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Review Article

SKP, CULLIN, F-BOX COMPLEX: MASTER REGULATOR OF METABOLIC ADAPTATIONS IN CANCER CELLS

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ABSTRACT

The Skp, Cullin, and F-Box (SCF) complex stands as a pivotal regulatory entity in cellular metabolism, exerting profound influence over metabolic adaptations crucial to cancer cell survival and proliferation. Operating at the intersection of ubiquitination and signaling pathways, the SCF complex orchestrates the degradation of key regulatory proteins that are engaged in metabolism, thereby finely tuning cellular responses to varying nutrient availability and metabolic stressors. In cancer cells, dysregulation of the SCF complex often leads to aberrant metabolic phenotypes, promoting enhanced glucose uptake, altered lipid metabolism, and increased dependence on aerobic glycolysis (the Warburg effect) for energy production. Moreover, the SCF complex plays a crucial part in modulating the stability and activity of metabolic enzymes and transcription factors essential for metabolic reprogramming in cancer cells. Understanding the intricate mechanisms by which the SCF complex regulates metabolic adaptations in cancer cells holds significant implications for therapeutic strategies. Targeting components of the SCF complex or its downstream effectors could potentially disrupt cancer cell metabolism, offering novel avenues for therapeutic intervention aimed at combating tumor growth and progression. Thus, elucidating the molecular intricacies of the SCF complex's role in metabolic adaptations will not only enhance the fundamental knowledge of cancer cell biology but also unveil promising therapeutic opportunities in the ongoing battle against cancer.

Keywords: Skp, Cullin, F-box, Cancer, Apoptosis, and Metabolic Pathways.

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INTRODUCTION

The Skp, Cullin and F-Box (SCF) complex is a E3 ubiquitin ligase that is a crucial component in the ubiquitin-proteasome system that regulates protein degradation in eukaryotic cells. This multiprotein complex plays a vital role in managing many cellular processes comprising the signal transduction, cell cycle, and transcriptional regulation, by tagging specific proteins for ubiquitination and subsequent degradation by proteasome [1]. The versatility of the SCF complex arises from the diversity of F-box proteins, each recognizing different substrates. This allows the SCF complex to regulate a wide array of proteins and pathways. For instance, the SCF complex targets cyclins and cyclin-dependent kinase inhibitors in the cell cycle, ensuring proper progression of the cell cycle and checkpoint control. Dysregulation of the SCF complex can lead to various diseases, consisting of cancer, neurodegenerative disorders, and developmental abnormalities, highlighting its significance in maintaining cellular homeostasis. Research into the SCF complex continues to uncover its complex regulatory mechanisms and potential therapeutic targets for disease treatment [2].

STRUCTURE OF SCF COMPLEX

This complex is a multi-protein constitution with four main components:

- Skp1 (S-Phase kinase associated protein1): This acts as an adaptor protein that conjoins F-box protein to Cullin. It binds specifically to the F-box motif of the F-Box protein, providing incorporation of various F-Box proteins into the complex [3].
- Cullin (CUL1): Cullin serves as the scaffold of the SCF complex. It provides a structural backbone that organizes the assembly of Skp1, the F-box protein, and Rbx1. Cullin proteins have an elongated structure, which creates a platform for the other components to interact.
- F-Box protein: This component confers substrate specificity to the SCF complex. F-box protein: It is a variable component that confers the substrate specificity to the SCF complex. This protein possesses an F-box motif that binds to Skp1 and a domain responsible for substrate recognition, such as WD40 repeats or leucine-rich repeats. There are numerous F-box proteins, each targeting different substrates for ubiquitination.
- Rbx1 (RING-box protein 1): Rbx1 consists of a RING finger which interacts with E2 ubiqitin conjugating enzyme. It helps to transfer the ubiquitin from enzyme E2 to the substrate protein, the critical step in the ubiquitination process (Fig. 1) [4].

FUNCTION OF SCF COMPLEX

The primary function of this complex is to catalyse ubiquitination of specific substrate proteins marking them from 26S proteasome degradation. This process involves several key steps:

- Substrate Recognition: The F-Box protein within the SCF complex binds to its specific substrate, often recognizing the post-translational modifications like phosphorylation. This recognition ensures that only appropriately marked proteins are targeted for degradation.
- Ubiquitin Transfer: The E2 enzyme, charged with ubiquitin, interacts with the Rbx1 component. The RING finger domain of Rbx1 facilitates ubiquitin transfer from the E2 enzyme to the lysine residues on the substrate protein [5].
- Polyubiquitination: Multiple ubiquitin molecules are attached to the substrate forming a polyuniquitin chain. This chain is a signal for the proteasome 26S to recognize and degrade the substrate protein.
- Proteasomal Degradation**:** The polyubiquitinated substrate is recognized by 26S proteasome, where it is unfolded and degraded into small peptides. This degradation process regulates the levels of various proteins within the cell, thus controlling numerous cellular processes [6].

