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Perspective

UFMylation-Dependent Stabilization of Emerin Suppresses Hepatocellular Carcinoma via β-Catenin

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Abstract: Hepatocellular carcinoma (HCC) ranks as a leading cause of cancer-related deaths. A recent article identified UFMylation as a suppressor of HCC metastasis. Xu et al. show that UFMylation is lost in HCC and this destabilizes the nuclear-membrane protein emerin, which promotes its degradation, thereby enabling the nuclear accumulation of β-catenin. Under physiological conditions, emerin prevents the nuclear localization of β-catenin. However, via nuclear β-catenin accumulation, loss of UFMylation leads to activation of transcriptional signatures associated with a pattern consistent with hybrid epithelial–mesenchymal transition (EMT), characterized by the expression of both epithelial and mesenchymal markers and enhanced cellular plasticity. The authors show that nuclear β-catenin drives increased migration, invasion, proliferation, and metastatic dissemination of HCC cells. Using mouse models, Xu et al. show that these changes all depend on emerin. The authors further demonstrate that nuclear β-catenin contributes to immune evasion by upregulating the expression of poliovirus receptor, thereby reducing the susceptibility of HCC cells to natural-killer cell surveillance. Conversely, restoration of emerin expression in UFMylation-deficient cells reduced nuclear β-catenin availability and reversed both EMT markers and immune-evasive transcriptional signatures and phenotypes. These findings establish the functional role of UFMylation-dependent stabilization of emerin in the regulation of β-catenin in HCC.

Keywords: UFMylation; hepatocellular carcinoma; emerin; β-catenin; epithelial-mesenchymal transition; poliovirus receptor

UFMylation is a ubiquitin-like post-translational modification that was first described in 2004 by Komatsu et al. [1]. UFMylation involves the covalent attachment of *ubiquitin-fold modified 1* (UFM1), a 9.1-kDa protein with similar tertiary structure but less than 20% sequence identity with ubiquitin, to the lysine residues of its target proteins. The reaction involves the E1 enzyme *ubiquitin-like modifier-activating enzyme 5* (UBA5), E2 enzyme *ubiquitin-fold modifier-conjugating enzyme 1* (UFC1), and E3 ligase *UFM1-specific ligase 1* (UFL1), which is linked to the endoplasmic reticulum via its binding partner UFBP1 [1,2]. The adaptor proteins *UFM1-binding and PCI domain-containing protein 1* (UFBP1), also known as *DDRGK domain-containing protein 1* (DDRGK1), and *CDK5 regulatory subunit-associated protein 3* (CDK5RAP3), also called C53, accelerate the UFMylation reaction. UFMylation is reversible; deUFMylating enzymes (DUFMs) *Ufm1-specific protease 1* (UFSP1) and UFSP2 cleave UFM1 from its substrates [3]. A recent review provides a comprehensive overview of the molecular mechanisms underlying UFMylation [4].

UFMylation plays a central role in the homeostasis of the endoplasmic reticulum, as demonstrated by its roles in ribosome-associated quality control and endoplasmic-reticulum stress [4,5]. Given that UFMylation associates with several cellular processes, dysregulation of the UFM1 system has been linked to human diseases, including

neurodegeneration, cancer, and metabolic disorders [5,6]. A recent review gives a comprehensive description of the functional roles of UFMylation in endoplasmic-reticulum stress, genome maintenance, antiviral signaling, immune-checkpoint regulation, and redox homeostasis [4].

Copy-number alterations of genes affecting UFMylation have been detected in several cancers [4]. Accumulating evidence suggests that dysregulated UFMylation can have either tumor-suppressive or tumor-promoting effects in cancer. Zhou et al. [7] analyzed the enrichment scores of UFL1 expressions across 33 cancer types in The Cancer Genome Atlas data and found that high UFL1 expression was associated with an immune-cell-enriched tumor microenvironment. Further, programmed death ligand 1 (PD-L1), which functions as a negative regulator of T-cell activation, is a target of UFMylation. Reduced UFMylation enhanced the stability of PD-L1, which suppressed the antitumor immunity mediated by CD8-positive T cells [7]. UFMylation also influences tumorigenesis by regulating the stability of p53, a key tumor suppressor. Liu et al. [8] showed that UFMylation stabilizes p53 protein by protecting it from degradation. Depletion of UFL1 or UFBP1/DDRGK1 reduced the stability of p53 protein, hence promoting cell growth and tumor formation [8]. Under normal conditions, p53 level is maintained low by the ubiquitin-proteasome system.

