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Review Article

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A Review on Deubiquitinating Enzymes as Oncodiagnostic Biomarkers

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ABSTRACT

Cancer is a fatal illness that is responsible for the deaths of millions of individuals all over the globe every year. It is possible that people will be able to survive for a longer period of time as a result of early identification, staging, and individualised biomarker therapy. Proteases known as deubiquitinating enzymes are responsible for removing ubiquitin tags from proteins so that they may be broken down by the proteasome. Enzymes that deubiquitinate proteins have several purposes throughout the body. One of the numerous roles that Deubiquitinating Enzyme plays is to keep an eye on the progression of tumours. The expression of members of the deubiquitinating enzyme family was shown to be elevated in a wide range of oncocells and tissues during various stages of cancer, according to a number of investigations. Based on these findings, deubiquitinating enzymes have the potential to be exploited as a therapeutic target in cancer treatment. In this article, the functions of members of the Deubiquitinating Enzyme family, as well as ubiquitin-specific proteases and other important family members, are dissected. Our goal was to get a better understanding of the connection between the expression patterns of deubiquitinating enzymes and carcinomas so that future research might investigate the possibility of developing inhibitors and gene therapies to improve the diagnosis and prognosis of cancer.

Key Words: *Oncobiomarkers, Oncodiagnostics, Oncotherapeutics*

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INTRODUCTION

Nearly eight million people throughout the world lost their lives to cancer in 2012, making it one of the leading causes of mortality in the world [1]. Recent advances in genetics and cell biology have led to considerable advances in cancer detection as well as treatment breakthroughs. The results of these more recent investigations suggest that the genes responsible for cancer have been decoded [2, 3]. The scientific community is responsible for the discovery of a significant number of the genes that are known to be carcinogenic. A protein that is encoded by the carcinoma gene controls cell growth and division and also has a role in cell death (apoptosis). The genes that mediate DNA repair are the ones most often affected by oncogenesis mutations [4].

Ubiquitin proteasome pathway

A transition that determines the destiny of a protein is called the post-translational binding of ubiquitin. In spite of the fact that ubiquitin is a very small protein, it is an integral component of a complex, covalently attached cellular machine that engages in interactions with protein substrates and other ubiquitin molecules. The inhibition of protein breakdown by the 26S proteasome is the most important and well-known function of the ubiquitin molecule. The breakdown of the protein substratum occurs as a consequence of the creation of an isopeptide bond between the carboxy-terminal glycine (Gly) on ubiquitin and the lysine side chains (Lys) on the protein. The multibiquity step occurs when one of the seven Lys residues of another ubiquitin (Lys6, Lys11, Lys27, Lys29, Lys33, Lys48, and Lys63) is connected with the C-Terminal Gly from the ubiquitin molecule, thereby generating a straight chain.

The protein degradation system is composed of ubiquitin, a 3-enzyme-ubiquitination complex, proteasomes, ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases. Targets for protein ubiquitination in the cell are also a part of this mechanism (E3).

Deubiquitinating enzymes

Proteases known as deubiquitinating enzymes are responsible for reversing the ubiquitination of proteins, which is a critical process for keeping homeostasis stable. Ubiquitin precursor purification, ubiquitin molecules recycling,

multiubiquitin chain cleavage, and ubiquitin conjugation revolution are the four key action methods employed deubiquitinating enzymes. Deubiquitinating enzymes are responsible for the regulation of a wide variety of cellular processes, including proteolysis, gene expression, progression of the cell cycle, separation of chromosomes, activation of kinase enzymes, the apoptotic pathway, containment, DNA repair, self-renewal maintenance, spermatogenesis, and degradation of signal intermediates [5-10].

Approximately one hundred deubiquitinating enzymes may be found in the human genome [10]. On the basis of the organisation of the catalytic area, deubiquitinating enzymes are classified into a wide variety of types, with cysteine proteases making up the majority of these enzymes. Other proteases that belong to this family include ubiquitin-specific proteases (USPs), ubiquitin C-terminal hydrolases, ovarian tumour proteases (OTUs), Machado-Joseph disease proteases (MJDs), Jab1/Mov34/Mpr1 (JAMM) metalloproteases, and the recently discovered MIU-containing novel DUB family, (MINDY) proteases.

