

Review Article

Post-translational modifications of proteins in tumor immunotherapy and their potential as immunotherapeutic targets



Yang Yang¹, Yuxue Jiao¹, Mohammad Reza Mohammadi^{2,*} 



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ABSTRACT

Protein is an important component of life. Protein modification after translation enriches the diversity of protein, regulates the structure and function of a protein, and participates in more life processes. Recent studies have found that post-translational modifications of proteins can regulate the occurrence and development of tumors. The human immune system should be able to eliminate cancer cells through an acquired immune response executed by T cells. However, clinical detection of cancer cells often results from the failure of immune surveillance. Therefore, relieving immune suppression and restoring antitumor immune response provides the possibility for tumor therapy. Tumor immunotherapy refers to exogenous intervention of the body's immune system, restart and maintain the "tumor-immune" cycle, restore and improve the anti-immune response of the group, strengthen the recognition and killing ability of tumor cells, so as to achieve the therapeutic effect of controlling or even clarifying the tumor specifically. Here, we review current knowledge of the current status of tumor immunotherapy and the types and effects of post-translational modifications of proteins, hoping to improve new ideas for the types of therapies.

1. Introduction

Tumor immunotherapy refers to exogenous intervention of the body's immune system, restarting and maintaining the "tumor-immune" cycle, restoring and improving the anti-immune response of the group, and strengthening the recognition and killing ability of tumor cells, to achieve the therapeutic effect of controlling or even clarifying the tumor specifically[1, 2]. Current developments and improvements in cancer immunotherapy (CIT) aim to restore and enhance antitumor immunity by identifying and forcefully eradicating cancer cells and preventing metastasis from primary tumors. Immunotherapy has led to a paradigm change in the treatment of some malignancies, providing lasting, long-term responses for patients with advanced cancer. Despite the

rapid development and success of CIT therapeutics, there are still challenges and problems with the limited efficacy of CIT in many tumor types. Targeting these tumor immune interactions could increase the effectiveness of other cancer therapies[3, 4]

In recent years, tumor immunotherapy has become a research hotspot due to its characteristics of enhancing the immune system, being suitable for a variety of tumors, and having long-lasting responses. The emergence of tumor immunotherapy has changed cancer treatment and brought good news to a vast number of cancer patients. Currently used cancer immunotherapies include oncolytic virus therapy, cancer vaccines, adoptive cell transfer, and immune checkpoint inhibitors [5].

¹Clinical Systems Biology Laboratories, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China

²Department of Bacteriology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

*Corresponding Author: Mohammad Reza Mohammadi (mreza.mohammadi@modares.ac.ir)

The concept of using viruses to treat tumors originated more than a century ago, but it is only in the past 20 years that the effects have gained strength. The species of OV's include DNA, single-stranded RNA (ssRNA), and double-stranded RNA (dsRNA) viruses, with varying immunobiological consequences following infection of tumors and/or other cells[6].

The effect of oncolytic virus therapy is to kill tumor cells directly. It may also facilitate in situ immunization against whole tumors without the need for personalization or pre-selection of tumor-associated antigens, also by establishing immunogenic (thermal) microenvironments. T-VEC has been approved for the treatment of skin melanoma since 2015. However, the oncolytic virus has certain limitations in tumor treatment, and combined therapy with radiotherapy and chemotherapy can make the oncolytic virus play a greater role [6].

2. Cancer vaccine

The use of tumor cells or tumor antigens to activate the immune system of patients, induce a cellular or humoral anti-tumor immune response, and prevent tumor growth, spread, and recurrence, to control or eliminate the tumor. According to the composition of cancer, vaccines can be divided into the virus, peptide vaccine, bacterial vector vaccine, nucleic acid vaccine, and dendritic cell vaccine. According to their functions, they can be divided into preventive cancer vaccines and therapeutic cancer vaccines. Preventive vaccines are available only for papillomavirus-caused cancers. Most vaccines are therapeutic, and designed to remove lesions [7].

3. Adoptive cell transfer

A passive immunotherapy in which immune cells derived from the patient are modified, activated, and expanded in vitro and then re-injected back into the patient to achieve the purpose of tumor identification. These include tumor-infiltrating lymphocytes (TILs), chimeric antigen-modified T cells (CAR-T), and T cell antibody-modified T cells (TCR-T) [8].