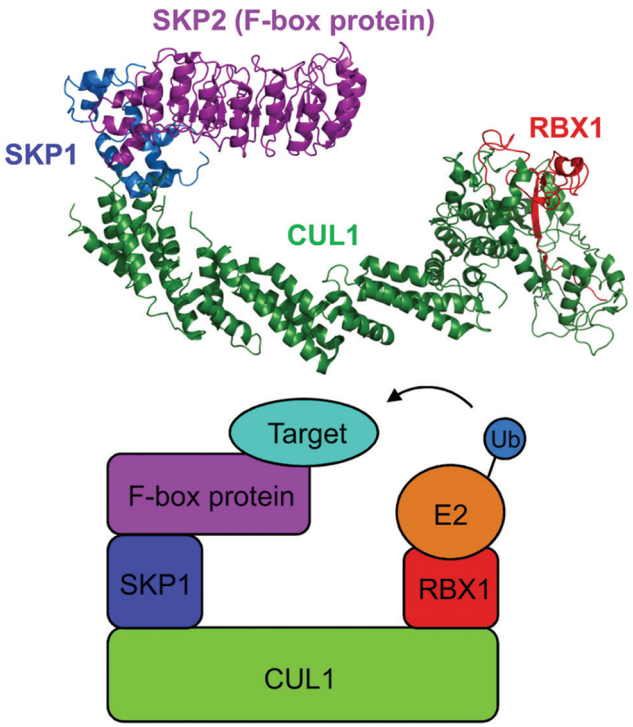

Fig. 1: Structure of Skp, Cullin, and F-Box complex

THE SIGNIFICANCE OF SCF COMPLEX IN CANCER BIOLOGY

This complex is essential in maintaining cellular homeostasis by targeting specific proteins for ubiquitination and subsequent degradation. Its significance in cancer biology is profound due to its involvement in controlling different cellular mechanisms such as cell cycle progression, signal transduction, and apoptosis, all of which are often dysregulated in cancer [7]. The activity of the SCF complex is regulated by neddylation, a process where neural precursor cell expressed, developmentally downregulated 8(NEDD8), a ubiquitin-like protein, conjugated to Cullin. This modification enhances the ubiquitin ligase activity of the SCF complex, thus promoting efficient ubiquitination of target proteins [8]. The SCF complex plays an important role in modulating apoptosis and cell survival pathways. For example, SCF^Fbw7 targets the anti-apoptotic protein Mcl-1 for degradation. Fbw7 function leads to Mcl-1 accumulation, providing cancer cells with a survival advantage, Fbw7 targets several oncogenic proteins, comprising cyclin E, c-Myc, and Notch for degradation. Mutations or downregulation of Fbw7 are frequently observed in various cancers, leading to the stabilization and accumulation of these oncogenic proteins, thus promoting cancer progression [9]. The SCF complex is integral to numerous signaling pathways that are often altered in cancer. For instance, SCF β-TrCP is involved in the Wnt/β-catenin pathway by targeting the β-canetin for degradation. Dysregulation of β-catenin turnover, due to mutations in components of the SCF complex or β-catenin itself, results in aberrant activation of Wnt signaling, which is implicated in colorectal and other cancers. Similarly, SCF^β-TrCP regulates the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway by targeting IκBα, the inhibitor of NF-κB, for degradation. Constitutive activation of NF-κB signaling, due to dysregulation of IκBα degradation, is the feature of many cancer types and contributes to inflammation, cell proliferation, and apoptosis resistance [10].

METABOLIC ADAPTATIONS IN CANCER CELLS

Metabolic adaptations in cancer cells are a set of changes that allow these cells to sustain their growth, survival, and proliferation under the challenging conditions of the tumor microenvironment (TME). Understanding these adaptations is important for developing effective cancer treatments. Below is an introduction to the key concepts and mechanisms involved in the metabolic adaptations of the cancer cells. These often undergo metabolic re-programming to meet the demands of rapid proliferation and survival in hostile environment that involve alteration in various metabolic pathways to ensure a continuous supply of energy, biosynthetic precursors, and redox balance [11].

AEROBIC GLYCOLYSIS (WARBURG EFFECT)

It is characterized by elevated glucose uptake and conversion into lactate, and reduced reliance on oxidative phosphorylation. Generation of adenosine triphosphate (ATP) more rapidly, albeit less efficiently, than through oxidative phosphorylation. Despite producing less ATP per molecule of glucose, aerobic glycolysis supports the high biosynthetic and energy demands of proliferating cancer cells by providing intermediates for nucleotide, amino acid, and lipid biosynthesis and maintaining redox balance through the production of nicotinamide adenine dinucleotide phosphate (Fig. 2) [12].

MITOCHONDRIAL ALTERATIONS

While glycolysis predominates, mitochondria in cancer cells remain active and adapt in various ways: Altered mitochondrial biogenesis and dynamics, changes in the tricarboxylic acid (TCA) cycle to support anabolic processes, and utilization of an alternative substrate, such as glutamine (glutaminolysis) to fuel the TCA cycle and generate biosynthetic precursors [13].

LIPID METABOLISM

Cancer cells often exhibit alterations in the lipid metabolism comprising increased *de novo* lipid synthesis to provide membrane components for rapid dividing cells. Enhanced uptake and storage of lipids. Utilization of fatty acid oxidation for energy production in certain contexts [14].

AMINO ACID METABOLISM

Alterations in amino acid metabolism support cancer cell growth and survival: Increased uptake and utilization of amino acids such as glutamine and serine. Glutamine, in particular, becomes a critical carbon and nitrogen source, supporting TCA cycle anaplerosis and nucleotide synthesis. Serine and glycine metabolism are often upregulated to support one-carbon metabolism and nucleotide synthesis [15].

MOLECULAR MECHANISMS DRIVING METABOLIC ADAPTATIONS

Several tumor suppressors and key oncogenes regulate metabolic adaptations in the cancer cells:

- MYC (Myelocytomatosis viral oncogene homolog): Up regulates glycolysis, glutaminolysis, and nucleotide biosynthesis.
- Hypoxia-Inducible Factor (HIF)-1: Induces glycolytic enzymes and glucose transporters, particularly under hypoxic conditions.
- p53: Tumor suppressor that can influence mitochondrial function and metabolism, often mutated in cancer to favor metabolic reprogramming.
- PI3K: Phosphoinositide 3-Kinase AKT: Also known as protein kinase B mechanistic target of rapamycin (mTOR): Mechanistic (or mammalian) Target of Rapamycin Pathway: Promotes glucose uptake, glycolysis, and lipid synthesis [16].

