao R, Tian WN, Wang J, Wan Y. siRNA agents inhibit oncogene expression and attenuate human tumor cell growth. Journal of Experimental Therapeutics and Oncology. 2003 Jul;3(4):194-204. https://doi.org/10.1046/j.1359-4117.2003.01092.x

[22] Pereg Y, Shkedy D, de Graaf P, Meulmeester E, Edelson-Averbukh M, Salek M, Biton S, Teunisse AF, Lehmann WD, Jochemsen AG, Shiloh Y. Phosphorylation of Hdmx mediates its Hdm2-and ATM-dependent degradation in response to DNA damage. Proceedings of the National Academy of Sciences. 2005 Apr 5;102(14):5056-61. https://doi.org/10.1073/pnas.0408595102

[23] Popowicz GM, Czarna A, Rothweiler U, Szwagierczak A, Krajewski M, Weber L, et al. Molecular basis for the inhibition of p53 by Mdmx. Cell Cycle. 2007 Oct;6 (19):2386–92. https://doi.org/10.4161/cc.6.19.4740

[24] Brown CJ, Lain S, Verma CS, Fersht AR, Lane DP. Awakening guardian angels: Drugging the p53 pathway. Nature Reviews Cancer. 2009 Dec;9(12):862-73. https://doi.org/10.1038/nrc2763

[25] Pazgier M, Liu M, Zou G, Yuan W, Li C, Li C, et al. Structural basis for high-affinity peptide inhibition of p53 interactions with MDM2 and MDMX. Proceedings of the National Academy of Sciences of the United States of America. 2009 Mar 24;106(12):4665–70. https://doi.org/10.1073/pnas.0900947106

[26] Chang YS, Graves B, Guerlavais V, Tovar C, Packman K, To K-H, et al. Stapled α−helical peptide drug development: A potent dual inhibitor of MDM2 and MDMX for p53-dependent cancer therapy. Proceedings of the National Academy of Sciences of the United States of America. 2013 Sep 3;110(36):E3445–54. https://doi.org/10.1073/pnas.1303002110

[27] Drakos E, Thomaides A, Medeiros LJ, Li J, Leventaki V, Konopleva M, Andreeff M, Rassidakis GZ. Inhibition of p53-murine double minute 2 interaction by Nutlin-3A stabilizes p53 and induces cell cycle arrest and apoptosis in Hodgkin lymphoma. Clinical Cancer Research. 2007 Jun 1;13(11):3380-7. https://doi.org/10.1158/1078-0432.CCR-06-2581

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