4. Immune Checkpoint inhibitors

Immune checkpoint proteins are used by cancer cells to avoid and suppress antitumor responses. ICIs provide a durable response in only a small proportion of patients. Targeted immunosuppression of tumor microenvironment is helpful to overcome ICIs resistance. Immune checkpoint blockade is arguably the most important development of the last decade. Currently, the applied targets include PD1/PD-L1 and CTLA-4[9, 10].

CTLA-4, usually on the surface of CD4+ and CD8+T cells, can bind to ligands on antigen-derived cells, produce signals that inhibit T cell activation, reduce cytokine production, and reduce the body's anti-tumor immune response. PD1 binds to PD-L1 or PDL2 ligands on the surface of T lymphocytes, inhibits intracellular signal transduction, and induces apoptosis of T cells, which is the immune escape of tumor cells. Immune checkpoint inhibitors are approved for use in a variety of cancers, including melanoma, renal cell carcinoma (RCC), advanced non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma (HL), bladder cancer, Merkel cell carcinoma, and head and neck cancer. Several immune checkpoint inhibitors are currently in clinical use, including Ipilimumab, Nivolumab, and Atezolizumab [9, 11].

5. Post-translational modification of protein

Post-translational modification refers to a covalent process that a protein undergoes during or after translation, that is, the addition of modifying groups to one or more amino acid residues or the removal of groups by proteolysis, which changes the properties of a protein[12, 13].

Protein modification after translation is a complicated process, almost the whole process of cell life activities, such as gene transcription, signal transduction, energy metabolism, protein interaction, etc., affect protein subcellular localization, stability, activity, and cancer, neurological disease, cardiovascular disease, and much other development is closely related to the occurrence of diseases. At present, there are more than 400 types of known post-

translational modifications of proteins, including methylation, alkylation, glycosylation, ubiquitination, phosphorylation, palmitoylation, and so on. Almost all proteins can undergo post-translational modifications [12, 14, 15].

6. Acetylation

Acetylation is a dynamic and reversible regulatory process involved in most biological processes and regulates tumor proliferation through various cellular pathways, such as control of the cell cycle, apoptosis, and different metabolic pathways. Branched-chain amino acid transaminase (BCAT2) is mainly acetylated at lysine 44, which inhibits BCAA metabolism and pancreatic tumorigenesis [16]. Malic enzyme 1 (ME1) is acetylated at K337 and dynamically regulates the occurrence of colorectal tumors [17]. In pancreatic cancer, K5 acetylation of lactate dehydrogenase A (LDH-A) is down-regulated [18]. 6SIRT2 can deacetylate IDH1 at K224 and exert a tumor-suppressive effect in colon cancer cell models through IDH1 enzyme activity and the HIF1a-SRC transcription axis [19].

7. Phosphorylation/ Glycosylation

Protein phosphorylation is the most common and important process in PTM, which is involved in almost all biological activities. Moreover, phosphorylation can also promote the occurrence and development of tumors by influencing the proliferation of cancer cells. AMPK mediates the phosphorylation of PDHA at S295 and S314, which drives the TCA cycle and promotes lung metastasis of breast cancer [20]. Pdk1-mediated phosphorylation of PDHK1 is closely related to the staging and prognosis of breast cancer, esophageal cancer, gastric cancer, and other cancers [21]. Phosphorylation of cAMP response element-binding protein (CREB) - specific coactivator CRTC2 at Ser238 promotes proliferation, migration, and invasion of colorectal cancer cells [22]. Phosphorylation of 10PIM1 target sites stimulates NFATC1 activity and enhances its ability to promote migration and invasion of prostate cancer cells [23].

Glycosylation is a common post-translational modification of proteins. By

forming glycosylated bonds, glycosylation affects the spatial conformation and localization of proteins and is involved in the signal transduction process, which is closely related to the occurrence of many diseases. According to the different glycosylation bonds, glycosylation can be divided into O-glycosylation and N-glycosylation. Mucin-type O-glycosylation is one of the most common post-translational modifications of many membrane-bound and secreted glycoproteins. It occurs in the Golgi apparatus and is regulated by glycosyltransferases. Aberrant glycosylation is increasingly recognized as a driver of tumorigenesis [24].

