SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 15: 8891-8900, 2018

F-box proteins involved in cancer-associated drug resistance (Review)

JIAN GONG, YUQIAN ZHOU, DELIANG LIU and JIRONG HUO

Department of Gastroenterology, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, P.R. China

Received July 11, 2017; Accepted January 24, 2018

DOI: 10.3892/ol.2018.8500

Abstract. The ubiquitin proteasome system (UPS) regulated human biological processes through the appropriate and efficient proteolysis of cellular proteins. F-box proteins are the vital components of SKP1-CUL1-FBP (SCF)-type E3 ubiquitin ligases that determine substrate specificity. As F-box proteins have the ability to control the degradation of several crucial protein targets associated with drug resistance, the dysregulation of these proteins may lead to induction of chemoresistance in cancer cells. Chemotherapy is one of the most conventional therapeutic approaches of treatment of patients with cancer. However, its exclusive application in clinical settings is restricted due to the development of chemoresistance, which typically results treatment failure. Therefore, overcoming drug resistance is considered as one of the most critical issues that researchers and clinician associated with oncology face. The present review serves to provide a comprehensive overview of F-box proteins and their possible targets as well as their correlation with the chemoresistance and chemosensitization of cancer cells. The article also presents an integrated representation of the complex regulatory mechanisms responsible for chemoresistance, which may lay the foundation to explore sensible candidate drugs for therapeutic intervention.

Contents

Correspondence to: Professor Jirong Huo, Department of Gastroenterology, The Second Xiangya Hospital, Central South University, 139 Middle Renmin Road, Changsha, Hunan 410011, P.R. China
E-mail: jironghuo@csu.edu.cn

Key words: F-box protein, chemoresistance, cancer, SKP2, FBXW7

1. Introduction

Cancer is a multifactorial disease and is considered as a major public health issue in both developing and developed countries (1). Due to the recent improvements in medical tools and techniques cancer death rates seem to be declining, at least for some types of cancer. However, if the bigger picture is to be considered, cancer incidence and mortality rates are still very high. Furthermore, the increased adoption of unhealthy lifestyle behaviors, such as smoking, alcohol abuse, poor diet and physical inactivity, further enhance the risk of cancer occurrence. Hence, the medical burden of cancer is increasing at a significant rate, particularly in the less economically developed countries. According to latest statistics, an estimated 14.1 million new cancer incidences and 8.2 million deaths from across the world were reported in 2012 (1).

As far as treatment and management of cancer is concerned, application of chemotherapy is quite customary. Cisplatin (DDP), which essentially functions by damaging the Deoxyribonucleic acid (DNA) of cancerous cells, had been widely used for many years in clinical settings and has shown satisfactory results. To date, cisplatin-based multidrug chemotherapy regimens remain a standard treatment method for many cancers. In the meantime, other chemotherapeutic drugs, like doxorubicin, paclitaxel, irinotecan (CPT), oxaliplatin, vincristine, hydroxyurea, rapamycin, have emerged as potential anticancer agents. In the recent years, targeted drugs such as cetuximab, trastuzumab, panitumumab and imatinib have also been identified as candidate drugs for the treatment of diverse types of cancers. However, it is noteworthy that the application of many such chemotherapeutic agents in clinical settings is limited, especially due to the development of drug resistance against them. Such conditions often lead to treatment failure and local recurrence of the disease. Considering the severity of the implications, chemoresistance in cancer has received a lot of attention by researchers and medical experts. It is not surprising that the study of chemoresistance is now considered as important as new anticancer drug development.

Drug resistance can be classified into two main categories: intrinsic and acquired (2,3). To devise methods and drugs that can overcome the effects of drug resistance, researchers have been focusing on elucidating the molecular mechanisms underlying the development of drug resistance which can further help in elucidating chemoresistance-related mechanisms and

devising methods of preventing it. The various mechanisms that were found to contribute toward the development of chemoresistance are described in Fig. 1. It is evident that factors, such as energy-dependent transporters (4), enhanced deoxyribonucleic acid repair abilities (4), drug-detoxification mechanisms (5), epithelial-mesenchymal transition (6), apoptosis evasion (7-9), cancer stem cells (CSCs) (10) as well as microRNAs (11,12), play a major role in inducing chemoresistance. However, the exact mechanisms that link these factors for bringing about resistance are yet to be elucidated. Almost all current studies on the mechanisms of chemoresistance in cancer are still in infant stage. Therefore, overcoming chemoresistance may possibly open new avenues for better treatment outcome in cancer patients (13).