KEY METABOLIC RE-PROGRAMMING IN CANCER CELLS

Aerobic glycolysis–Warburg effect

Otto Warburg discovered the Warburg effect for the 1st time in the 1920s, is the fundamental metabolic hallmark of cancer cells. It refers to the observation that these cancer cells mainly convert glucose to lactate via glycolysis in adequate oxygen rather than through oxidative phosphorylation in the mitochondrial cells. This mechanism is known as aerobic glycolysis and distinguishes cancer metabolism from that of healthy cells [17]. Under aerobic conditions, (Fig. 3) normal cells primarily utilize oxidative phosphorylation, a highly efficient process occurring in the mitochondria that generates approximately

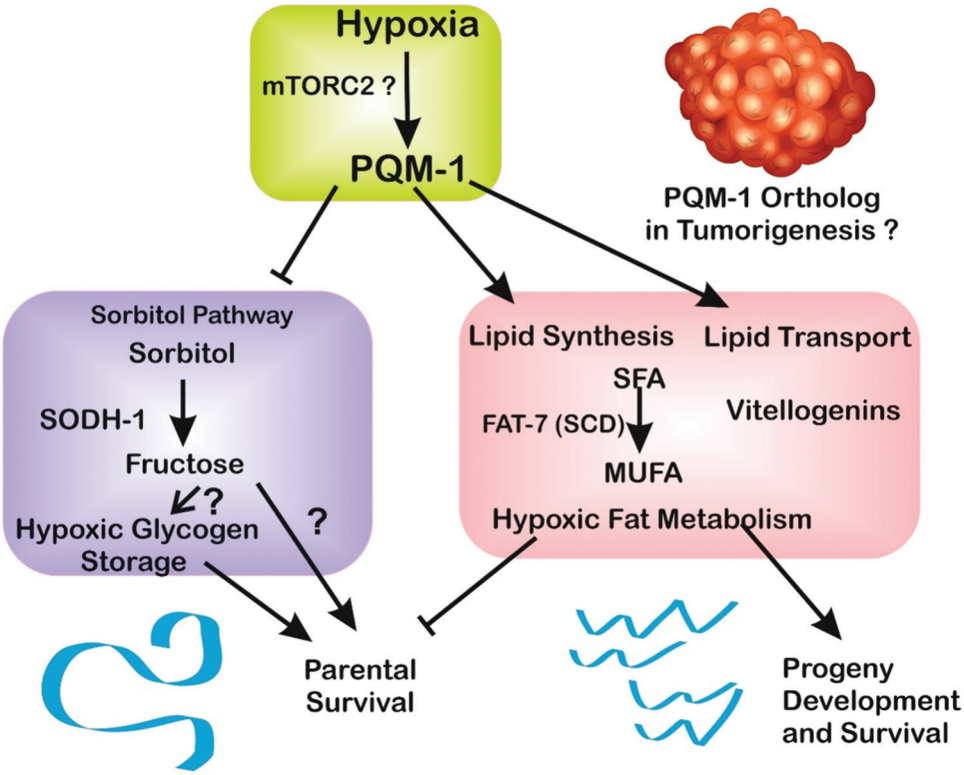

Fig. 2: Role of Hypoxia in cancer cell adaptation

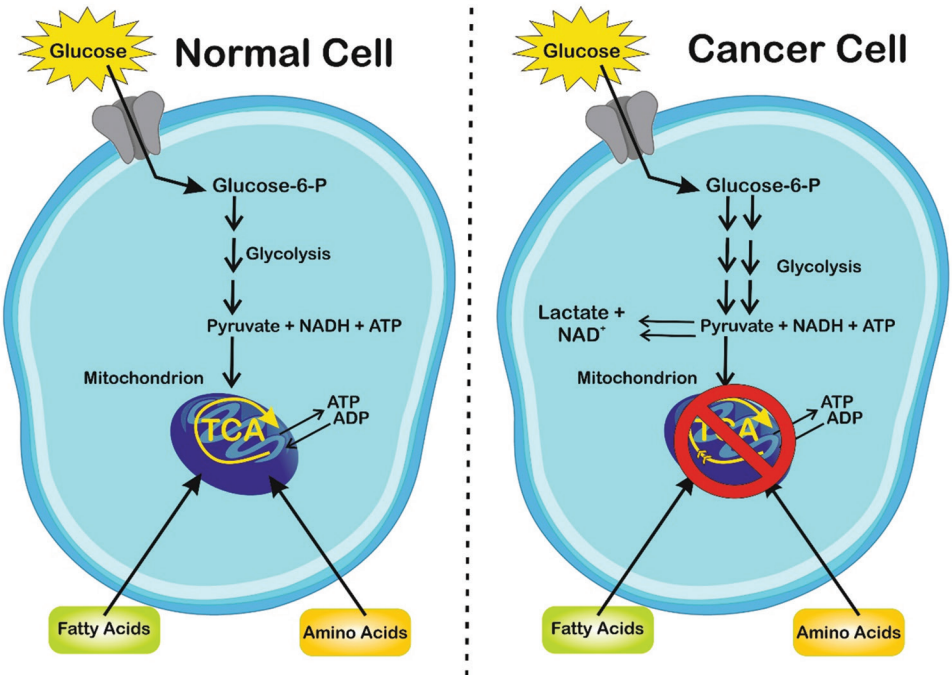

Fig. 3: Warburg effect in Normal and cancer cells

36–38 molecules of ATP/glucose molecule. In contrast, cancer cells predominantly use glycolysis, followed by lactate fermentation in the cytosol, producing only 2 molecules of ATP/glucose molecule. This occurs even when oxygen is plentiful, which is atypical for most non-cancerous cells [18]. Despite being little efficient in terms of the ATP yield per glucose molecule, glycolysis generates ATP at a much faster rate than oxidative phosphorylation. This rapid production can be advantageous for cancer cells, which often need a quick energy supply to assist their rapid proliferation [19]. The intermediates of glycolysis serve as precursors for various biosynthetic pathways. This metabolic reprogramming helps support nucleotides, amino acids, and lipids synthesis required for cell growth and division. Thus, glycolysis not only provides energy but also supplies the building blocks needed for biomass accumulation in proliferating cancer cells [20].

Glucose conversion leads to TME acidification. This acidic milieu can promote cancer cell invasion and metastasis, suppress immune responses, and create a hostile environment for normal cells. This

feature further enhances the survival and aggressive behavior of cancer cells [21].

