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REVIEW

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Targeting Mouse Double Minute 2 Homolog (MDM2) Oncogene in Breast Adenocarcinoma

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ABSTRACT

Introduction: *Breast adenocarcinoma (BAC) is a leading cause of cancer-dependent morbidity and mortality in females worldwide. Concerning critical genes that are implicated in its onset and progression in BAC, the tumor suppressor protein Tp53 (gene locus: 17p13.1) and its negative regulator the Mouse Double Minute 2 Homolog (MDM2) – an oncogene (gene locus: 12q14.3) – form a significant feedback loop.*

Objective: *The aim of the current molecular review was to investigate the MDM2 oncogene deregulation mechanisms in BAC and the corresponding targeted therapeutic approaches.*

Material and method: *A set of fifty (n=50) published papers in the international database of PubMed was selected based on the new exposed knowledge in the field of mdm2 gene and protein normal function and deregulation. They also focused on the anti-mdm2 targeted regimens in BAC. The following keywords were used: breast, cancer, oncogene, mdm2, targeted therapies.*

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Results: *Mdm2 oncogene amplification – combined or not with specific gene polymorphisms – is a crucial molecular event in BAC onset and progression. These genetic alterations negatively affect the Tp53-MDM2 balance and cell homeostasis in breast epithelia.*

Conclusions: *MDM2 oncogene overexpression – due predominantly to amplification – is a relatively frequent event in BAC. Understanding the impact of mdm2 on genetic substrate and biological behavior of BAC, many study groups have experimentally explored the role of specific anti-mdm2 agents and suggested a fragment of them for targeting its oncogenic activity in BACs characterized by specific genetic signatures.*

Keywords: breast, cancer, oncogene, MDM2, TP53, targeted therapies.

INTRODUCTION

Progressive transformation of normal epithelial cells to their neoplastic and malignant phenotype is a multi-step process, including a combination of oncogenes' overactivation and suppressor genes' silencing in the cellular, nuclear and cytoplasmic microenvironment (1, 2). Interestingly, there are some critical genes that act as major regulators for significant cell functions, such as apoptosis, proliferation, cell differentiation and cell cycle balance (3-5). Among them, the tumor protein 53 (TP53)/ Mouse Double Minute 2 Homolog (MDM2) interaction secures the cell homeostasis implicating in the previous referred functions (6-9). TP53 nuclear phosphoprotein is encoded by the corresponding gene (gene locus: 17p13.1) acting as a strong transcription factor and a central "genome guardian" due to its involvement in cell division, apoptosis enhancement and DNA repair (10, 11).

TP53 forms a complex with MDM2. In fact, this conjunction acts as an auto-regulatory pathway. Concerning the biochemical result, MDM2 direct binding to the N-terminus TP53 sub-domain reduces the transcriptional activity of the molecule leading to an increased TP53 ubiquitination and degradation mediated by proteasomes in the cytoplasmic environment (12, 13). Normally, there is a balance between the TP53/MDM2 co-expression in epithelial cells securing their stable functionality. In contrast, in neoplastic – as early genetic events – and malignant cell phenotypes, the two molecules demonstrate altered expression patterns (loss, reduced or over expression) that significantly influence their normal activity. This imbalance at the genetic – including specific deregulation mechanisms and oncogenic polymorphisms – and protein level is detected in a broad spectrum of epithelial malignancies including breast, head and neck, liposarcomas and adipocytic tumors (14-18). The impact of this co-deregulation on the progression and biological behavior of those cancers is under investigation. Additionally, these proteins are important targets for experimental development and clinical application of novel, individualized oncological therapeutic agents and regimens in subgroup of cancer patients characterized by specific genetic signatures (19, 20).

In the current molecular review, we focused on the MDM2 involvement in the onset, development and progression of breast adenocarcinoma (BAC). Additionally, we selected and presented new published data in the field of anti-MDM2 therapeutic strategies in BAC analyzing the mechanisms of MDM2 gene deregulation that lead to its over activation in this malignancy. Because BAC is a leading cause of cancer-dependent morbidity and mortality in females worldwide, development of strong anti-oncogenic agents is a most promising field in modern molecular oncology.

The MDM2 oncogene: molecular structure, function, deregulation mechanisms

MDM2 proto-oncogene is harbored on chromosome 12 (gene band: 12q14.3-15). It is a member of MDM gene family that includes also MDM1, MDM3, MDM4 and MDMX. It consists of 12 exons and two promoters (P1/P2) and encodes for a 491 amino-acid (56 kDa) nuclear-localized protein acting as an E3 ubiquitin-protein ligase/transferase (21). Additionally, it produces eleven more protein isoforms due to alternative splicing mechanism It was discovered and cloned analyzing genetically specific mouse fibroblasts which demonstrated amplification in

double minute chromosomes (22). Besides the previous referred negative regulation of TP53 protein expression, MDM2 controls the intracellular zinc ion concentration and the rates of its binding to the corresponding eligible enzymatic substrates. Concerning its structural polypeptide anatomy, the molecule comprises a C-terminal domain, a central one and an N-terminal domain. The first one is implicated in zinc transfer, the second domain represents the main functional part of the molecule, whereas the third one interacts with the TP53 protein forming a negative autoregulatory, feedback loop (23). Biochemically speaking, phosphorylation of multiple residues – mainly located in its central zone – is the mechanism that activates MDM2 functionality (24).