2. The ubiquitin-proteasome system

Protein degradation plays a key role in maintaining cellular homeostasis. It has already been established that ubiquitin-proteasome system is crucial for protein degradation (14). It is also known to be involved in various physiological responses, like cell cycle control, DNA replication, transcription and cell signaling (15,16). Ubiquitin (Ub) is a small protein which remains covalently conjugated to lysine residues (17). Furthermore, ubiquitination and deubiquitination are complex reactions whose cellular roles are considered analogous to phosphorylation (18). The degradation of proteins by the UPS is a multi-step enzymatic process (Fig. 2) (19) that includes ubiquitin-activating enzyme (E1), ubiquitin conjugating enzyme (E2) and ubiquitin-protein ligase (E3). Human genes encode over 600 E3 ligases that participate in the ubiquitylation of their individual targets (20). The SCF complex (21,22), which consists of four principal components: Skp1, Cul1/Cdc53, Roc1/Rbx1/Hrt1 and a F-box protein, is one of the major categories of E3 ligases. UPS regulates an array of biological processes, including tumor progression and chemoresistance. Evidently, its defective functioning is often manifested in human beings as diseases. Ubiquitination/deubiquitination is closely related to the occurrence of a wide variety of tumors.

3. F-box proteins

F-box protein has the protein-protein interaction site that determines the substrate specificity of SCF complex (23,24). It has been identified that there are 69 FBPs in the human genome. They are known to contribute to cancers since they can recognize individual targets (25). The recognizable domains beyond the F-box domain can be organized into three categories viz. WD 40 repeats (FBXW), leucine-rich repeats (FBXL) and other diverse or unknown domain-containing proteins (FBXO) (10). Then again, there are 10 members of FBXW in the human genome. FBXW1 (or β-TrCP) and FBXW7 (Cdc4) are well known FBXW. In addition, the FBXL subfamily has 21 members. FBXL1 (also known as SKP2) is a typical FBXL family protein. As far as FBXO are concerned, 38 members have been identified till yet. It is important to note that FXBO has no common substrate recognition motif. A given F-box protein can recognize more than one substrate (e.g. Skp2 targets FOXO1, RASSF1, ATF4). Similarly, one substrate can be targeted by many F-box proteins (e.g. cyclin D1 can be targeted by FBXW8 or FBXO31).

4. F-box proteins and chemoresistance

Aberrant activation of FBPs has been extensively reported in numerous cancer types, particularly in digestive system tumors (26,27). Out of the 69 FBPs, notably, only a few have been studied extensively. It has also been established that FBPs can recognize and degrade a number of oncoproteins and tumor suppressor proteins, such as p27, c-Myc and cyclin D1, including key regulators of cell death and DNA damage response. The overexpressed or downregulated FBPs can further contribute to the dysregulation of their target proteins. Therefore, the possible roles of FBPs in inducing drug resistance are just beginning to emerge. In the next section, we will discuss the recent research advances pertaining to the role of FBPs in chemoresistance and how the same can be used for directing drug discovery.

FBXW7. FBXW7, a well-established FBXW subfamily protein, was first identified in budding yeasts in the year 1973 (28). FBXW7 gene resides on human beings chromosome 4 (4q31.3) which has already been identified as a key player in the occurrence of many forms of cancers. FBXW7 mutation has been observed in 6% primary human tumors (29). Mutations in FBXW7 lead to the rapid accumulation of degradable proteins, which in turn facilitates tumor progression (30). It is therefore obvious that FBXW7 plays crucial tumor suppressor functions in many tumors. FBXW7 primarily exerts its antitumor functions by regulating the degradation of an entire network of proteins, including cyclin E (31), c-Myc (32), c-Jun (33), Notch (33), presenilin (34), (myeloid cell leukemia-1) Mcl-1 (35), many of which have oncogenic functions. Mutated FBXW7 is also known to mediate the stabilization of oncoproteins in tumors and thus causes induction of chemoresistance (36,37). Therefore, the downregulation of FBXW7 protein levels may contribute to the tumor progression and chemoresistance.

