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Review Article

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Ubiquitin - Dysfunction of cell signaling and its modification in cancer (ERK/MAPK pathway).

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Abstract

The 76 amino acid regulatory protein ubiquitin may be covalently joined to target proteins through a sequence of enzymatic activities involving the enzymes ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating (E3). Ubiquitin is a highly conserved regulatory protein. Ubiquitination is one of the main types of PTM (post-translational modification) of proteins. Ubiquitination is the term used to describe the covalent modification of a substrate protein with ubiquitin, an amino acid residue protein. If ubiquitination is not operating correctly, cells might have undesirable consequences. For instance, this might result in the inactivation of signaling pathways, the accumulation of misfolded proteins, or the improper transport of proteins away from their appropriate cavities, all of which can severely impair cell function. Like kinase, dysregulation of ubiquitin-dependent signaling plays a role in a variety of illnesses, including cancer, neurological problems, and immunological problems. Excessive activation of the ERK (Extra Cellular Signal-regulated Kinase), which is necessary for growth, considerably aids in the spread of cancer. The primary signaling pathways known as the MAPK (Mitogen Activated Protein Kinase) cascades are responsible for a broad variety of cellular functions, including proliferation and differentiation. The alteration of the system to prevent the growth of human tumors is highlighted in this article's overview of the cancer signaling pathway (EPK/MAPK).

Keywords: Ubiquitin, Ubiquitin-cancer, Etiology of cancer, ERK, MAPK Pathway, Modification.

Introduction

Metabolic reprogramming, which promotes the growth of cancer cells by changing energy metabolism, upping the creation of macromolecules, and preserving redox homeostasis, is a trait of cancer. Metabolic reprogramming is a particularly complicated process since the regulation of cancer metabolism includes various signaling pathways, transcription

factors, and metabolic enzymes. One of the most important post-translational modifications, ubiquitination, is an enzymatic process that takes place in many steps and is involved in several cellular biological processes**.** The dysregulation of ubiquitination and deubiquitination is linked to several illnesses, including cancer [1]. a disorder where uncontrollably multiplying aberrant cells harm bodily tissue. the investigation of causes or origins. Proto-oncogenes, which are latent cancer-causing genes, are thought to be present in all living things. It has been demonstrated that a variety of physical, chemical, or biological elements may change and activate these proto-oncogenes, converting them into active, cancer-causing oncogenes. Genetic factors may potentially affect the development of cancer. When to divide and die, a person's cells are given instructions by their genetic code. Genes have an impact on how proteins are made by cells, and proteins contain most of the instructions for cellular growth and division. [2]. Cancer spreads by encouraging cell proliferation rather than by bringing about mutations. As a result, the enhanced cell division they cause is what propels the early-stage expansion of a proliferative cell population. Through the activation of PROTEIN KINASE C, PHORBOL ESTER promotes cell division [3]. Proteasome and nondegradative signaling are only two of the numerous locations where ubiquitin is transported with the help of ubiquitin ligases. Unbalanced ubiquitin ligases are the cause of the initiation and spread of cancer. The etiology of human malignancies and variations in the activity of different E3 ligases are significantly correlated. Tumor suppressors may degrade rapidly because of the E3 ligases mutation, or, once more, oncogenic proteins may not be ubiquitinated. Gideon Goldstein first discovered the term "UBIQUITIN" in 1975. A post-translational change known as ubiquitination (or) ubiquitylation entails the conjugation of the 76 amino acid ubiquitin to the lysine residue and other proteins [1].76 amino acids make up the highly potent regulatory protein ubiquitin, which may covalently mark target proteins through a flurry of enzymatic reactions [2].

Numerous proteins' functions are synchronized by mono- or polyubiquitination in a variety of physiological and pathological conditions. A family of DEUBIQUITINATING ENZYMES causes the removal of ubiquitin from the substrate. Deubiquitinates, which is essential for almost all cellular signaling processes, including the cell cycle, death, and gene transcription, may also revoke the activity of ubiquitin ligase by releasing ubiquitin from substrate proteins [3]. In several physiological and pathological circumstances, mono- or polyubiquitination synchronizes the actions of many proteins. The removal of ubiquitin from the substrate is brought on by a class of DEUBIQUITINATING ENZYMES. By liberating ubiquitin from substrate proteins, deubiquitinate, which is necessary for nearly all cellular signaling events, such as the cell cycle, death, and gene transcription, may also inhibit the function of ubiquitin ligase [4].