Nevertheless, increased UFMylation has also been linked to tumor progression. Zhou et al. [9] reported that depletion of the UFM1 deconjugase UFSP2 accelerated the proliferation of colon cancer cells, whereas Fang et al. [10] showed that the E1 enzyme UBA5 was overexpressed in a subset of breast cancers, and its overexpression correlated with poor prognosis.

The tumor-suppressive role of UFMylation is particularly evident in hepatocellular carcinoma (HCC). Chen et al. [11] used mouse models to study the role of UFMylation machinery in HCC. Hepatocyte-specific loss of UFL1 or UFBP1/DDRGK1 increased the susceptibility of mice to high-fat-diet-induced fatty liver and spontaneous HCC. The study also reported that UFL1 and UFBP1/DDRGK1 co-precipitated with the mechanistic target of rapamycin (mTOR) and regulated its activity. Deletion of UFL1 or UFBP1/DDRGK1 resulted in pathological activation of mTOR, thereby driving HCC development.

A recent publication by Xu et al. [12] links UFMylation to HCC metastasis and immune evasion. In clinical HCC samples, low UFMylation levels correlated with vascular and microvascular invasion and poor prognosis in patients. The authors also found lower UFMylation levels in metastatic tumors compared with their paired primary tumors. Using mouse models injected with HCC cells depleted of UFL1 or UFBP1/DDRGK1 via tail vein, spleen, or liver, Xu et al. showed that depletion of UFMylation increased circulating tumor cells and enhanced the infiltration of the HCC cells in liver and lung, suggesting that reduced UFMylation enhances tumor metastatic capacity *in vivo* [12].

Xu et al. [12] further analyzed The Cancer Genome Atlas HCC dataset and identified epithelial-mesenchymal transition (EMT) as a key pathway associated with UFMylation status. Immunoblotting confirmed that the epithelial marker E-cadherin and the mesenchymal marker vimentin were both elevated in the UFMylation-deficient HCC cell lines, indicating a pattern consistent with hybrid EMT. Hybrid EMT has been shown to favor enhanced migratory and invasive phenotypes [13].

To investigate the underlying mechanism by which UFMylation affects the HCC cell phenotype, Xu et al. [12] studied datasets of proteins interacting with the key UFMylation components. The nuclear-envelope and endoplasmic-reticulum protein emerin was identified as a common interactor of UFM1, UFL1, and UFBP1/DDRGK1. The interaction of emerin with the three UFMylation proteins was confirmed by co-immunoprecipitation and GST pulldown. Further, knockdown of UFL1 or UFBP1/DDRGK1 reduced emerin protein levels and this reduction was inhibited by proteasome inhibition but not by lysosomal inhibition, suggesting that UFMylation protects emerin from proteasomal degradation. Further, knockdown of UFL1 or UFBP1/DDRGK1 in HCC cells increased ubiquitin immunostaining in immunoprecipitates of endogenous emerin. Furthermore, the authors showed that low emerin expression was associated with poor prognosis in clinical HCC samples.

Emerin is known to restrict the accumulation of β-catenin into the nucleus [14]. In agreement with this, Xu et al. [12] showed that reduction of emerin protein level in UFMylation-deficient HCC cells led to increased nuclear β-catenin. Mechanistically, reduced UFMylation destabilized emerin, which was shown to impair β-catenin binding to the nuclear-export receptor chromosome region maintenance 1 (CRM1), leading to nuclear retention and activation of β-catenin. Nuclear β-catenin subsequently induced a pattern consistent with hybrid EMT, associated with enhanced cellular plasticity, invasion, proliferation, and metastatic capacity. Restoration of emerin protein levels by overexpression in the UFMylation-deficient HCC cells reversed the pro-metastatic effects of UFMylation loss.