Mechanisms driving the Warburg effect

MYC and Rat Sarcoma virus oncogene (RAS) oncogenes, as well as the mutations in tumor suppressor genes such as p53, can influence cellular metabolism and promote glycolysis. These genetic changes can activate signaling pathways that up regulate glycolytic enzymes and glucose transporters, thereby enhancing glucose uptake and glycolytic flux [22]. HIFs-1α are stabilized under hypoxic conditions and can induce gene expression engaged in glycolysis. In the presence of oxygen, HIF-1α can be activated by oncogenic signaling, contributing to the Warburg effect [23]. Many cancer cells exhibit dysfunctional mitochondria, which can impair oxidative phosphorylation and force cells to rely more heavily on glycolysis for ATP production [24].

GLUTAMINE ADDICTION

Glutamine addiction, also known as glutamine dependency, is a metabolic framework hallmark observed in many cancer cells. Glutamine is abundant in the bloodstream and is a crucial nutrient for rapidly proliferating cells, providing the source for both carbon and nitrogen for biosynthesis and production of energy. Cancer cells exhibits an increased glutamine dependence to sustain their growth and survival, a phenomenon termed "glutamine addiction." Glutamine is the main substrate for TCA cycle replenishment that intermediates through a process called anaplerosis (Fig. 4). This is then converted to glutamate by glutaminase and later into α-ketoglutarate that enters the TCA cycle. This replenishment is crucial for maintaining the TCA cycle's function in energy production and biosynthesis. Nitrogen is provided by glutamine for nucleotides and amino acids synthesis, required for DNA, RNA, and protein synthesis. This is particularly important for rapidly dividing cancer cells, which have high biosynthetic demand [25]. Glutamine takes part in the glutathione production, which is a major cellular antioxidant. Glutathione helps maintain redox balance by neutralizing reactive oxygen species (ROS), protecting cancer cells from oxidative stress, and promoting survival under harsh conditions. Glutamine metabolism influences key signaling pathways that are engaged in cell growth and proliferation. For instance, glutamine-derived α-ketoglutarate can affect mTOR signaling, which is critical for cell growth regulation [26]. Oncogenes – MYC can upregulate the glutamine transporters and glutaminase, enhancing glutamine uptake and metabolism. MYC-driven cancers are particularly dependent on glutamine to meet their metabolic needs. The heterogeneous nature of the TME, including regions of hypoxia and nutrient deprivation, can drive cancer cells to rely on alternative nutrients like glutamine. This adaptability helps cancer cells survive and thrive under suboptimal conditions [27]. Some cancer cells have compromised mitochondrial function and thus rely on glutamine to support TCA cycle activity and ATP production through alternative pathways [28].

LIPID METABOLISM

Lipid metabolism plays a key role in cancer adaptation and progression. Cancer cells frequently up regulate de novo lipogenesis, even in the presence of abundant extracellular lipids. Key enzymes participating in this process are as follows: (1) Fatty acid synthase – It catalyzes palmitate synthesis, a saturated fatty acid; (2) Acetyl CoA carboxylase – It converts Acetyl CoA to Malonyl CoA, a crucial step in fatty acid synthesis [29]; (3) Carnitine palmitoyl transferase 1 - regulates the fatty acid transportation to mitochondria for oxidation. Enhanced FAO provides ATP and reduces ROS by maintaining redox balance. Lipid droplets (LDs) are the dynamic organelles that store neutral lipids, including triglycerides and cholesteryl esters. Cancer cells often accumulate LDs, which can serve as an energy reserve and protect cells from lipotoxicity and oxidative stress. Sterol regulatory element binding proteins (SREBPs) regulate the genes that are involved in cholesterol and fatty acid synthesis (Fig. 5) [30]. Lipids can act as signaling molecules, influencing cancer progression: (1) Lysophosphatidic Acid: Promotes cell proliferation, migration, and survival; (2) Shingosine-1-phosphate: Involved in cell growth and apoptosis resistance [31].

Several oncogenes and tumor suppressors regulate lipid metabolism:

- PI3K/Akt/mTOR Pathway: Stimulates lipogenesis by activating SREBPs and increasing glucose uptake. AMPK: A cellular energy sensor that can inhibit lipid synthesis pathways and promote FAO under metabolic stress [32].

INTERACTION WITH HIFS

These factors play a significant role in cancer biology, particularly in how cancer cells respond to low oxygen levels (hypoxia). Hypoxia is the common feature of the TME that occurred with the rapid cancer cell proliferation and the aberrant structure of tumor vasculature. Here's an overview of the interaction between HIFs and cancer [33]:

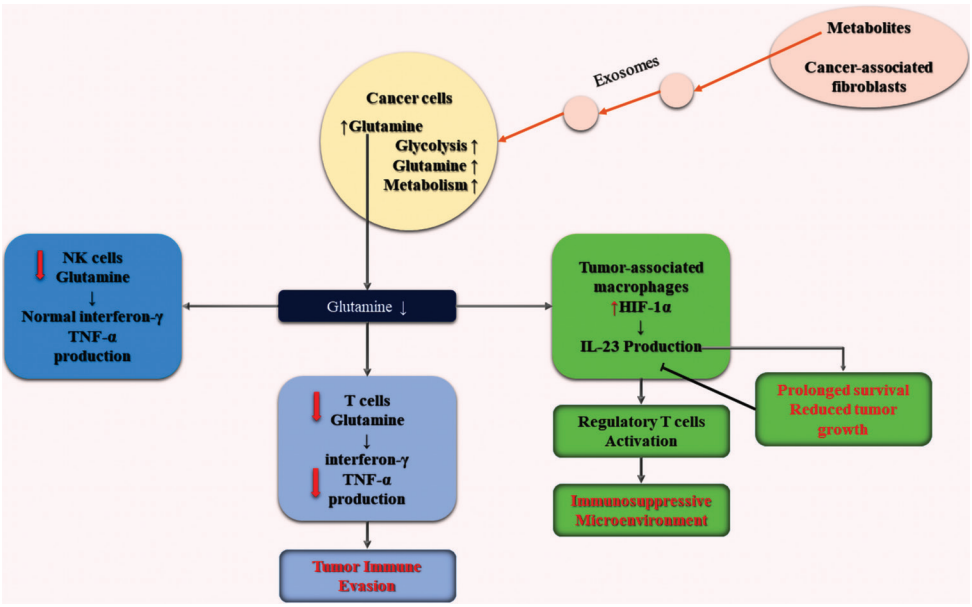

Fig. 4: Addiction pathway of Glutamine by cancer cells

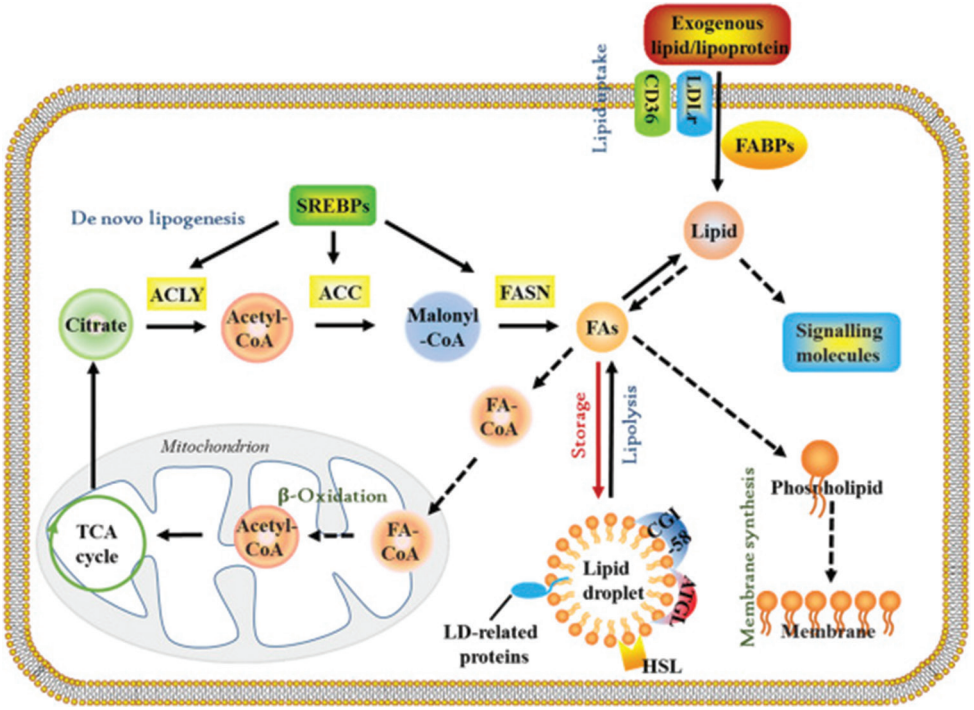

Fig. 5: Role of Lipid Metabolism in cancer adaptation and progression

Structure and function of HIFs

HIFs are transcription factors composed of two sub-units:

- HIF-α (alpha): Includes HIF-1α, HIF-2α, and HIF-3α
- HIF-β (beta): It is an Aryl hydrocarbon receptor nuclear translator (ARNT).

Under normal oxygen condition (normoxia), HIF-α is hydroxylated by prolyl hydroxylase enzymes, thus leading to its degradation via ubiquitin-proteasome pathway. Under hypoxia, this hydroxylation is inhibited, allowing HIF-α to stabilize, translocate to the nucleus, and dimerize with HIF-β and then bind to Hypoxia response elements in the DNA, activating the target genes transcription involved in various adaptive responses to hypoxia [34].

Role of HIFs in cancer

- Angiogenesis: HIFs up regulate vascular endothelial growth factor expression (VEGF), promoting new blood vessel formation and further supplying oxygen and nutrients to the growing tumor.
- Metabolism: Cancer cells often exhibit the Warburg effect, where they depend wholly on glycolysis for energy production even in oxygen presence. HIFs induce the expression of glucose transporters and glycolytic enzymes (e.g., GLUT1), facilitating this metabolic adaptation.
- Cell Survival and Proliferation: HIFs enhance gene expression involved in cell survival and proliferation (e.g., erythropoietin, transforming growth factor-alpha), helping cancer cells survive in the hostile hypoxic TME.
- Metastasis and Invasion: HIFs promote the expression of proteins that degrade the extracellular matrix (ECM) (e.g., Matrix metalloproteinases), facilitating the invasion of cancer cell and metastasis. They also upregulate genes involved in the epithelial-mesenchymal transition (EMT) – A key process in metastasis (Fig. 6) [35].
- Therapeutic Resistance: Hypoxia and HIF activation are linked to resistance to chemotherapy and radiotherapy. HIFs can induce the expression of multidrug resistance proteins and enhance DNA repair mechanisms, reducing the efficacy of these treatments [36].

Therapeutic targeting of HIFs

Given their central role in cancer progression, HIFs are attractive targets for cancer therapy. Approaches to inhibit HIFs include:

- Direct inhibitors: Molecules that directly inhibit HIF-α or its dimerization with HIF-β.
- Prolyl hydroxylase inhibitors: Agents that prevent the degradation of HIF-α, though these are typically used to treat anemia rather than cancer.
- Gene therapy: Techniques to suppress HIF-α expression using RNA interference or CRISPR/Cas9 [37].
- Natural compounds and repurposed drugs: Some natural compounds and existing drugs have been found to inhibit HIF activity.
- HIFs are critical regulators of the adaptive response to hypoxia in cancer, influencing angiogenesis, metabolism, cell survival, invasion, and therapeutic resistance. Targeting the HIFs presents an optimistic approach for treating cancer, with ongoing research focused on developing effective inhibitors and understanding their potential in combination therapies [38].