Abnormal O-glycosylation is a contributing factor to the development and progression of colorectal neoplasms [25]. In pancreatic cancer cells, 2-DG increases the phosphorylation of GFAT1 and induces ER apoptosis by disrupting the N-glycosylation of the protein [26]. The targeted intervention of glycosylation modification of B7H3 protein to promote its protein degradation can be used as an entry point to enhance immunotherapy for triple-negative breast cancer, and provide a promising treatment strategy for triple-negative breast cancer. C-Jun modified by O-glycosylation can resist ferroptosis by inhibiting the synthesis of glutathione. Therefore, blocking the modification of O-glycosylation can inhibit the occurrence of liver cancer and contribute to the treatment of liver cancer [27].

8. Ubiquitination and Lactate

refers to the process in which one or more ubiquitin molecules, under the action of a series of special enzymes, classify intracellular proteins, select target protein molecules from them, and specifically modify the target proteins. Ubiquitination is an important protein modification that plays an important role in protein regulation [28, 29].

The Ubiquitin proteasome degradation pathway is the most important protein degradation pathway in eukaryotic cells, which is involved in various physiological processes, including signal transmission, transcriptional regulation, cell cycle, apoptosis, DNA damage repair, and is closely related to tumors and cardiovascular diseases.

Ubiquitin binding enzyme E2T (UBE2T) overactivates the Wnt/ β -catenin signaling pathway by inducing the polyubiquitin and degradation of activated protein kinase receptor (RACK1) at K172, K225 and K257, thereby promoting the progression of gastric cancer [28]. Deubiquitinase FSP20 can deubiquitinate SNAI2 and inhibit its degradation, which promotes the metastasis of breast cancer [30].

A novel post-translational modification of whole proteins was discovered by Yingming Zhao's team in Chicago in 2019. Lactate can act as a precursor to lactate histone lysine, which is involved in cancer and other diseases. Moreover, lactic acid accumulation helps cancer cells evade the immune system and inhibits immune killing [31]. Lactate regulates Treg cell production through Lys72 lactation in MOESIN, and then improves the interaction mechanism of MOESIN with TGF- β and downstream SMAD3 signaling, which provides a new theoretical basis for tumor immunotherapy by targeting Treg cells [32].

9. Methylation, Crotonylation, Succinylation and Malonylation

In addition to phosphorylation and acetylation, methylation is the most important post-translational modification of proteins. Proteins can be monomethylated, dimethylated, or trimethylated on lysine residues, and monomethylated, symmetric, or asymmetric dimethylated on arginine residues. Methylation is more involved in epigenetic processes, but also DNA damage repair, signal transduction, cell development, carcinogenesis, and other processes [33].

Crotonylation can occur at serine and lysine residues and usually plays an important role in regulating gene expression. Crotonylation is closely related to transcriptional regulation, DNA damage repair, reproductive regulation, and cancer metabolism. Crotonylation levels were decreased in liver, stomach, and kidney cancers and increased in thyroid, esophageal, pancreatic, and lung cancers. In particular, the increase of crotonylation can inhibit the viability and proliferation of hepatocellular carcinoma cells [34].

Compare with methylation Succinylation and acetylation, succinylation can cause more changes in protein properties, resulting in greater changes in protein structure and function. Succinate is involved in cell energy metabolism and ATP synthesis and is an important intermediate of the tricarboxylic acid cycle. Studies have shown that succinate dehydrogenase (SDH) mutations are present in most tumors, and the accumulation of succinate and succinylation of protein lysine caused by SDH mutations may be important factors in promoting tumor development [35]. In colon cancer cells, high succinylation of citrate synthase at k393 and k395 significantly reduces its activity, which can inhibit the proliferation and migration of colon cancer cells [36].