Overactivation of the MDM2 gene – leading to an excessive protein expression in solid malignancies – is mediated by three genetic mechanisms: mainly amplification due to the production of multiple copies of the gene in its initial loci, point mutations and direct aberrant gene expression provided by MDM2 regulators, especially in liposarcoma and adipocytic tumors (25-27). Interestingly, translocation is another, alternative to amplification mechanism of MDM2 gene deregulation. It is under investigation in malignancies that demonstrate resistance to tyrosine kinase inhibitors interacting with the mitochondrial transcription factor (TFAM) regulating the mitochondrial DNA (28).

MDM2 gene in BAC: deregulation mechanisms and targeted agents

According to significant epidemiological studies derived from national and international health organizations, BAC is a leading cause of cancer-dependent morbidity and mortality in females worldwide (29, 30). More specifically, BAC is the major type in newly detected cancer cases in females, whereas is the second cancer – related type in them following the lung cancer (31). Concerning the involvement of the altered TP53/MDM2 complex in BAC onset and progression, many studies have reported the combination of TP53 mutations and MDM2 amplification/specific single nucleotide polymorphisms as a significant genetic signature in the corresponding patients characterized or not by germline BRCA1/2 mutations. Deregulation of them negatively affect the biological behavior of the malignancy and for this reason both of them are considered remarkable targets for applying specific chemotherapeutic oncological regimens (32-35).

Referring to the anti-MDM2 inhibition targeted therapies, there is an increasing interest for developing, testing, validating, and finally applying a broad spectrum of natural products and substances derived from plants (36). A study group analyzed experimentally a potential selective MDM2 inhibitor, the JapA lead substance. They observed that this natural compound demonstrated an anti-oncogenic activity by decreasing the MDM2 protein expression in breast cancer cell lines, reducing also their proliferation rates (37). Another study group focused on the impact of ginkgetin – a natural compound derived from *Ginkgo biloba* plant – on breast cancer cell cultures (38). According to their experimental results, this biflavone demonstrative a suppressive action to MDM2/TP53/YAP 1 axis by increasing a specific iron-related programmed cell death called ferroptosis. Furthermore, ginkgetin provided an induction of paclitaxel's anticancer activity, which with the addition of carboplatin and pembrolizumab form the core of anti-BAC neoadjuvant chemotherapeutic regimens (39).

Besides the previous referred natural agents, specific enzymes and small molecules seem to be implicated also in anti-MDM2 BAC strategies. Inulanolide is a dual MDM2/NAFT transcription factor that reduces cancer cell proliferation enhancing also apoptosis (40). Other small molecules – including isoquilinone, spirooxindole, piperidinone, and nutlins – demonstrate different levels of TP53/MDM2 activity inhibition (41). Focused on nutlins, especially the Nutlin 3a is significantly involved in MDM2/TP3 complex antagonism by blocking the E2F1 transcription factor binding to MDM2 and thus disrupts its activity in cell cycle progression (it mediates transition from G1 to S phase). Interestingly, Nutlin 3a exposes its anti-oncogenic action in BAC cells that harbor TP53 mutations (42, 43). In conjunction with the previous mentioned studies, an analogue of nutlin-1, the L2 small molecule, acts as a strong MDM2/TP53 inhibitor by preventing their interaction and decreasing proliferation rates (44). As nutlins, some proteases that belongs to the proteasome-ubiquitin intracellular system are involved in the regulation of MDM2/TP53 activity. More specifically, ubiquitin

specific protease 7 (USP7) is a target for inhibition in BAC (45). Besides the cis-imidazolines (nutlins), a class of novel synthetic small molecules such as chalcones, spiro-oxindoles, pyrazolidinedione sulfonamides, benzodiazepines and triazolyl-thio-oxazines represent promising anti-MDM2 agents (46-49).

In conclusion, MDM2 gene – as a crucial component of the TP53/MDM2 complex and the main negative regulator of TP53 activation and expression – demonstrates amplification and specific polymorphisms in subsets of BACs. In these cases, there is an increasing need for applying inhibitory agents, including small natural or synthetic molecules that block its aberrant expression (50). Understating the structure and the mechanisms of MDM2 at the gene and protein level is a critical step for developing and applying targeted inhibition regimens in BAC patients characterized by specific genetic signatures. ❑

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