Consistent with these findings, Wu et al. [15] independently demonstrated that emerin knockdown induced EMT and enhanced the migration and invasion of HCC cells. They also showed that emerin silencing increased

the cytoplasmic localization of cyclin-dependent kinase inhibitor 1A (CDKN1A, also called p21) protein, and that CDKN1A/p21-knockdown partially prevented EMT and the migratory and invasive phenotype.

Importantly, Xu et al. [12] showed that the effects of UFMylation loss on the pattern consistent with hybrid EMT depended on emerin. Gene Set Enrichment Analysis of The Cancer Genome Atlas HCC dataset stratified by emerin expression level revealed EMT as a hallmark. Transcriptomic analysis of HCC cells with knockdown of UFL1 or emerin, or UFL1 knockdown combined with emerin overexpression, showed that markers of hybrid EMT were elevated in cells deficient in UFL1 or emerin, whereas overexpression of emerin reversed the effect in UFL1-deficient cells. Immunoblotting confirmed that the protein levels of E-cadherin and vimentin were regulated in an emerin-dependent manner. *In vitro* assays with HCC cell lines showed that emerin knockdown and UFMylation loss had similar effects in promoting cell migration, invasion, and proliferation, while emerin re-expression reversed these effects. Likewise, in mice injected with emerin-deficient or control HCC cells, the former produced more circulating tumor cells and liver metastases. These findings suggest that UFMylation loss promotes HCC progression through an emerin-dependent mechanism.

Xu et al. [12] further showed that, as a result of reduced emerin protein levels, elevated nuclear β-catenin also activated the transcription of poliovirus receptor (PVR, also called CD155). The upregulated PVR/CD155 expression in UFMylation-deficient or emerin-depleted HCC cells evaded killing by natural-killer (NK) cells. Importantly, the depleted HCC cells avoided NK-cell cytotoxicity despite increased binding between the two cell types. PVR/CD155 is an important immunoregulatory molecule that is frequently upregulated in cancer cells and can contribute to immune evasion by engaging inhibitory receptors such as T-cell immunoreceptor with immunoglobulin and immunoreceptor Tyrosine-based inhibitory motif domain (TIGIT) on NK cells and T cells [16,17]. Thus, increased PVR/CD155 expression may provide tumor cells a mechanism to attenuate antitumor immune responses, even when immune cells are able to recognize and establish physical contacts with the tumor cells. Xu et al. [12] demonstrated that emerin suppressed PVR/CD155 transcription by promoting the nuclear export of β-catenin, thereby limiting the binding of TEA domain transcription factor 4 (TEAD4) to the promoter of the PVR/CD155 gene. Together, these findings suggest that the loss of UFMylation promotes immune evasion in HCC by impairing NK-cell cytotoxicity through the emerin–β-catenin–TEAD4–PVR/CD155 pathway. In agreement with these findings, in mice injected with HCC cells into the tail vein, depletion of NK cells promoted metastasis by control cells but had no effect on metastasis by UFL1- or emerin-deficient cells.

Xu et al. [12] also studied whether the effects of UFMylation loss could be prevented by cancer immunotherapy. The programmed cell death protein 1 (PD-1) pathway (PD-1/PD-L1) inhibits the activation of CD8-positive T-cells and thus allows tumor cells to evade immune surveillance [18]. Previous work had shown that UFMylation destabilized PD-L1 [7]. Given the increase in PVR/CD155 expression in UFMylation-deficient HCC cells, Xu et al. [12] investigated whether a combination of anti-PD-1 and anti-TIGIT treatment could reduce the metastatic properties of UFMylation-deficient HCC cells. Injection of HCC cells into mouse tail veins showed that the combination immunotherapy effectively decreased metastases. Similarly, when HCC cells were injected into the liver, anti-PD-1 reduced tumor growth, and in combination with anti-TIGIT further improved the reduction. Thus, the findings suggest that the pro-cancer effects of UFMylation loss could be counteracted by targeting PD-1 and PVR/CD155-TIGIT pathways by the combination immunotherapy.