The stability and localization of substrate proteins, such as nonhistone proteins, are controlled by ubiquitination, a significant post-translational modification. Numerous biological functions, including DNA repair, transcription, signal transduction, and apoptosis, depend on the ubiquitin-proteasome system (UPS) on nonhistone proteins. The discovery of this mechanism may offer novel therapeutic targets for cancer treatment. Its dysregulation causes a variety of illnesses, including cancer. The regulatory functions of important UPS members on significant nonhistone substrates in cancer-related processes, such as cell cycle, cell proliferation, apoptosis, DNA damage repair, inflammation, and T cell dysfunction in cancer, are summarized in this study. Ubiquitin post-translational modification is crucial for controlling protein turnover and breakdown. A tiny 76 amino acid protein called ubiquitin can form mono- or polyubiquitinated forms when it is covalently joined to target proteins. E1-activating enzymes, E2-conjugating enzymes, and E3 ubiquitin ligases are just a few of the enzymes that play a role in this process. Different functional effects of polyubiquitin with various

chain topologies are linked to certain lysine residues on substrates [5]. In most cases, polyubiquitin chains connected at the K48 or K11 sites resulted in 26S proteasome-mediated proteolysis, which is crucial for preserving protein homeostasis and controlling cell cycle and death. Contrarily, Mono ubiquitination and chains with the K63 site, which reflect non-proteolytic ubiquitination, are involved in a variety of physiological functions, including signal transduction, autophagy, and DNA damage repair [6]. They are directed to the proteasome for degradation after being covalently modified by ubiquitin, as is the case with most substrates. Deubiquitinating enzymes (DUBs), which remove ubiquitin from substrate proteins and contribute to the regulation of different biological processes, can also reverse the action of ubiquitin ligases [7]. The prevalence of ubiquitination is second only to that of phosphorylation [8]. According to several studies, histone ubiquitination controls DNA-dependent activities including gene transcription and DNA damage repair [9], and abnormal histone ubiquitination is common in malignancies. Numerous cellular processes, including DNA repair, transcription, signal transduction, autophagy, apoptosis, and others, are known to be significantly influenced by the ubiquitylation of nonhistone proteins [10]. General transcription factors, transcriptional activators or repressors, nonhistone chromatin-associated proteins, and nuclear receptor coactivators are nonhistone protein substrates for ubiquitination. Numerous malignant malignancies are strongly correlated with dysregulation of nonhistone lysine ubiquitination. Numerous drugs have been found that specifically target the E1 enzyme, which oversees activating ubiquitin molecules in the UPS. The ubiquitin-activating enzyme and NEDD8-activating enzyme, respectively, are inhibited by adenosine sulfamate analogues, such as MLN7243 [11] and MLN4924. After the E2 enzyme attaches to E1, the E1 enzyme transfers active ubiquitin to a cysteine in the E2 enzyme. As a result, ubiquitin is conjugated to substrates by the action of E2 enzymes. The transfer of ubiquitin from E2 to the lysine of the target protein is catalyzed by E3 ligase, which also recognizes substrate proteins. As a result of E3 ligase's great substrate specificity, targeting it has the potential to be an effective tumor therapy method.

The Ubiquitination and Deubiquitination Process:

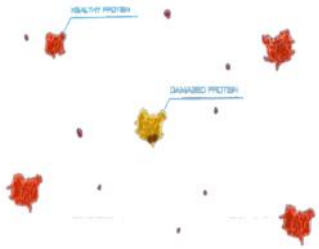
There are three phases in the ubiquitylation process. A thioester bond is first created when an ATP-dependent connection between the -carboxyl group of the C-terminal glycine residue of ubiquitin and a cysteine residue on E1 occurs. The combination of E1 and ubiquitin is then transported to the catalytic cysteine of E2 through a trans (Thio)esterification process when E2 binds to the activated ubiquitin. The substrate is then recognized by E3, who then catalyses the linking of ubiquitin to a particular lysine residue on the substrate. DUBs, which mediate ubiquitin removal and processing, can reverse the action of E3 ligases. The cell cycle, DNA repair, death, inflammation, and signaling pathways are just a few of the basic activities that DUBs control.