SCF COMPLEX IN AUTOPHAGY AND APOPTOSIS

SCF complexes are involved in autophagy and apoptosis, two critical processes for maintaining cellular homeostasis [39]. Autophagy is a cellular degradation process where the cytoplasmic components are sequestered in the autophagosomes and then delivered to lysosomes for degradation and cycling. The SCF complex regulates autophagy by targeting key autophagy-related proteins for ubiquitination, influencing their stability and function [40]. SCF complex targets proteins involved in the initiation of autophagy, such as serine/threonine kinase, a kinase essential for autophagy initiation. SCF complexes can ubiquitinate and degrade negative regulators of autophagy, promoting the autophagy process. SCF complex influences the stability of proteins involved in autophagosome membrane formation, such as ATG proteins. By targeting certain ATG proteins for degradation, the SCF complex can modulate the formation and expansion of autophagosomes [41]. SCF complexes are involved in the regulation of selective autophagy, such as mitophagy, where damaged mitochondria are specifically targeted for degradation. Proteins such as PINK1 and Parkin, which are critical for mitophagy, are regulated by SCF complexes [42].

SCF COMPLEX IN APOPTOSIS

The SCF complex contributes to apoptosis by regulating the stability of Pro and Anti-apoptotic proteins. SCF complex can ubiquitinate and

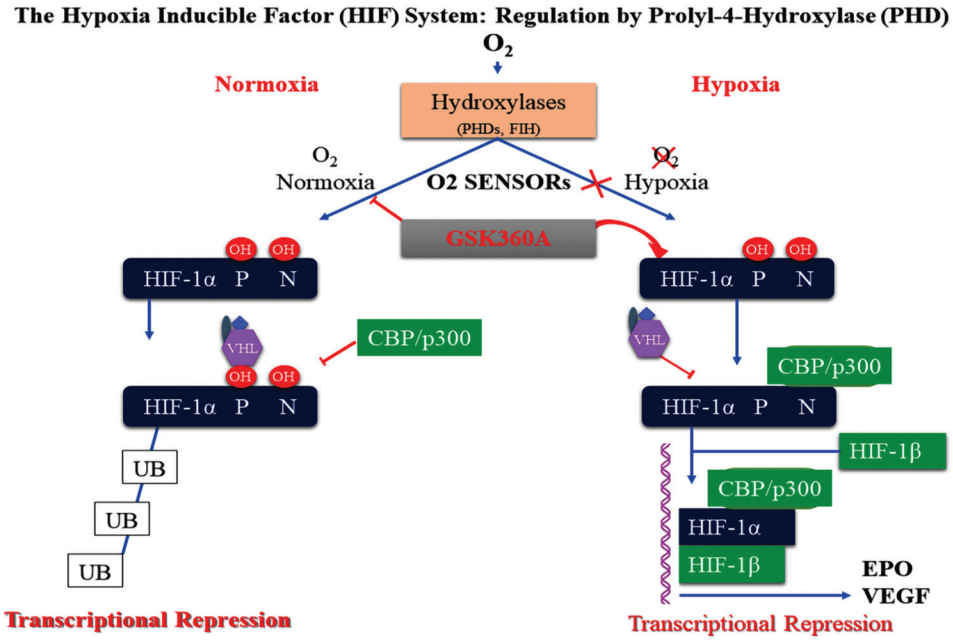

Fig. 6: Role of HIFs in Normoxia and Hypoxia process

Table 1: Therapeutic Targeting of SCF Complex in Cancer Treatment

SCF Complex Component	Targeted Cancer Type	Mechanism of Action	Therapeutic Agent	Clinical Status	References
Skp 2 (S-phase kinase-associated protein 2)	Breast and Prostrate cancer	Promotes degradation of p27, leading to uncontrolled cell cycle progression	Skp2 inhibitors (e.g., SZL-P1-41)	Preclinical studies	[69]
CUL1 (Cullin-1)	Various cancers	Core scaffolding protein of SCF, required for its activity	MLN4924 (NEDD8-activating enzyme inhibitor)	Phase I/II clinical trials	[70]
F-box proteins	Leukaemia, Lymphoma	Determines substrate specificity for ubiquitination and degradation	Small molecules targeting specific F-box proteins	Preclinical studies	[71]
Rbx1 (RING-box protein 1)	Lung Cancer, Colon Cancer	Essential for Ubiquitin transfer to substrates	Rbx1 inhibitors	Preclinical research	[72]
Skp 1 (S-phase kinase associated protein 1)	Multiple myeloma	Forms part of the core SCF complex, facilitating the assembly	Skp1 inhibitors	Early-stage research	[69]
SCF complex inhibitors	Various cancers	Inhibit the entire SCF complex, blocking Ubiquitin-mediated degradation of tumor suppressors	SCF complex inhibitors (e.g., Pevonedistat)	Clinical trials (PhaseI/II)	[73]

promote the degradation of pro-apoptotic proteins like p53, a tumor suppressor that induces apoptosis in response to cellular stress. By modulating pro-apoptotic protein levels, SCF complexes influence the threshold for apoptosis initiation. SCF complexes also target anti-apoptotic proteins such as as Bcl-2 and IAPs (inhibitor of apoptotic proteins) for degradation. Degradation of anti-apoptotic proteins by SCF complexes can promote apoptosis in response to apoptotic signals [43]. SCF complexes are involved in the integration of various apoptotic signals by regulating the stability of signal transducers and transcription factors involved in apoptosis. This complex as a crucial E3 ubiquitin ligase, plays significant roles in regulating both autophagy and apoptosis. By targeting specific proteins involved in these processes for ubiquitination and degradation, the SCF complex ensures proper cellular homeostasis, responding to stress, and maintaining tissue integrity. Understanding the detailed mechanisms by which SCF complexes regulate autophagy and apoptosis can provide insights into therapeutic strategies for diseases where these processes are dysregulated, such as cancer and neurodegenerative disorders [44].