Some limitations of the study by Xu et al. [12] should be considered. First, conclusive proof is still lacking to whether the interaction between emerin and the UFMylation machinery is direct, and whether emerin is a direct target of UFMylation. Komatsu et al. [4] state in their recent review that "stringent criteria are required to define authentic UFM1 substrates". The substrates should be detectable in UFM1 immunoblots, either after immunoprecipitation of endogenous candidate substrate under denaturing conditions, or in immunoblots of cell lysates from cells grown under UFMylation-promoting conditions (e.g., knockdown of deUFMylating enzymes) [4]. Definitive validation would additionally require evidence demonstrating dependence on the UFM1 conjugation machinery, identification of the modified lysine residue(s) in emerin, and, ideally, reconstitution assays using purified proteins. Xu et al. [12] used immunoprecipitation of both overexpressed and endogenous proteins to demonstrate the interaction of UFMylation machinery with emerin, and tumor-cell lysate rather than purified recombinant proteins to study the interaction of GST-emerin with the UFMylation machinery. These approaches do not demonstrate direct interaction between emerin and the UFMylation machinery. Therefore, additional evidence showing emerin as a direct target of UFMylation is required.

The second limitation concerns the mechanism of emerin destabilization. Xu et al. [12] showed that proteasome inhibition but not lysosomal inhibition prevented emerin downregulation in UFMylation-deficient cells. They further demonstrated that loss of UFMylation promoted ubiquitin staining in emerin immunoprecipitates, but it is unclear whether the ubiquitin was attached to emerin or other proteins that co-precipitated with emerin. Showing an increase in direct emerin ubiquitination would help to distinguish whether emerin loss is due to ubiquitin-proteasome-mediated

degradation or alternative indirect mechanisms. The findings of Xu et al. [12] supporting proteasome-mediated degradation of emerin are in line with the study by Buchwalter et al. [19] showing that emerin is primarily degraded by the proteasomal pathway. However, Buchwalter et al. [19] also described lysosomal accumulation of emerin under acute endoplasmic-reticulum stress. Given that depletion of UFMylation triggers acute endoplasmic-reticulum stress [20], the absence of lysosomal involvement in emerin clearance in Xu et al. [12] is partially inconsistent with Buchwalter et al. [19] and requires further investigation. However, we cannot exclude the possibility that differences in cellular context, stress responses, and experimental conditions contribute to this discrepancy.

Third, the part of the metastasis models used in Xu et al. [12] have limitations. Tail-vein and splenic injection models mainly assess cancer-cell survival, seeding, and colonization rather than the complete spontaneous metastatic process including local invasion, intravasation, circulation, and spontaneous distant metastasis. The orthotopic liver implantation model, which was also used by Xu et al. [12], provides a more physiologically relevant approach. Fourth, as also noted by Xu et al. [12], the clinical cohorts analyzed were relatively small, comprising only 100 HCC patients, and therefore provide only preliminary evidence of clinical correlations.

Liver cancer is a major global health concern and HCC is the most common type of primary liver cancer. The annual number of new cases is predicted to surpass 1.4 million by 2040 [21]. The five-year survival rate is less than 20% for advanced cases due to high rates of tumor recurrence and metastasis. Thus, new treatment options are needed, and increased understanding of the molecular pathogenesis may reveal new drug-target molecules. The study by Xu et al. [12] provides evidence in support of the crucial roles of UFMylation, emerin and β-catenin in HCC. Figure 1 summarizes the main findings of the article. However, the main findings in Xu et al. [12] are preclinical, made using cell cultures and mouse models. Global activation of UFMylation in patients may have toxic and context-dependent effects. Nevertheless, evaluation of UFMylation status could be utilized as a potential prognostic biomarker, guiding patient selection for targeted therapies such as combined immunotherapy with anti-PD-1 and anti-TIGIT. Further, targeting of β-catenin or PVR/CD155 should also be investigated as possible treatments for HCC. The study provides a rationale for further investigating the roles of UFMylation, emerin, β-catenin, and PVR/CD155 in cancer.