UBIQUITIN-SPECIFIC PROTEASE FAMILY

USP2

USP2a is an enzyme that deubiquitinates proteins such as fatty acids synthase, Mdm2, and MdmX. It also inhibits apoptosis and has androgenic properties. USP2a is associated to the evolution of malignant glioma and serves as a helpful indication for glioma prognosis since its expression is greater in glioma cells than in normal brain tissue. Glioma cells express USP2a more than normal brain tissue does [11]. Additionally, the USP2 modifies the function or expression of MMP2, which opens up the possibility of using it as a breast cancer diagnostic [11].

USP4

USP4 has been associated to the control of tumour metastasis in many different types of cancer, including breast carcinoma [12], liver carcinoma [13], and colorectal carcinoma [14]. [14] High levels of melanoma are associated with USP4, which also plays a supportive function in oncogenesis by facilitating the spread of tumours and inhibiting apoptosis in response to stress [15]. Given that USP4 is a necessary protein for the development of hepatocellular carcinoma (HCC) and the MAPK/CrkII signalling pathways, it is possible to employ USP4 as an additional HCC prediction and treatment predictor [16]. Through breast cancer's RLX-mediated TGF-/Smad2/MMP-9 pathways, USP4 makes it easier for cancer cells to migrate and invade, which is essential for successful breast cancer treatment [17]. According to the findings, a high level of USP4 expression in some carcinomas seems to be the cause of the stability of additional oncogenes in a variety of carcinoma types. When it comes to the early diagnosis of carcinoma, targeting USP4 as a biomarker is typically helpful.

USP5

Exopeptidase USP5 is responsible for the production of monobicitin. This is accomplished by severing the isopeptide link that connects polyubiquitin by the use of its free carboxy-terminal [18]. Overexpression of USP5 promotes colony expansion, migration, pharmacological resistance, and cancer. USP5 is responsible for controlling cell proliferation, replication, and pharmacological tolerances [19]. Inactivation of the p14-p53 signalling pathway by USP5 during hepatocarcinogenesis is a critical contributor to the development of tumours and treatment tolerance [20]. USP5, which is responsible for stabilising the FoxM1 protein and producing treatment resistance, plays an essential part in the development of pancreatic cancer [21].

USP7

At first, USP7 was thought to be a ubiquitin-specific protease that was coupled to a viral-encoded protein known as Herpes associated protease Vmw110 [22]. There is a possibility that the regulatory Herpes simplex virus Type 1 protein, also known as HSV-1, is coupled to the herpes-associated ubiquitin-specific protease known as infected cell polypeptide. When combined with USP7 and MARCH7 expression projections, the proteins USP 7 and MARCH 7 are intriguing candidates for use as biomarkers in the diagnosis of epithelial ovarian cancer [23]. The incidence of HCC is consistently ranked among the highest among all kinds of cancer. When compared to samples of typical liver tissue, HCC tissue had a significantly higher concentration of USP7 mRNA and protein [24]. Experiments on living cells have shown that USP7 is capable of proliferating, moving across, and attacking living cells. According to the findings, USP7 has a good chance of becoming a contemporary independent HCC indicator. According to a new study, the proliferation of non-small pulmonary cell cancer (NSCLC) cells is driven by Ki-67, USP7 deubiquitinases. This is the conclusion drawn from research that was published recently [25]. It was discovered that NSCLC cells express both the Ki-67 and USP7 genes. The statistical evidence supports the hypothesis that USP7 and Ki-67 are correlated with one another. On the other hand, siRNA targeting USP7 led to an increase in the ubiquitination of Ki67 and a reduction in the rate of tumour development. According to the information that was shown before, USP7 has the potential to be an effective therapeutic target for a variety of cancer types.

USP8

USP8 is a member of the USP Deubiquitinating Enzymes superfamily, which targets a wide range of substrates [26], such as smoothened [27] and frizzled neuregulin receptor degradation protein-1, as well as receptor TK [28]. Recently,

an investigation was carried out to determine the expression profile of USP8 in cervical squamous cell carcinoma (CSCC) [29]. USP8 expression was shown to be elevated in cervical squamous cell carcinoma (CSCC) tissue samples, in contrast to non-cancerous cervical tissue. In addition, high levels of USP8 expression have been shown to be connected to the stage of the tumour and identified as a distinct marker for CSCC. A high amount of USP8 facilitates the proliferation of cells, as well as their migration and invasion of other cell lines. As a consequence of this, USP8 has the potential to serve as both a diagnostic and a therapeutic target in people who have CSCC.