Protein Degradation Process:

Ubiquitin protein

***Ubiquitin-activating enzyme(E1) *Ubiquitin-conjugating enzyme(E2) *Ubiquitin- ligase enzyme(E3).**

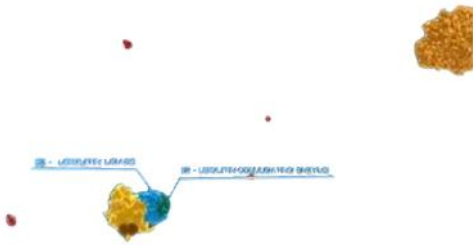
A mono- or polyubiquitinated protein is created when ubiquitin is activated with E1 in an ATP-dependent way, transported to E2, and then transferred to the substrate by E3 ligase recognition. Degradation mediated by the 26S proteasome is caused by K48 or K11 polyubiquitin chains. Nonproteolytic ubiquitination signals, such as Mono ubiquitination or K63 polyubiquitin chains, are involved in several biological processes. Substrate protein ubiquitin's are altered or removed by DUBs. A technique for treating cancer that shows promise is the targeting of E1s, E2s, E3s, proteasome, and DUBs. The Functions of E3 Ligases and DUBs in Cancer Development Regulation: Cell cycle arrest, cell proliferation, and apoptosis are just a few of the critical cellular activities that the UPS controls. As a result, dysregulation of its important constituents and the network that controls them is frequently linked to human disorders, including cancer. E3 ligases and DUBs are implicated in the development of cancer through a variety of biological processes, including the cell cycle, cell proliferation, apoptosis, DNA damage repair, inflammation, and T cell malfunction in cancer, according to an increasing number of studies. Biological processes are governed by a protein modification known as ubiquitin (UB). The E1 enzyme starts UB's transfer through the E1-E2-E3 cascade onto the target protein by activating the C-terminal carboxylate.



Healthy Protein **Damage Protein**

•E2 & E3 Enzyme bind with damage protein

E3-Ubiquitin Ligase **E2-Ubiquitin- conjugating enzyme**



Ubiquitin attaches to the E1 Activating Enzyme; then, the two molecules separate. E1-activating enzymes bind to damaged protein through E2, E3, and other enzymes. The protein is activated by enzymes. The proteasome then accepts the protein.

DUBs and ubiquitin ligases work together to control cell cycle progression. Cell division cycle 20 (cdc20) and CDC20-like protein 1 (CDH1) are attracted by the E3 ligase APC/C (anaphase-promoting complex, commonly known as the cyclostome). APC/C-CDH1 facilitates mitotic exit and early G1 entrance, whereas APC/C-CDC20 promotes the cell cycle transition from metaphase to anaphase. A subset of cyclins and CDK inhibitors are used by E3 ligases SCF (S-phase kinase-associated protein 1-cullin 1-F-box protein) complexes to control the transition from G1 to the start of mitosis. Well-researched F-box proteins include FBXW7, SKP2, and -TrCPs. Some G1/S kinases are downregulated by E3 Parkin. Several DUBs are essential for the advancement of the cell cycle in malignancies. The grey boxes display a few examples of E3 and DUB substrates. Tumor promoters include E3 and DUBs, whereas tumor suppressors include those in blue. Numerous oncogenes can promote the growth of cancer cells, and UPS controls the transcription of these oncogenes by modifying general transcription factors, transcriptional activators, and transcriptional coactivators by proteolytic and nonproteolytic ubiquitination [12]. The overexpression of c-Myc, which is connected to cell development, proliferation, apoptosis, and metabolic pathways, is frequently observed in various malignancies. Poor cancer outcomes are also linked to its buildup [13].Myc levels are managed by UPS through targeted degradation. [14] In order to demonstrate how ubiquitination controls the transcription of oncogenes in cancer, we will use the oncogene c-Myc as an example. The deubiquitinating enzymes can stop c-Myc from degrading, keep it stable, and ultimately speed up the development of cancer. The first DUB to be proven to control c-Myc stability was USP28. It interacts with FBW7alpha to bind to Myc and stabilize Myc in the nucleus. It is significantly expressed in colon and breast carcinomas [15]. Through deubiquitination, USP22 improved c-Myc stability in breast cancer cells [16]. We previously discovered that USP37, which directly deubiquitinated and stabilized c-Myc independent of Fbw7, was markedly increased in human lung cancer tissues [17]. In a subset of human breast and lung malignancies, USP36, a highly expressed USP, may interact with the nucleolar Fbw7 to preserve c-Myc stability in the nucleolus [18]. Human U three protein 14a (hUTP14a), a new E3 ligase, has recently been found to be increased in human colorectal cancer tissues. By stabilizing c-Myc through the formation of a complex with USP36/Fbw7 in the nucleolus, hUTP14a aids in the development of cancer [19].