Malonylation is an evolutionarily conserved post-translational modification of a protein that occurs on lysine. Malonyl coal is used as a substrate to modify lysine residues, thereby affecting the composition of the protein. Malonylation has a feedback effect on fatty acid biosynthesis [37]. Malonylation can also inhibit mitochondrial function. mTOR malonylation inhibition of FASN reduces the enzymatic activity of mTORC1, resulting in vascular defects [38]. Depletion of mitochondrial transcription factor TFAM can inhibit the tricarboxylic acid cycle of mitochondria, promote the accumulation of malonyl-CoA in the cytoplasm, and lead to malonylated modification and nuclear translocation of actin-binding protein mDia2. This can promote F-actin formation of nuclear actin, and then induce the expression of metastasis-related genes, including extracellular matrix remodeling, angiogenesis, cell migration, and adhesion, and finally promote the metastasis of liver cancer [39].

10. SUMO (small ubiquitin-like modifier)

An isopeptide bond is formed between the C-terminal carboxyl group of the small ubiquitin-like protein SUMO1 and the ϵ -amino group of the lysine residue of the target protein. The most common types of SUMOylation in mammalian cells are SUMO1, SUMO2, and SUMO3. Overexpression of SUMOylation-modified enzymes in cancer cells can change the transcriptional activity of genes, gene expression, and cell proliferation,

leading to the occurrence and development of cancer [39].

Adp-ribosylation: ADP-ribosylation is a macromolecular dynamic reversible chemical modification that regulates a variety of cellular processes, such as DNA damage, transcription, translation, and aging. ADP ribosylation is a process in which ADP-ribose groups generated by NAD⁺ cleavage are covalently linked to target proteases. The ADP-ribose polymerase is a potential target in cancer therapy, and can also be used as a sensitizer in combination with conventional chemotherapy in cancer therapy [40]. The key proteins involved in tumor immunotherapy can undergo post-translational modification and its effect on tumor progression: Protein is an important component of life, is the essential material of life, and is an essential part of life activities. Changes in protein often have an impact on the state of life. In tumors, pathogenesis modification has an unknown role in tumorigenesis and progression [41].

11. PD1, PD-L1, and p53

The post-translational modification types of PD1 include ubiquitination, deubiquitination, and glycosylation. An abnormal E3 line will lead to the deregulation of the PD-1 signaling pathway, thereby affecting tumorigenesis. The glycosylation sites of PD1 include N49, N58, N74, and N116, and the abnormality of these sites can affect the stability and expression level of PD1. Glycosylation of PD1 can affect its ability to bind to PD-L1 ligands [42].

PD-L1 can undergo ubiquitination, deubiquitination, phosphorylation, acetylation, palmitoylation, and glycosylation. Gene or drug regulation of PD-L1 acetylation can block its nuclear translocation, thereby enhancing the antitumor effect of PD-1 blockers. Disruption of palmitoylation of PD-L1 enhances immune responses. The glycosylation sites of PD-L1 include N35, N192, N200, and N219, which are related to the stability of PD-L1. Blocking PD-L1 glycosylation can significantly improve the antitumor effect. Some glycosyltransferases that catalyze the modification of PD-1/PD-L1 glycosylation have also been found to be involved in tumor invasion and metastasis,

and are closely related to the prognosis of tumor patients. The development of therapeutic methods targeting PD-1/PD-L1 glycosylation has obvious advantages and is expected to become a new approach and method for cancer treatment [43].

P53 is one of the most commonly mutated genes in human cancers. Active p53 is affected by multiple covalent posttranslational modifications, including phosphorylation, methylation, ubiquitination, acetylation, and other types, which significantly affect the expression of p53 target genes. Phosphorylation is the most common posttranslational modification of P53. Phosphorylation and acetylation of p53 usually lead to its stabilization and accumulation in the nucleus, followed by activation [44].

Expression of hepatitis C virus (HCV) core proteins induces hyperacetylation of p53 at Lys373 and Lys382 and increases (low expression levels) or inhibits (high expression levels) phosphorylation of p53 at Ser15, depending on the level of HCV expression. The target of p53 ubiquitination is Lys386, and ubiquitination has been reported to regulate the transcriptional activity of p53. P53 is degraded through an ubiquitin-dependent process mediated primarily by MDM2. Posttranslational modification of P53 has many effects on P53. Therefore, targeting the posttranslational modification site of p53 may be a novel strategy for tumor treatment [44].