FBXW7 and chemoresistance. FBXW7 has already been categorized as a chemoresistance-related gene. Mounting evidences show that FBXW7 genetic status has an intricate relationship with chemotherapeutic drug resistance in cancer patients. Therefore, FBXW7 is proposed as a promising therapeutic target to improve sensitivity and efficacy of chemotherapeutic drugs. Wertz *et al* (37) have already reported that loss of FBXW7 led to increased resistance of colon cancer cells towards taxol. On the other hand, inhibition of Mcl-1 was found to restore the cancer cells' sensitivity toward taxol- and vincristine-induced cell death. Mcl-1, a key pro-survival BCL2 family member, is known to be involved in mitotic arrest. This further indicates that there exists a molecular link that forms the basis of antitubulin agent resistance and chemotherapy induced polyploidy. Hence, Mcl-1 degradation can be implied for the development of targeted therapeutic methods intended towards the eradication of colon cancer cells (38). Detailed analysis has shown that FBXW7 mutations in colorectal cancer cells are responsible for blocking Mcl-1 degradation and thus mediating the development of resistance of against targeted therapies (regorafenib) (39). In consistent

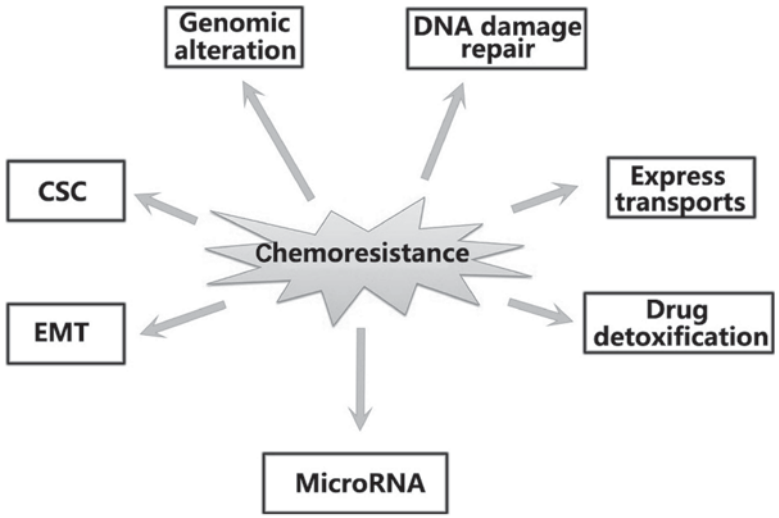

Figure 1. Illustrated presentation of the seven mechanisms related to chemoresistance in cancer. CSC, cancer stem cell; EMT, epithelial-mesenchymal transition

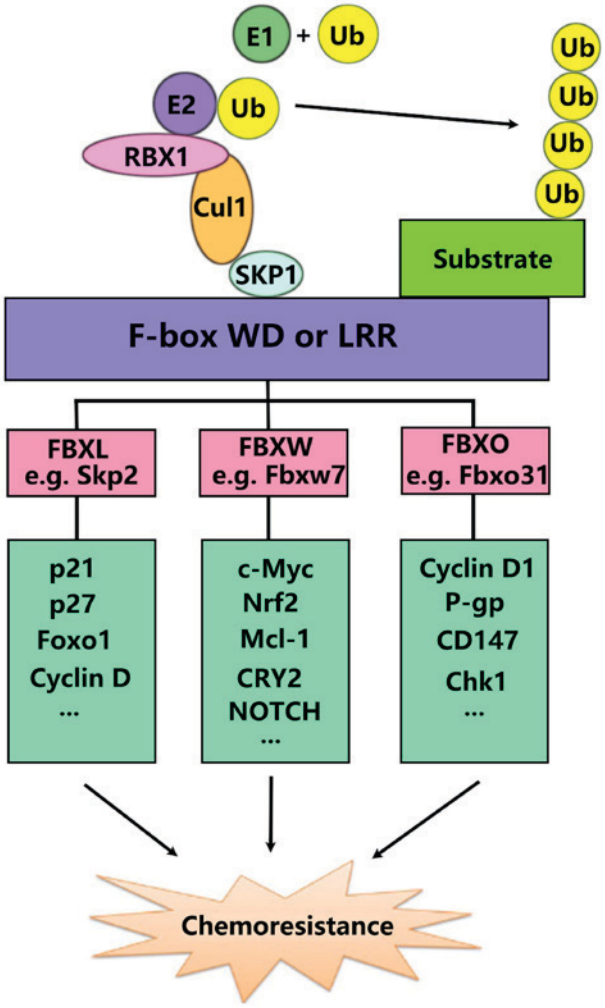

Figure 2. Illustration of ubiquitination cascade reactions, representative F-box protein and its major downstream targets involved in chemoresistance. E1 and E2 firstly activate and then transfer ubiquitin to the substrate at the help of E3. Ubiquitinated proteins can be recognized and degraded by the 26S proteasome. F-box protein in E3 determines the specificity of the target proteins in this process. SKP2 is the most profound one of FBXL family, the main targets of this family protein are p27, p21, Foxo1 and cyclin D1. FBXW7 is the representative of FBXW family, the main targets of this family protein are Nrf2, Mcl-1, CRY2 and NOTCH. FBXO31 is one member of FBXO family, the main targets of this family protein are P-gp, CD147 and Chk1.