E3 Ligases and DUBs Regulate Apoptosis: Apoptosis is regulated by E3 ligases and DUBs, which may block cancer and abnormal cell cycle progression. The cells might not properly initiate apoptosis if apoptotic pathways are suppressed, which might result in cancer. Most malignancies commonly include mutations in the tumor suppressor protein p53, which is essential for apoptosis, genomic instability, and mutation.

It has been discovered that ubiquitination is essential for controlling p53 activity and localization as well as its destruction. For instance, it has been discovered that MDM2 (murine double minute 2) adversely regulates p53 through a variety of methods. It can directly engage and destroy p53 by ubiquitination. Additionally, it may link p53 and pRb to create a trimeric Rb-Mdm2-p53 complex for controlling p53-induced apoptosis [20]. Additionally, Mdm2 and MdmX (Mdm4) can heterodimerize and take part in the ubiquitin-mediated degradation of p53 [21]. Additionally, Mdm2 is elevated in several malignancies, including breast cancer, cutaneous melanoma, and colorectal cancer. Therefore, blocking the link between p53 and MDM2 makes it easier for cancer cells to undergo apoptosis or cell-cycle arrest caused by p53. In vitro and in vivo, hUTP14a can bind to the tumor suppressor pRb and encourage polyubiquitination and pRb's destruction [22]. As a result, hUTP14a may have the potential to be a target for cancer treatment. Genomic instability is frequently caused by errors in DNA replication and repair, which are regulated by E3 ligases and DUBs [23]. To preserve genomic integrity and avoid cancer, DNA damage repair is essential. Numerous E3s, such as MDM2 and BRCA1, are involved in controlling the DNA damage response and cell cycle checkpoints that contribute to the development of cancer. In short, DNA double-strand breaks (DSBs) cause the activation of DNA damage sensors, which in turn causes MDM2 to be inactivated, p53 to remain stable, CDK phosphatase to be promoted for degradation by SCF--TrCP, and CDK activity to decrease. In the interim, ubiquitination-controlled recruitment of DNA repair machinery to DNA damage sites. APC/C-CDH1 and Kelch-like ECH-associated protein 1 (KEAP1)-mediated ubiquitylation is necessary for the suppression of homologous recombination (HR) during the G1 phase. USP11 is also involved in the control of DNA double-strand break repair, which is frequently turned on in cancer cells and leads to resistance to PARP inhibitors [24]. BRCA2 is deubiquitinated and stabilized by USP21, which also increases the effectiveness of homologous recombination and tumor cell proliferation [25]. RAP80 is deubiquitinated by USP13, which also encourages the DNA damage response.

DUBs and E3 Ligases Control Inflammation:

Inflammation caused by cancer is crucial to the growth and development of tumors. Inflammation, immunology, cell proliferation, and death are just a few of the biological processes that are regulated by the transcription factor NF-B. The development of tumors has been linked to abnormal NF-B activation. Through both proteasome-dependent and independent processes, ubiquitination controls NF-B pathways. The role of DUBs and ubiquitin ligases in controlling NF-kB activation. TRAF6 worked with the E2 enzyme Ubc13-Uev1A to synthesize K63 polyubiquitin chains and add them to the TAB2 subunit of the TGF-activated kinase 1 (TAK1) kinase complex, which causes TAK1 to be activated. IL-1 activates the ubiquitin E3 ligase TRAF6. IK is then phosphorylated by TAK1. After being phosphorylated, IB is then ubiquitinated and broken down by the 26S proteasome, allowing NF-B to go to the nucleus and activating the NF-B pathway. Deubiquitinates like A20 and CYLD prevent the NF-B pathway from being activated. Deubiquitinating enzymes might operate as IK negative regulators to strictly regulate NF-B activation.