SCF COMPLEX IN TME

The TME consists of cancer cells, immune cells, stromal cells (pericytes, fibroblasts, and endothelial cells), ECM, and signaling molecules. It plays a vital role in tumor progression by providing a supportive niche for cancer cells and thus modulating the interactions between cancer cells and their surroundings [45]. One of the primary ways the SCF complex affects the TME is through the regulation of tumor cell proliferation. By targeting key cell cycle regulators like p27^Kip1, Myc and Cyclin E for degradation, the SCF complex promotes cell cycle progression and proliferation of cancer cells. For instance, SCF^Skp2 mediates ubiquitination and degradation of p27^Kip1 – a cyclin-dependent kinase inhibitor, thereby facilitating G1-S phase transition and promoting cell proliferation. Overexpression of Skp2 has been linked to various cancers, correlating with poor prognosis [46].

SCF COMPLEX IN ANGIOGENESIS

The SCF complex influences angiogenesis by regulating the stability of HIFs. Under normoxic conditions, SCF^VHL (von Hippel-Lindau)

targets HIF-1α for degradation, preventing angiogenesis. However, under hypoxic conditions often found in the TME, HIF-1α escapes degradation, leading to the transcription of angiogenic factors such as VEGF. Dysregulation of this pathway, due to mutations in VHL or other components of the SCF complex, can result in enhanced angiogenesis and (Table 1) tumor progression [47]. The SCF complex also plays a role in immune evasion, a hallmark of cancer. SCF^β-TrCP targets IκBα, an inhibitor of NF-κB, for the degradation which leads to NF-Kb activation that promotes the immune checkpoint molecules expression like PD-L1, aiding the tumor in evading immune surveillance [48]. The SCF complex contributes to metastasis by regulating the proteins that are involved in cell migration, EMT as well as invasion. For instance, SCF^FBW7 targets Notch, c-Myc, and cyclin E for degradation, proteins that are often involved in promoting EMT and metastasis. Loss of FBW7 function is frequently observed in metastatic cancers, underscoring its role in inhibiting cancer spread [49].

THERAPEUTIC TARGETING OF SCF COMPLEX IN CANCER TREATMENT

Targeting the SCF complex has evolved as a promising therapeutic strategy for treating cancer, and metabolic and neurodegenerative disorders. Below are some current therapeutic strategies aimed at targeting the SCF complex [50].

MLN4924 (pevonedistat)

MLN4924, a small molecule inhibitor that targets NAE – NEDD8 activating enzyme which is crucial for the neddylation of Cullin proteins. Neddylation is crucial for the activation of the SCF complex. By inhibiting NAE, MLN4924 prevents Cullin-RING ligases, including the SCF complex, leading to the accumulation of SCF substrates and induction of apoptosis and cell cycle arrest in cancer cells. MLN4924 - is currently implemented in the clinical research for many types of cancer including acute myeloid leukemia and solid tumors [51-53].

Inhibitors of Skp2

Skp2 targets the cell cycle inhibitor p27^Kip1 for degradation. Overexpression of Skp2 is linked with poor prognosis in many cancers. Small molecule inhibitors like C1 and SZL-P1-41 have developed to specifically inhibit Skp2, which leads to stabilization of p27^Kip1, cell cycle arrest, and apoptosis in cancer cells [54-58].

TARGETED PROTEIN DEGRADATION (PROTACs)

PROTACs – Proteolysis targeting chimeras are the bi-functional molecules which employ a target protein to an E3 uniquitin ligase, promoting its ubiquitination and subsequent degradation by the proteasome [59].

PROTACs targeting SCF complex components

PROTACs have been developed to degrade specific components of the SCF complex or its substrates. For instance, PROTACs that target Skp2 for degradation can effectively reduce Skp2 levels and stabilize p27^Kip1, inhibiting cancer cell proliferation [60-62].

GENETIC APPROACHES

Genetic approaches, including RNA interference (RNAi) and CRISPR/Cas9, are used to downregulate or knock out specific components of the SCF complex.

RNAi

RNAi techniques using the small interfering (siRNAs) or Short hairpin RNAs (siRNAs) that specifically target mRNA transcripts of SCF complex components, reducing their expression. For example, siRNAs targeting Skp2 or FBXW7 can decrease their levels, leading to the stabilization of their substrates and inhibition of tumor growth [63,64].

CRISPR/Cas9

CRISPR/Cas9 gene editing can be employed to knock out specific genes encoding SCF complex components. This mechanism has been used in preclinical research to investigate the role of SCF components in various diseases and to validate potential therapeutic targets [65].

NATURAL COMPOUNDS

Natural compounds with anti-cancer properties have been identified to modulate SCF complex activity.

Curcumin, a natural compound derived from turmeric, has been shown to inhibit Skp2 expression, leading to p27^Kip1 accumulation and cell cycle arrest in cancer cells. Curcumin's ability to modulate the SCF complex makes it a potential therapeutic agent for cancer treatment. Genistein, an isoflavone found in soy products, can down-regulate Skp2 expression and has been demonstrated to apoptosis induction in cancer cells [66].

Targeting the SCF complex represents a promising therapeutic strategy for various diseases, particularly cancer. Approaches such as small molecule inhibitors, PROTACs, genetic manipulation, and natural compounds offer diverse mechanisms to modulate the activity of the SCF complex. The ongoing research and clinical trials are crucial to further understand the therapeutic potential and optimize these strategies for clinical use [67,68].

POTENTIAL FOR COMBINATION THERAPIES

Combination with chemotherapy

Combining SCF complex inhibitors with traditional chemotherapeutic agents can enhance cell cycle arrest and apoptosis [70,74]. For example, MLN4924 (Pevonedistat), an inhibitor of NEDD8-activating enzyme, can be combined with DNA-damaging agents such as doxorubicin or cisplatin [5,75]. This combination can lead to increased accumulation of SCF substrates such as p27^Kip1 and Wee1, enhancing the cytotoxic effects of chemotherapy by promoting cell cycle arrest and apoptosis. The combination of SCF^Skp2 inhibitors with chemotherapeutic drugs can induce synergistic apoptosis in cancer cells. Skp2 inhibitors stabilize pro-apoptotic proteins and enhance the cancer cell sensitivity to chemotherapeutic agents, leading to increased cell death [76,77].