12. Skp2 (S-phase kinase-associated protein 2)

An oncoprotein that regulates tumor proliferation, invasion, and metastasis. Skp2 is an oncogene discovered in recent years. Skp2 overexpression is often observed in a variety of human cancers, including lymphoma, prostate cancer, melanoma, nasopharyngeal cancer, pancreatic cancer, and breast cancer, promoting the progression and metastasis of human cancers [45].

Ku70: Ku70 is an SKP2-binding protein. Superacetylation of Ku70 can eliminate the inhibitory effect of Ku70 and Bax on tumor cell apoptosis. Acetylation of Ku70 may be a potential new therapeutic target [46]. *PARP1:*

Acetylated at Lys949. Acetylation of PARP1 inhibits its degradation, thereby increasing the ability of cells to repair DSBS. PARP inhibition (PARPi) has been used clinically to treat ovarian, breast, prostate, and pancreatic cancers. Acetylation of PARP1 at different lysine sites has opposite functions in the efficiency of DNA double-strand damage repair, suggesting that precise regulation of PARP1 acetylation may be a potential novel therapeutic target [47].

13. Ras protein

RAS protein participates in multiple cascade reactions, regulates multiple key cellular processes, and is a key component of cell survival, proliferation, transformation, and differentiation signaling pathways. RAS proteins have several types of posttranslational modifications, including sumoylation, phosphorylation, palmitoylation, ubiquitination, and acetylation. RAS proteins undergo palmitoylation at C181 and L184, providing an affinity trap for RAS proteins associated with membrane binding [48]. Phosphorylation of 27RAS at S181 results in its transfer from the plasma membrane to the inner membrane, affecting its toxicity, limiting cell growth, and even causing cell death [49]. RAS can undergo double ubiquitination and single ubiquitination modification, which can promote the endosomal association of RAS and control the rate of its signal output [50].

14. STAT (Signal Transmitter and activator of Transcription protein)

STAT affects many physiological processes, including cell proliferation, apoptosis, division, and differentiation. The current STAT family has seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Among them, STAT3 has a great correlation with tumors, which can promote tumor proliferation and survival, and promote tumor growth. STAT3 underwent S-palmitoylation at C687 and C712, which not only activated STAT3 but also enhanced its transcriptional activity (Figure 1) [51]. Zdhhc19-mediated palmitoylation of STAT3 plays an important role in lung squamous cell carcinoma and high fat-related tumorigenesis in vivo [52].

15. Types and roles of signaling pathways in tumor immunotherapy

15.1 PIK3/AKT/mTOR9 (PAM)

The PAM pathway consists of three major players: PI3K, protein kinase B (AKT), and the mammalian target of rapamycin (mTOR)(Figure 2). PAM pathway has three main characteristics: multilevel regulation, cascade amplification; Phosphorylation-based signal transduction; relatively simple, straight line, single conduction mode. The phosphoinositol 3-kinase (PI3K)AKT-mTOR cascade is often overactivated in cancer and plays an integral role in many cellular processes, including tumor growth and survival, that can serve as a basis for therapeutic resistance [52]. PI3K, AKT, and mTOR regulate important cancer signal transduction crossroads, which makes the PAM pathway play an important role in tumor immune regulation. The PAM pathway can influence regulatory T cells and myeloid-derived suppressor cells to maintain an immunosuppressed tumor microenvironment. The PI3K pathway is activated in most glioblastomas [53].

16. TGF- β

Abnormal TGF- β signaling pathway can lead to physiological dysfunction of cells and affect the occurrence and development of tumors. There are two types of receptors on the cell membrane: type I TGF- β receptor and type II TGF- β receptor, both of which are transmembrane proteins with filamentous threonine kinase activity. TGF- β binds to type II TGF- β receptor and then recruits' type I TGF- β receptor to form a ligand-receptor complex. Type II receptor phosphorylates the intracellular region of type I receptor, and activated type I receptor phosphorylates intracellular SMAD2 and SMAD3, which form dimers and bind to SMAD4 and are transferred into the nucleus for transcriptional regulation[47].

