Editorial

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Journal of In Silico & In Vitro Pharmacology
ISSN 2469-6692

2021
Vol.7 No.3:1

In Carcinogenesis, Phosphorylation Regulates Cullin-Based Ubiquitination

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Received: May 01, 2021; Accepted: May 14, 2021; Published: May 21, 2021

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Citation: Williams C (2021) In Carcinogenesis, Phosphorylation Regulates Cullin-Based Ubiquitination. In Silico & In Vitro Pharmacology. Vol.7 No.3:1

Editorial Note

Numerous cellular activities are influenced by phosphorylation-dependent ubiquitination and proteasome degradation, which can contribute to the emergence of various illnesses, most notably cancer. To provide new approaches and tactics for tumour therapy, this study explains the processes and biological activities of crosstalk between phosphorylation and ubiquitination, as well as its impact on carcinogenesis.

Cullin-RING Ligases (CRLs) are important members of the E3 ubiquitin ligase family in the ubiquitin-proteasome system, transferring ubiquitin to substrates and controlling the ubiquitination and destruction of over 20% of proteins in human cells. Cullin 3-RING Ligases (CRL3s) lack substrate receptor proteins, thus adaptor proteins engage directly with substrates and facilitate ubiquitination. After being changed by diverse posttranslational modifications such as phosphorylation, methylation, and acetylation, degrons found in substrate proteins facilitate or hinder CRL recognition. Phosphorylation and ubiquitination have a lot of crosstalk, which has a big impact on how receptors and substrates interact.

Many signalling pathways, including cyclin-dependent kinase tyrosine kinase, cadherin-catenin complex and MAP kinase, have been shown to have a role in the phosphorylation-DE phosphorylation cascade in the onset and progression of many malignancies. Furthermore, phosphorylation of receptors or adaptors influences recognition and interaction, implying that phosphorylation has a significant impact on the ubiquitin-proteasome system. The diversity of substrates and their specific functions in organisms determine how crosstalk can influence and regulate different cellular biological functions, such as genomic stability, cell cycle, transcription factor activity, and oxidative stresses, according to Regulation of the crosstalk between phosphorylation and ubiquitination in biological processes. The interplay of phosphorylation and ubiquitination has been shown to control cyclin F and denticleless E3 ubiquitin protein ligase homolog Cell Division Cycle protiencdt2 , both of which are CRL substrate receptors and critical for the cell cycle. The protein level of cyclin D1 is regulated by CDK4-induced phosphorylation dependent ubiquitination and its E3 ligase F-Box protein (FBXO31) works as a regulator of the G1/S transition. When Cyclin Dependent Kinase 2 (CDK2) phosphorylates the de-ubiquitinating enzyme Ubiquitin Specific Peptidase 37 (USP37) at Ser858, it can bind to SCF-TrCP for ubiquitination and destruction in G2. While USP37 S858A-expressing cells lose the production of mitotic markers, the instability of USP37 in G2 is required for mitotic entrance.

Some CRL substrates, as well as their adaptors or receptors, act as tumour suppressors or oncoproteins. Oncogenes, for example, encode the CRL3 substrates ETS transcription factor ERG (ERG) and SRC-3, which are overexpressed in prostate and breast cancers, respectively. VACM-1, a CRL5 receptor, has been identified as a potential tumour suppressor due to its ability to decrease cell proliferation. Furthermore, through regulating the cell cycle, the CRL1 receptor F-Box and WD repeat domain containing 7 (FBW7) can inhibit carcinogenesis. The interplay between phosphorylation and ubiquitination regulates the stability of critical proteins implicated in carcinogenesis, and hence plays a key role in tumour regulation.

Phosphorylation increases the interaction between oncoproteins and CRLs in some situations, slowing cancer growth. Through crosstalk, it is possible to efficiently limit tumour growth by inducing the breakdown of proteins overexpressed in tumours, such as ERG, SRC-3, and HIF2. Other proteins with important pathological functions in tumorigenesis, such as X-box Binding Protein 1 (XBP1) and Checkpoint Kinase 1 (CHK1), can be phosphorylated and then induced to ubiquitin-proteasome degradation, blocking their functions of activating oncogenic pathways or regulating DNA damage repair. As a result, cancer treatment may involve modulating the phosphorylation

modification of these substrates, such as activating the associated kinases.

Different protein translational modifications can interact with one another in a variety of ways. Phosphorylation, acetylation, and methylation are the major regulators of ubiquitination, which is carried out by E3 ligases that are mostly members of the CRLs family. Many biological processes have interaction between phosphorylation and ubiquitylation, which affects physiology and disease by altering the amounts of targeted proteins.