DUBs and E3 Ligases Control T Cell Dysfunction in Cancer:

For the start and control of the immune response in cancer immunotherapy, T cell activation is essential. To be completely active, it needs at least two signals. One happens after the T cell receptor (TCR) and major histocompatibility complex (MHC) are activated. Another is produced when the co-stimulator CD28 interacts with the antigen-presenting cells' (APCs') CD80 and CD86. However, intertumoral T cells are ineffective because of the many inhibitory signals that were present in the tumor microenvironment. Some inhibitory receptors, such as PD-1, inhibitory cells, such as Treg cells, suppressive soluble mediators, such as TGF, transcriptional factors, such as T-bet, etc. are the key

characteristics of T cell dysfunction [26]. With a variety of methods, UPS has been revealed to play a crucial regulatory role in sustaining T cell dysfunction. The dynamic regulation of ubiquitination and deubiquitination is essential for the control of the TGF signaling pathway. Many E3s and DUBs take a role in activating the TGF pathway. USP4 interacts with TGF-RI directly at the receptor level to keep the receptor stable [27]. DUBs that are connected to the scaffold protein SMAD7, such USP11 and USP15, stabilize the receptor complex [28]. E3 ligases Arkadia, AIP4/Itch, and RNF12-mediated ubiquitination may cause the degradation of SMAD7 [29]. By stopping the ubiquitination of R-SMAD, OTUB1 promotes the development of the R-SMAD/SMAD4 complex and preserves the stability of SMAD2/3 [30]. It also prevents the ubiquitination of SMAD2 and USP9X. SnoN, a transcriptional repressor, is susceptible to ubiquitination in the nucleus through the actions of E3's Arkadia, SMURF2, and CDH1-APC [31]. R-SMADs can be monoubiquitinated to inhibit the R-SMAD/SMAD4 complex from binding to DNA, but USP15 can undo this alteration and encourage TGF-dependent transcription [32]. The transcription factor of the T-box family T-bet controls the development of Th1 cells and stimulates IFN- production. It has recently been demonstrated that it is expressed in Treg and takes part in important immunosuppressive activities. T-bet has been hypothesized to be necessary in T cell dysfunction. UPS could control TCR activation. For instance, through proteolysis-dependent pathways, the E3 ligases Cbl, Itch, and Grail destroy the TCR complex and prevent T cell activation [33]. In contrast, it has been discovered that USP12 stabilizes the TCR complex and supports TCR signaling in primary mouse T cells by deubiquitylating the TCR adaptor proteins LAT and Trat1 [34]. In addition to being hyperproliferative in USP9X-deficient T cells, Naik et al. discovered that USP9X controlled TCR signaling and tolerance induction [35].

Proteasome Activity:

The proteasome has been effectively employed as a target for cancer therapy among all the UPS components. The destruction or processing of intracellular proteins is carried out by the proteasome, a large multiprotein complex that contains multicatalytic proteases (such as chymotrypsin and caspase-like enzymes). As a result, it controls the concentrations of several critical mediators for cell-cycle progression and death in both healthy and cancerous cells, including cyclins, caspases, BCL2 and nuclear factor b [36]. The first proteasome inhibitor authorized for the treatment of recurrent, refractory multiple melanoma (MM) was bortezomib in 2003 [37].

The RAF-MEK-ERK Mitogen activated protein kinase cascade is the centre of the cancer treatment:

The important signaling system known as mitogen-activated protein kinase (MAPK) controls cell proliferation, differentiation, death, and stress responses. The mitogen-activated protein kinases (MAPKs), which transmit extracellular signals to intracellular responses, control a variety of cellular programmers. More than a dozen MAPK enzymes coordinately control cell division, motility, proliferation, and survival in mammals [38]. Three major kinases that activate and phosphorylate downstream protein kinases are part of the MAPK pathway. These include MAPK, MAPK Kinase, and MAPK. The major signaling cascade in the group of all MAPK signal transduction pathways are RAS, RAF, MAPK, ERK [39]. All the above-mentioned pathways play a crucial role in the development of cancer. The MAPK cascade are the central signaling elements that synchronize basic processes like cell proliferation, differentiation and stress responses. ERK cascades are highly controlled cascades that are mainly responsible for cell proliferation and differentiation. As a result of importance of the ERK cascade the disorganization is harmful to cell and eventually to the body of upstream proteins and kinase in the ERK pathway induces