TGF- β plays a dual role in malignant tumors. The tumor suppressor effect of TGF- β is that it induces the expression of tumor suppressor-related genes to maintain the homeostasis of normal tissues and prevent the early formation of tumors. When TGF- β

signaling loses its tumor suppressor effect, cancer cells can use this pathway to promote tumor development [47].

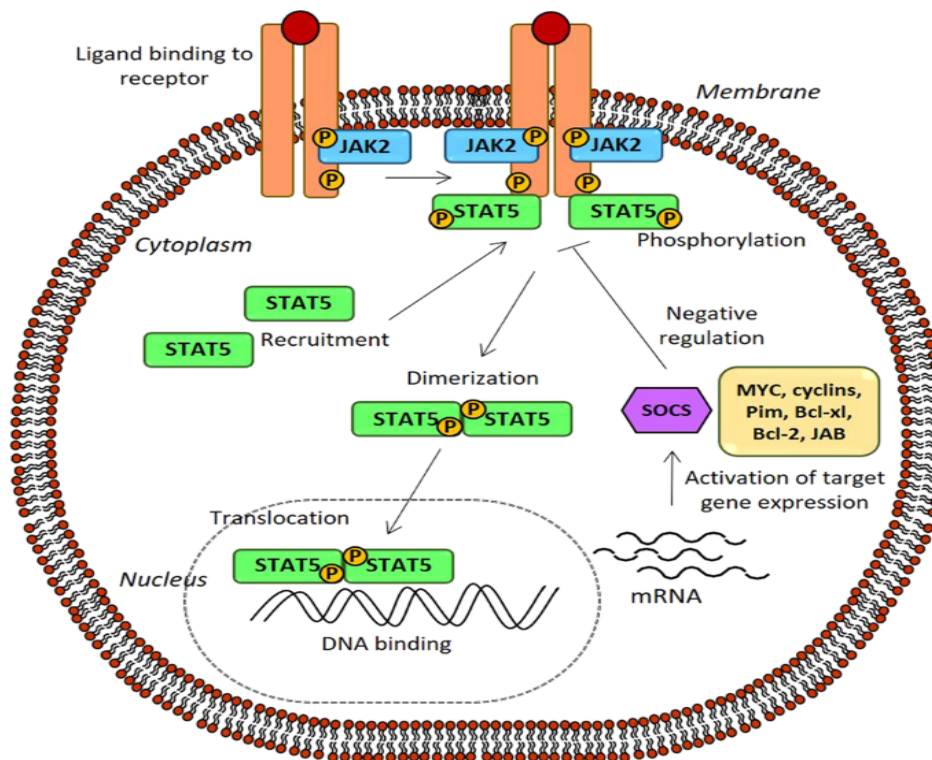


Fig. 1. Signal transducer and activator of transcription (STAT) [54]. This figure is licensed under a Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>)