USP10

It was identified that the protein known as USP10 (UBPO) is a deubiquitinating enzyme that interacts with the Ras-GAP SH3 domain-binding protein. USP10 is composed of 798 amino acids [30]. In trials involving glioblastoma and breast cancer, in particular, there was an uptick in the expression of UBPO. A bad prognosis in patients with multiform glioblastoma has been connected to overexpression of UBPO, while reduced UBPO has been discovered in gastric cancer tissue, and its down-regulation has been linked to invasion, metastasis, and a poor prognosis in patients. Studies have indicated that UBPO may inhibit the expansion and generation of pancreatic cancer cells, which is a positive finding. UBPO is a new deubiquitinating enzyme that is involved in a number of pathogenic events associated with tumours. Low expression of UBPO in gastric carcinomas has been documented in clinical samples and cell lines. Negative expression of UBPO has been connected with a significant propensity for gastric invasion, lymph node metastases, increased malignancy, and poor survival. It is possible that the detection of UBPO in patients with gastric cancer might serve as a novel prognostic signal that could be utilised to predict the clinical outcomes of patients with gastric cancer.

USP22

USP22 is a Deubiquitinating Enzyme that was only identified lately and is connected to the advancement of the cell cycle, therapeutic tolerance, and metastasis. When compared to the expression level seen in normal liver tissues, the amount of USP22 found in HCC was very high [29]. According to the findings of the Kaplan Meier analysis, larger USP22 volumes were connected to higher mortality in patients with advanced tumour processes and were associated with worse HCC survival. According to the findings of multivariate research, USP22 functions as an auto-regulatory marker for HCC prediction. According to the findings of a number of other studies, USP22 is overexpressed in both salivary canal carcinoma [31], as well as oesophageal squamous cell carcinoma [32]. According to the findings, elevated levels of USP22 expression may be a crucial element in the development of tumours and may potentially be utilised as a molecular marker on its own.

USP32

The exceptionally high level of conservation shown in the USP32 gene, which is located at the 17q23.1–17q23.2 chromosomal unit, remains unexplained [33]. In contrast to mammalian tissue that does not include cancerous cells, USP32 has been discovered in 22% of breast cancer tumours that originate from primary breast tissue. The USP32 gene was shown to be endogenous in the MCF7 cell line; however, there was no indication of any cell line alterations; thus, the wild gene was found to be overexpressed. There is also evidence that USP32 has a role in human lung cell cancer (SCLC) [34]. USP32 had an increased expression level in SCLC tissue samples, in contrast to normal tissue levels. During the time when the illness was at its worst, there was a positive link between SCLC and USP32. On the other hand, when SCLC cell migration and proliferation were studied in vitro, USP32 inhibition resulted in a decrease in both. Through an increase in p21 and a decrease in CDK4-cyclin D1 complex concentrations, this down-regulation even caused cells to stop moving through the G0 and G1 phases of the cell cycle. The epithelial-mesenchymal apoptosis that occurred as a consequence of the silencing of the USP32 gene was caused by the activation of cleaved caspase-3 and cleaved-PARP. As a result, USP32 has the potential to be an effective treatment option for both breast and lung cancer.

OTUBAIN PROTEASE FAMILY

OTUB1

It is believed that the OTU domain of ubiquitin aldehyde binding protein 1, which is abbreviated as OTU1 and is a member of the Deubiquitinating Enzyme class of OTU, has a role in a number of different cancers [35–38]. Recent research has shed light on the role OTUB1 plays in the development of human gliomas [39]. In immunoblots and immunohistochemistry tests, OTUB1 levels confirmed their overexpression in glioma tissue. Furthermore, statistical data show that the OTUB1 expression pattern is highly associated to the WHO glioma categories. On the other hand, downregulation of OTUB1 was connected to EMT-related sluggish migration and increased expression of E-cadherin protein. OTUB1 is also capable of contributing to the ECM's stability regulation in several ways. OTUB1 has the potential to be both an efficient cancer marker in gliomas and other types of malignancies as well as a viable source of active cancer treatment.