various diseases including cancer, and neurological disorders [40]. The MAPK'S Signaling pathways general structure tangles a small G-Protein (RAS)and three protein kinases (ERK, RAF, MEK). An enzyme that transfers phosphate from donary molecule to an acceptor is known as kinase. The pathway begins by binding of ligand to a transmembrane protein, a receptor tyrosine kinase. The protein kinase plays a major role in cell proliferation in this MAPK pathway. The RTK will start the typical MAPK signaling cascade, comprising of the subsequent phosphorylation of the RAS Proteins, MEK Protein, ERK Protein. These proteins will transfer into the cell nucleus, where the transcription factors are controlled by protein. These factors synchronize the transcription of genes involved in cellular processes like proliferation & differentiation. The crosstalk in the middle of the RAF-MEK-ERK axis and other signaling pathways increase the proliferative potential of MAPK pathway in human tumors. All cancers have altered RAS genes because of abnormal RAF-MEK-ERK Signaling pathway activation. Through the activation of maturation and the ubiquitination of proteins, which is necessary for cell cycle activity, normal/ERK function also suppresses tumors. Cell proliferation is suppressed by terminal cell cycle arrest during ageing [41].

•RAF (MAPKKK)

MEK (MAPKK) KINASES

ERK (MAPK)

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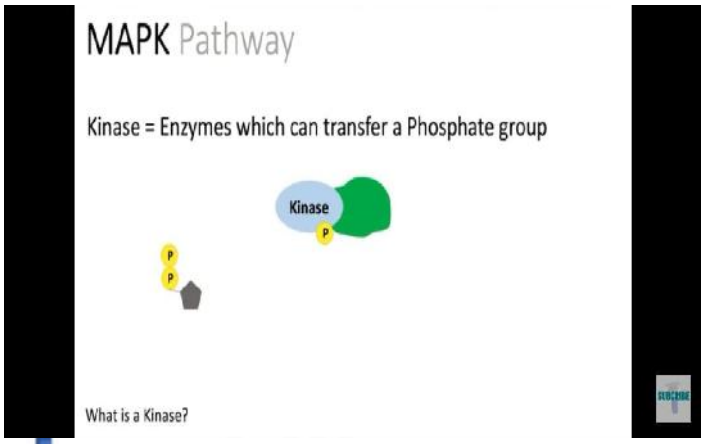
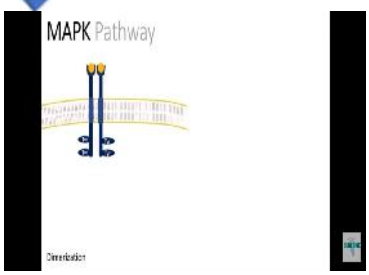
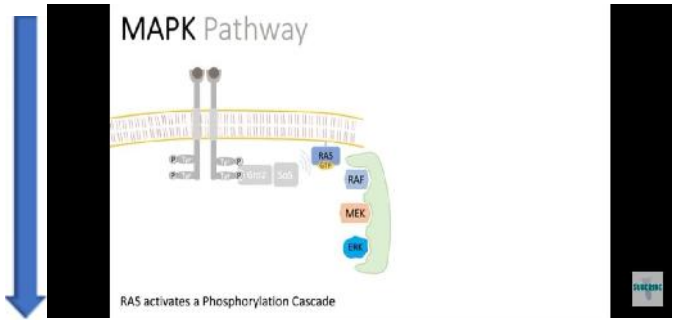




DIMERIZATION.

•After dimerization, activation of RAS.

•RAS activates a phosphorylation cascade.



•ERK enters the nucleus. ERK activates transcription factors.

•Transcription – cell proliferation& cell survival:

•The ERK/MAPK Signaling pathway is not only associated with regulating cellular biological functions like cell proliferation, cell differentiation and in tumor formation. The extracellular signal-regulated kinases (ERK)are divided into ERK1, ERK2.The ERK1&ERK2 are growingly conserved ubiquitous serine-threonine kinases that balance cellular signaling under both normal and pathological state. ERK interpretation is critical for development and their hyperactivation plays a major role in tumor development and progression. The RAS-ERK pathways dysfunction is the development of human malignancies.