with the results observed in colon cancer cell lines, FBXW7 ablation in ovarian cancer cells was also found to inhibit c-Myc degradation. This makes the cells more resistant to vincristine-induced cell death. The above mentioned research

studies on the one hand showcased the key roles of FBXW7 in inducing therapeutic effects of the chemotherapeutic drugs, while on the other hand, they also provided the much needed information for identifying the possible ways to increase the sensitivity of cancer cells to vincristine. Inuzuka *et al* (35) also found that E3 ubiquitin ligase SCF (FBXW7) plays key regulatory roles in cellular apoptosis by targeting Mcl-1 for ubiquitylation in a manner which depends on phosphorylation by glycogen synthase kinase 3. Notably, loss of FBXW7 and the resultant subsequent higher levels of Mcl-1 were found to increase the sensitivity of cancer cells to the targeted therapy drug sorafenib. However, it was observed that these cells acquired resistance to the Bcl-2 family inhibitor ABT-737 in T-acute lymphoblastic leukaemia (T-ALL) cells.

In addition, multidrug resistance-associated protein (MRP) is also found to be closely related to FBXW7 in nasopharyngeal carcinoma (NPC) cells. MRP makes FBXW7-deficient cells more resistant against antitumor drug DDP. Conversely, upregulation of FBXW7 expression restores CDDP chemosensitivity in these cells (40). Cryptochrome 2 (CRY2), a circadian clock protein, is another such protein which is overexpressed in chemoresistant colorectal cancer cells (40). Fang *et al* (41) proved that CRY2 is one of the direct targets of FBXW7 in DLD-1 and SW480-colorectal cancer cell lines too. Furthermore, cells with low levels of expression of CRY2 were found to be more sensitive to oxaliplatin. It has also been proved that FBXW7 mutation in T cell acute lymphoblastic leukemia (T-ALL) causes stabilization of c-Myc, which is the Notch-1 target. Due to these reasons these cells were found to be more resistant to γ-secretase inhibitor treatment (42). The findings of the study conducted by O'Neil *et al* (43) in 2007 were also found to be in agreement with the report of Thompson *et al* (42), which indicated that FBXW7 ablation increased resistance to γ-secretase inhibitors in leukemic cells via Notch pathway activation. Both the studies indicated that patients harboring FBXW7 mutation were more resistant to treatment with GSI. It can thus be concluded that FBXW7 inactivation had relationship with chemotherapeutic drugs by its diverse targets. Although many chemoresistance targets of FBXW7 have been identified in different types of cancer cells, it still remains enigmatic that which one is the most relevant.

A more recent study showed that inhibitor of growth 5 (ING5)-mediated chemoresistance is also positively associated with FBXW7 hypoexpression (44). It was found that ING5 overexpression increased U87 cells' chemosensitivity towards cisplatin, MG132, paclitaxel and suberoylanilide hydroxamic acid (SAHA). Further studies indicated that ING5-associated chemoresistance may be the result of dysfunction of Akt and NF-κB pathways. Furthermore, epithelial-mesenchymal transition (EMT) is one of the main factors responsible for the induction of chemoresistance. Notably, FBXW7 is known to play a central role in controlling the EMT in cancer cells (45). Reduced expression of FBXW7 is proposed to reduce the polarity and adherent junctions of cells, promote tumor cell invasion and migration, thus resulting in reduced chemosensitivity of non-small-cell lung cancer cells towards cisplatin (45).

Cancer stem cells (CSC) are another facet of the molecular mechanism of chemoresistance. It has been observed that destruction of the CSCs can be an effective strategy for improving chemotherapeutic effects of anticancer agents. Some highly intricate multidimensional studies indicated that FBXW7 also plays a crucial role in the maintenance of both normal stem cells and cancer-initiating cells (CICs) (46). Evidently, FBXW7-deficient leukemia-initiating cells (LICs) were more found to be resistant against conventional chemotherapy, but sensitive to imatinib. Studies conducted in cancer mouse models revealed that combining FBXW7 genetic ablation and imatinib is more effective than any of these strategies applied alone (47). When all these aspects are considered together, it becomes apparent that FBXW7 plays prominent role in the induction of chemoresistance in cancer cells.