Combination with targeted therapy

Targeting the SCF complex can complement the effects of kinase inhibitors. For instance, combining SCF^FBXW7 modulators with inhibitors of oncogenic kinases (e.g., EGFR, HER2, or BRAF inhibitors) can be effective. FBXW7 targets several oncogenic proteins, including Myc and cyclin E. Inhibiting FBXW7 in combination with kinase inhibitors can reduce the degradation of these proteins, enhancing the therapeutic effects of kinase inhibition [78,79]. Combining SCF complex inhibitors with agents that target the other signaling pathways such as the PI3K/AKT/mTOR pathway, can result in synergistic anti-cancer effects. For example, SCF^β-TrCP inhibitors can be combined with mTOR inhibitors to simultaneously disrupt protein degradation and nutrient signaling pathways, leading to enhanced cancer cell death [80,81].

Combination with immunotherapy

The SCF complex can influence immune evasion mechanisms in cancer cells. Combining SCF complex inhibitors with the immune checkpoint inhibitors – anti-PD1 or anti-CTLA4 antibodies that can enhance anti-tumor immune responses. By stabilizing proteins that promote apoptosis and inhibit immune evasion, SCF complex inhibitors can make the cancer cells more susceptible to immune-mediated destruction [82,83]. Targeting the SCF complex also modulates the immune cell function in the TME. For instance, SCF^β-TrCP inhibitors can affect NF-Kb signaling in the immune cells, potentially that enhances the antitumor activity of immune cells when combined with immunotherapy [84,85].

Combination with radiotherapy

The SCF complex plays a role in DNA damage response and repair. Inhibiting SCF components can impair the repair of DNA damage induced by radiation therapy. For example, combining SCF^Skp2

inhibitors with radiotherapy can lead to increased DNA damage, reduced repair capacity, and enhanced radiosensitivity of cancer cells [86-88]. Inhibitors of SCF^FBXW7 can be combined with radiotherapy to prevent the degradation of proteins involved in DNA damage repair [89,90]. This combination can enhance the cytotoxic effects of radiation by preventing cancer cells from repairing radiation-induced DNA damage. Combining SCF complex inhibitors with other therapeutic modalities offers a promising route that enhances the efficacy of cancer therapy. By targeting the multiple pathways and mechanisms involved in cancer progression, combination therapies can potentially overcome the resistance and improve clinical outcomes. Ongoing clinical trials are crucial to optimize these strategies and learn the interactions between SCF complex inhibition and other treatments [91].

CLINICAL IMPLICATIONS AND THERAPEUTIC POTENTIAL

Cancer cells often develop resistance to standard therapies through metabolic adaptations and stabilization of oncogenic proteins. Targeting the SCF complex can disrupt these adaptations, sensitizing cancer cells to conventional treatments and overcoming drug resistance. Biomarkers of SCF complex activity help the patients that are likely to show response to SCF-targeted therapies [92]. Personalized treatment regimens based on SCF complex dysregulation can improve clinical outcomes and reduce adverse effects. Since the SCF complex regulates fundamental processes in various cancer types, targeting it has broad therapeutic potential. This approach can be applied to multiple malignancies, including those with little prognosis and limited treatment options [93,94].

FUTURE PERSPECTIVES

Future research should focus on the development of more advanced and selective SCF complex inhibitors. The design of next-generation PROTACs that can target a broader range of SCF complex components and substrates with high specificity will be crucial. These targeted therapies could reduce off-target effects and improve clinical outcomes. Identifying biomarkers of SCF complex activity will be essential for selecting the patients who are likely to be benefited from SCF-targeted therapies [95]. Biomarkers could include specific mutations, expression levels of SCF complex components, or the stability of SCF-regulated proteins. Personalized treatment regimens based on these biomarkers could enhance therapeutic efficacy and minimize adverse effects. Further mechanisms are required to completely know the diverse roles of the SCF complex in cancer metabolism and progression [96]. Investigating the interplay between the SCF complex and other metabolic regulators, signaling pathways, and the TME will provide deeper insights into its functions and therapeutic potential. Conducting well-designed clinical trials for the evaluation of the safety and efficacy of SCF complex inhibitors in various types of cancer is imperative. These clinical trials should explore the effects of SCF complex inhibitors as both monotherapies and in combination with other treatments. Long-term studies will be necessary to further access the responses durability and potential resistance mechanisms. Research should also focus on understanding and overcoming resistance mechanisms to SCF complex-targeted therapies. Investigating how cancer cells adapt to the inhibition of the SCF complex and identifying combination strategies that can prevent or overcome resistance will be critical for improving treatment outcomes [97,98].

CONCLUSION

The SCF complex regulates the activity and stability of numerous proteins that are essential for metabolic processes in cancer cells. This comprises the degradation of key metabolic enzymes and signaling proteins, ensuring that the cancer cells can adapt their metabolic process to reach the demands of rapid growth and survival in diverse and often hostile environments. Various strategies have been developed to target the SCF complex in cancer therapy. Small molecule inhibitors like MLN4924 and Skp2 inhibitors have shown a promise in the pre-clinical and clinical studies. PROTACs offer a novel approach to selectively degrade SCF complex components or substrates, while genetic approaches such as RNAi and CRISPR/Cas9 provide precise methods to down-regulate or knockout SCF complex genes.

Combining SCF complex inhibitors with other treatment modalities, such as chemotherapy, targeted therapy, and immunotherapy, has the potential to enhance therapeutic efficacy. These combinations can disrupt multiple pathways involved in cancer progression, sensitize cancer cells to treatment, and overcome drug resistance.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

The authors declare no conflict of interest.

AVAILABILITY OF DATA AND MATERIAL

All data generated during this study/systematic review is included in this published article since this data only includes information acquired from published studies (see references).

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AUTHOR CONTRIBUTION

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