Treatment or modification:

E1, E2, E3, E4, deubiquitinates (DUBs), and the proteasome are the enzymes that control ubiquitin metabolism. The system is favorable for the development of new cancer medication targets and therapeutics. **Bortezomib**, a proteasome inhibitor, is the only medication licensed by the **FDA** for the treatment of cancer that targets the ubiquitin/proteasome system. The synthesis of bortezomib began in 1995. Under the brand name VELCADE, bortezomib was the first anticancer proteasome inhibitor to receive FDA approval. A dipeptide boronic acid derivative and proteasome inhibitor called bortezomib is used to treat mantle cell lymphoma and multiple myeloma. The 26S proteasome is a protein complex that breaks down ubiquitinated proteins in the ubiquitin-proteasome pathway; reversible inhibition of the 26S proteasome is assumed to be the primary mode of action of bortezomib, causing cell cycle arrest and apoptosis in cancer cells.

Bortezomib inhibits tumor survival pathways and stops tumor development, tumor dissemination, and angiogenesis through a variety of mechanisms. The 26S proteasome is inhibited by the drug bortezomib's reversible binding to its chymotrypsin-like component, stopping the degradation of numerous pro-apoptotic proteins [42]. There are several chances to cure cancer and neurological disorders via the ubiquitin-proteasome system. Vemurafenib, an oral medication, inhibits the most prevalent BRAF mutation [43]. BRAF is a part of the MAPK Signaling pathway, which activates the transcription factor crucial for cell growth. In contrast to trametinib, dabrafenib also inhibits mutant BRAF (V600E and V600K), while the latter inhibits MEK. Another element of the MAPK pathway after BRAF is the MEK.

Ubiquitin application:

A well-researched mechanism known as the ubiquitin-proteasome is responsible for controlling protein homeostasis and trafficking. Numerous physiological functions, such as immunological response, angiogenesis, cell proliferation, apoptosis, and DNA repair, are regulated by ubiquitination. Each place where a protein is ubiquitinated has a unique impact on the target protein, which may occur with any given protein. It is difficult to target a particular ubiquitination location. Although some medications have been created to inhibit the proteasome pathway, such as bortezomib, their therapeutic uses are restricted due to their non-specific actions. E3 ligases frequently have a variety of substrates with various functions. If an E3 ligase is inhibited, other proteins that are not of interest may not be ubiquitinated, which could have an unintended or off-target effect. Although it has been difficult to target protein ubiquitination, new treatment approaches should become available as we gain more knowledge of the ubiquitination mechanism.

Conclusion

A select group of enzymes, including as E1s, E2s, E3s, and DUBs, closely regulate ubiquitination, which dynamically regulates inflammation and several pathways leading to programmed cell death. Numerous physiological activities, such as the cell cycle, cell proliferation, DNA repair, apoptosis, inflammation, immunological response, etc., depend on the ubiquitination of nonhistone proteins. The emergence of certain human malignancies is tightly correlated with dysregulation of nonhistone lysine ubiquitylation. As a result, UPS has emerged as a prospective therapeutic target for cutting-edge cancer medications. An effective strategy for treating inflammatory diseases, malignancies, and infectious diseases is to target defective elements of the ubiquitin system. Proteasome inhibitors diminish osteoblast activity, slow down tumor cell growth, and increase immune cell sensitivity. In a variety of illnesses, such as malignancies and autoinflammatory diseases, abnormal ubiquitin control of inflammatory pathways has been seen [44]. Their review encapsulated how the ERK/MAPK pathway involved in the development and progression of tumors/malignancies. Further this review will detail the signaling pathway and the modification or treatments in the ubiquitin cancer. By sharing a substrate and interacting across cascades, the MAP kinase signal transduction pathways regulate proliferation in mammalian cells in a manner that is inseparable from other signal transduction systems. It's also crucial to investigate the intricate overlapping mechanism. It is well recognized that multicellular organisms must maintain a normal cell cycle for proper growth and development. Cancer ultimately results from a loss of control. Therefore, it is crucial to research the cell cycle's process [45].

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