Despite the innumerable number of studies conducted on FBXW7, little is known about the regulatory mechanisms that control the molecular pathways leading up to FBXW7 induced chemoresistance. As far as the possibility and scope of applicability of FBXW7 in devising therapeutic strategies against cancer is concerned, it has been observed that tumor suppressor gene p53 directly targets FBXW7 and promotes the transcription of FBXW7 mRNA (48). Recently, upstream regulators like EBV Nuclear Antigen (EBNA1)-binding protein 2 (Ebp2) (49), CCAAT/enhancer-binding protein-δ (C/EBPδ) (50), microRNA (miRNA)-27a (51) were identified. It has thus been proposed that all these referred proteins or miRNAs can be candidate targets that can be implicated to increase drug sensitivity, particularly by targeting FBXW7. Increasing number of research studies are indicating that miRNAs have regulatory roles in the process of tumor progression that are particularly attributed to chemoresistance or radioresistance. In addition, it has also been elucidated that FBXW7 is directly regulated by the dysregulation of microRNA pathway. MicroRNAs, such as miR-25 and miR-223, play essential role in regulating FBXW7, particularly by reducing their mRNA levels (52). miR-223 is an oncogenic microRNA and highly expressed in human erythroleukemic cell line K562 (52). miR-223/FBXW7 pathway received increased attention, especially after the discovery of the possible implications of miR-223/FBXW7 as an efficient therapeutic target for overcoming chemoresistance. In the past three years alone, three separate research studies have independently identified miR-223/FBXW7 as a key signal pathway involved in chemoresistance. The study conducted by Zhou *et al* (53) showed that miR-223 could promote DDP resistance in gastric cancer cells by downregulating FBXW7. Notably, low expression of FBXW7 contributed to cell cycle arrest and apoptosis. In support of this notion, miR-223 inhibitor can significantly upregulate the expression of FBXW7 mRNA and protein in 7901/DDP cells (gastric cancer cell line). Conversely, miR-223 mimic can downregulate the expression of FBXW7 mRNA and protein. Further analysis of the same indicated that the overexpression of miR-223 induced significant increase of the expression and activity of cyclin E, while reduced miR-223 expression led to increased FBXW7 expression and decreased cyclin E activity. Yet, another study that was conducted by Li *et al* (54) demonstrated that miR-223/FBXW7 axis regulates doxorubicin sensitivity through epithelial mesenchymal transition in non-small cell lung cancer. miR-223/FBXW7 pathway has also been investigated for drug resistance in cancers (38,55-57). FBXW7 mutation drives acquired resistance to targeted agents cetuximab or panitumumab (58).

Eto *et al* (59) were the first to report that the overexpression of miR-223 decreases FBXW7 expression and the sensitivity of gastric cancer cells to trastuzumab. These studies provided important insights into the possibility of application of miR-223/FBXW7 as a biomarker that can be used to estimate the efficacy of DDP-based chemotherapy. However, in order to do so it is imperative that the upstream stimuli and downstream targets of the above-mentioned pathway are studied in detail. As of now, it is said that almost all of the relevant studies indicate that FBXW7 is a chemosensitizer in cancer cells, which when lost enhances the risk of chemoresistance.

SKP2. In 1995, the Beach group discovered that S phase kinase associated protein 2 (SKP2) gene is located on the 5p13 chromosome (60). Since then, numerous studies have highlighted it's oncogenic roles (61-64). Furthermore, the overexpression of SKP2 has been reported in many tumor types (65-69). These results are a clear indication that SKP2 has significant impact on the progression of tumors and also induction of drug resistance in different types of cancer cells.

SCF SKP2 is a multicomponent RING-type E3 ligase that targets and degrades many tumor suppressor proteins, such as p27, p16, p21, p57, E2F-1, TOB1, RBL2, cyclin D/E, BRCA2, FOXO1 and RASSF1A, and regulates numerous cellular processes. As cell cycle regulation is a key mechanism by which most chemotherapy agents exert their cytotoxic effect, their alterations are likely to have major implications in the drug induced responses (70). When collectively studied, these studies clearly indicated that SKP2 is an oncoprotein and also the chief regulator of cell cycle inhibitor $p27^{Kip1}$, which is known as a cell cycle protein that is involved in tumor progression. It was thus proposed that SKP2 may also be associated with chemoresistance (71). The present article reviewed the available information regarding the possible roles of SKP2 towards the induction of chemoresistance. The authors hope and desire that the information presented in here is implicated towards achieving a better treatment outcome for the chemoresistant subset of human cancer patients.