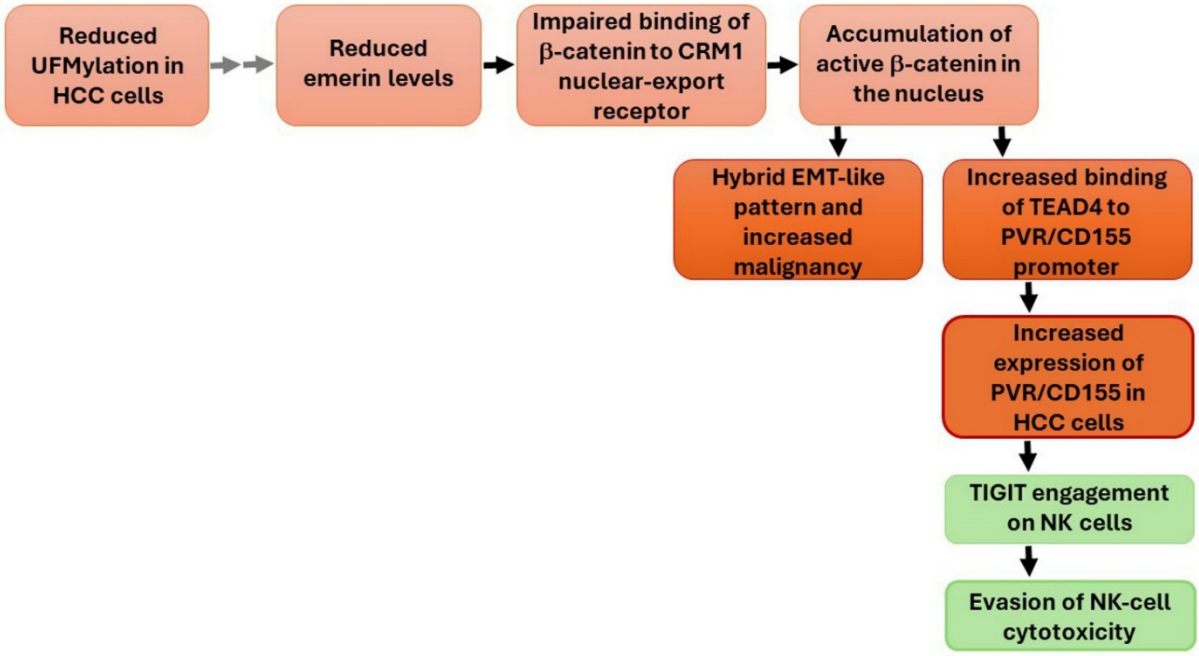

Figure 1. Schematic of the main findings in Xu et al. [12].

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

Keenious and Microsoft Copilot were used for searching relevant literature.

Acronyms

CDKN1A	cyclin-dependent kinase inhibitor 1A, also called p21
CDK5RAP3	CDK5 regulatory subunit-associated protein 3
CRM1	chromosome region maintenance 1
DDRGK1	DDRGK domain-containing protein 1, also called UFBP1
DUFM	deUFMylating enzyme
EMT	epithelial-mesenchymal transition
GST	glutathione S-transferase
HCC	hepatocellular carcinoma
mTOR	mechanistic target of rapamycin
NK	natural killer
PD-1	programmed cell death protein 1
PD-L1	Programmed death ligand 1
TEAD4	TEA domain transcription factor 4
TIGIT	T-cell immunoreceptor with immunoglobulin and immunoreceptor Tyrosine-based inhibitory motif domain
UBA5	ubiquitin-like modifier-activating enzyme 5
UFBP1	UFM1-binding and PCI domain-containing protein 1, also called DDRGK1
UFC1	ubiquitin-fold modifier-conjugating enzyme 1
UFL1	UFM1-specific ligase
UFM1	ubiquitin-fold modified 1
UFSP1	Ufm1-specific protease 1
UFSP2	Ufm1-specific protease 2
PVR	poliovirus receptor, also called CD155

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