A20

The deubiquitinating enzyme known as A20 has a history of being linked to allergy and inflammatory disorders [40]. On the other hand, findings from recent studies reveal that A20 plays a crucial role in the metastasis of cancer [41]. In this particular instance, basal-like Snail1 breast cancer metastasis is brought on by over expression of A20. It was shown that A20 was over expressed in human basal-like breast carcinomas, and its over expression was held responsible for the

metastasis of the carcinoma. In breast cancer, A20 also acts as a mediator of the TGF-1-induced EMT. The passing knockdown of A20 has been demonstrated to diminish lung cancer metastases in orthotopic breast carcinoma and mice xenograft models. Additionally, this has been proven to be the case.

Deubiquitinating Enzyme INHIBITORS

According to a number of papers, very small molecules of enzymes that deubiquitinate proteins have been isolated and successfully used as anti-cancer medicines [42]. The inhibition of deubiquitinating enzymes causes cellular changes such as the aggregation of polyubiquitin proteins, a decrease in the population of monomeric ubiquitin moieties, an improvement in polyubiquitin assembly, a total reduction in the number of deubiquitinating enzyme events, and a transition in cellular activity such as the activation of the deubiquitinating oncoprotein control enzyme [43]. The inhibition of the deubiquitinating enzyme causes a reduction in the activity of the proteasomes, which in turn leads to the proliferation of non-functional proteins, which causes cell death and toxicity. Small compounds may be used to target deubiquitinating enzymes, which are responsible for controlling oncogenic proteins. These enzymes can then be prevented from deubiquitinating through the UPS degradation pathway. Deubiquitinating enzymes, which control tumour suppressors, may be damaged when there is an increase in the development of deubiquitination, which slows the growth of oncogenic mutations. Numerous studies have been conducted on teeny-tiny molecule Deubiquitinating Enzyme inhibitors due to the fact that they are simpler to create and provide higher levels of competition compared to the enzyme's activators [44, 45].

Ubiquitin aldehyde (Ubal) and ubiquitin vinyl sulfone (UbVS) are two pharmaceuticals that have been subjected to intensive research because of their ability to inhibit deubiquitinating enzymes and so contribute to the detection [46]. The total molecular weight of these substances, the structure of their peptides, and the general lack of selectivity made it impossible for them to be used in pharmacology [46]. During the process of deubiquitination in the UCH protein family, ubiquitin is removed from adducts at the C-terminus [46]. After that, the scientists made an effort to determine the nature of their inhibitors and came upon the isatin O-acyl oxime sequence [46]. The series is competitive and has the ability to link to the active site directly while maintaining low IC50 values. UCH-L1 inhibits the proliferation of neuroblastoma cells; nevertheless, there is a correlation between the addition of this inhibitor and an increase in cell proliferation. These findings provide further evidence that UCH-L1 proteins possess antiproliferative qualities. It has been determined via synthesis that the novel chemical b-AP15 may inhibit the proteasome [47]. This b-AP15 molecule interferes with the activity of USP14 and UCHL5, both of which are highly connected to 19S RP. Compound b-AP15 has been shown to have potent anti-cancer actions against resistant types of carcinoma in other kinds of cancer.

CONCLUSION

With the assistance of deubiquitinating enzymes, the researchers in this study were able to offer a full diagnostic and prediction of cancer. Recent developments in carcinoma therapy, as well as the rapidity with which these treatments are being implemented in clinical trials for a variety of tumours, lend credence to the possibility that deubiquitinating enzyme-based medications may one day be developed. Enzymes that deubiquitinate typically carry out their function by attaching themselves to the proteins they target for deubiquitination. Under some conditions, the Deubiquitinating Enzyme may serve as a good pharmacological target all by itself. In addition, more study may assist scientists in determining the roles, locations, controls, and substrates of deubiquitinating enzymes in the process of oncogenesis as well as the therapeutic uses of inhibitors of these enzymes. The development of tiny pharmaceutical compounds that specifically target deubiquitinating enzymes will make it possible to treat cancer and other fatal illnesses more effectively.

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