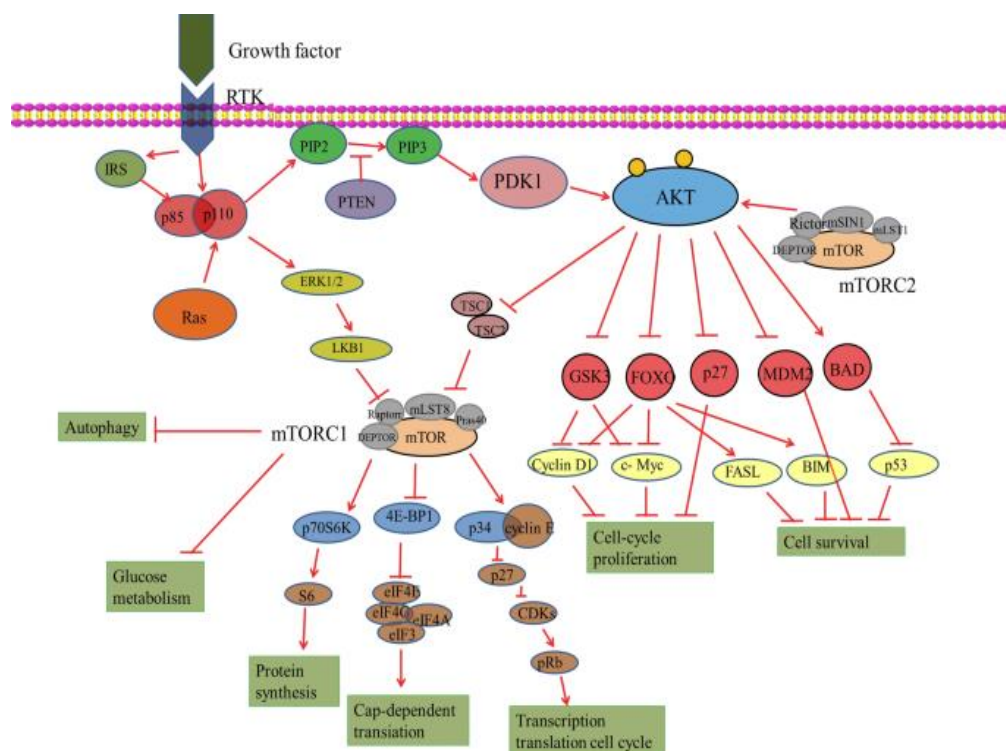


Fig. 2. PI3K/AKT/mTOR signalling pathway

17. NK- κ B and Jak-STAT

NK- κ B can be activated by a variety of factors, including cytokines, ionizing radiation, and chemotherapy drugs. NK- κ B is functional in the immune inflammatory response of the body. The NK- κ B pathway is highly active in cancers such as prostate, breast, pancreatic, gastric, and head and neck cancers. The high expression or mutation of the NK- κ B signaling pathway may lead to the continuous activation of the NK- κ B signaling pathway, which may lead to the occurrence and development of tumors [55].

JAK is a non-receptor tyrosine-protein kinase. As a direct substrate of JAK, STAT can transmit signals into the nucleus and regulate the expression of specific genes STAT. Compared with other signaling pathways, the transmission process of the JAK-STAT pathway is relatively simple. After activation of JAK, the tyrosine residues on the catalytic receptor are phosphorylated, and then JAK catalyzes the STAT protein bound to the receptor. The activated STAT protein enters the nucleus in the form of a dimer and activates and regulates gene transcription with target genes. This signaling pathway can be activated in tumors, and activated STAT seems to be more prognostic [56].

18. PD-1/PD-L1

After PD-1 in immune cells binds to tumor cell biaoPD-L, specific aggregation protein tyrosine phosphatase (SHP1)h and protein tyrosine phosphatase 2 (SHP2) bind to ITIM. The downstream signaling pathway phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT) is dephosphorylated, which blocks activation, hinders the formation of activated T cells, and reduces the expression of cytokines such as interleukin-2, interferon- γ , and tumor necrosis factor. The study of this signaling pathway has greatly promoted the development of immunotherapy and the targeting of immune checkpoints. However, the interaction between PD-L1 and PD-1 on the cell surface is only the tip of the iceberg, which needs to be further studied to open up a broader prospect for cancer diagnosis and treatment [57, 58].

19. Conclusion

The tumor is a systemic chronic disease with multi-etiology, multi-process, and multi-outcome, involving molecular changes at multiple levels including genome, transcriptome, proteome, and metabolome. Posttranslational modification is an extremely important aspect of the protein domain. There are many kinds of post-translational modifications, which can change protein structure and regulate protein function. Post-translational modified proteins can participate in physiological processes such as cell proliferation, differentiation, and apoptosis, or even be a member of signaling pathways, changing the outcome of signal transduction[59].

Posttranslational modifications not only regulate tumor therapeutic targets such as PD1 and PD-L1 but also regulate key enzymes such as STAT and RAS. Although the mechanism of post-translational modification is not fully understood, it is undeniable that it is involved in tumorigenesis [59]. Development and prognosis are also closely related to the diagnosis, treatment, and prognosis assessment of tumors, and provide opportunities and conditions for personalized and accurate prediction, diagnosis, treatment, and prognosis of treatments. Therefore, target therapy for post-translational modifications of proteins may become a future research direction.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors read and approved the final manuscript for publication.

Informed Consent

The authors declare not used any patients in this research.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal role in study design, work, statistical analysis and manuscript writing.

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