SKP2 involved in chemoresistance. SKP2 supposedly interacts with a variety of substrates that determine the outcome of chemoresistance in cancer cells. SKP2 is known to act as an oncoprotein that also has close correlations with paclitaxel sensitivity, which is especially brought about in human lung cancer cells by regulating Mad2 via p27-CDKs-E2F1 signaling axis (72). Patients with high levels of expression of SKP2 show that small molecule inhibitors of SKP2 combine paclitaxel and bring about better lung cancer treatment responses (72). High levels of expression of SKP2 is a recognized biomarker for poor prognosis in cancer. Davidovich *et al* revealed that high levels of SKP2 are known to have poor response towards preoperative doxorubicin-based chemotherapy in breast cancer patients in 2008 (73). Furthermore, SKP2 expression not only contributes to drug resistance but also extrinsic induction of apoptosis. It has also been shown that high levels of expression of SKP2 in pancreatic ductal adenocarcinoma cell lines makes them resistant towards the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (74). Hence, SKP2 expression levels can be considered as a key determinant of antitumor responses to mTOR inhibitors. In addition, overexpression of SKP2 also increases cellular resistance to rapamycin (75). Furthermore, SKP2 determines sensitivity of tumor xenograft to rapamycin, which highlights it as a potential pharmacogenomic marker that can predict therapeutic sensitivity of the cells towards rapamycin.

Study of SKP2 in relation to target therapy indicated that SKP2 deficiency enhances herceptin sensitivity in Her2-positive cancer cells and tumors (76). Except for FBXW7, SKP2 is yet another F-box family protein that forms the SKP2 SCF complex, which functions for the regulation of stem cells. Hematopoietic stem cells, that are the most critical factors in prevention of bone marrow failure in humans, are also regulated by SKP2.

It has also been studied that SKP2 deficiency leads to elevated cyclin D1 expression levels, which in turn contribute to increase hematopoietic stem cell cycling. Doing so enhances sensitivity of leukemia cells towards other chemotherapeutic agents, such as cyclophosphamide, 5-FU, and DOX (77). All the above described data highlight the central role of SKP2 in chemoresistance. It is also proposed that SKP2 may be used as a biomarker to identify those patients who are likely to respond to doxorubicin in a more effective manner.

5. Other F-box proteins involved in chemoresistance

β-TrCP. β-TrCP (FBXW1), β-transducin repeats-containing proteins, is a representative of the FBXW family. IκBα and β-catenin are two well-characterized substrates of β-TrCP, thus β-TrCP is linked closely to tumorigenesis and development (78). IκB is the inhibitor of NF-κB, which always functions as a tumor suppressor. β-catenin is a downstream molecule of Wnt signaling pathways. Notably, βTrCP acts as an oncoprotein in colorectal cancer, but it is known to act as a suppressor in gastric cancer. The simultaneous elevation of NF-κB activity with elevated β-TRCP1 expression indicate that it can be considered as a contributor to chemoresistance towards anticancer drug etoposide in pancreatic carcinoma cells (79). Furthermore, cyclin D1 overexpression is also related to chemoresistance in cancer cells.

Berberine (BER) is a traditional Chinese drug, which is essentially an isoquinoline alkaloid purified from the Berberis species. It has been reported that the drug possesses multiple functions including enhancing chemotherapy sensitivity in cancer (80). Berberine functions by inhibiting cyclin D1 expression in human hepatoma cells HepG2 and MHCC97L via the ubiquitin-proteasome signal pathway. Berberine promotes the phosphorylation of cyclin D1 at the T286 site and then accelerates binding of β-TrCP to cyclin D1 thus mediating its degradation. It was thus apparent that knockdown of β-TrCP expression could reduce this phenomenon (81). On the other hand, Nrf2 is a newly identified substrate of β-TrCP (82). Nrf2 is controlled by two distinct β-TrCP recognition motifs in its Neh6 domain, one of which can be modulated by GSK-3 activity (83). Furthermore, overexpression of Nrf2, nuclear factor (erytheroid-derived-2)-like 2, increases resistance to the chemotherapeutic drug in breast cancer, acute myeloid leukemia and pancreatic cancer (84-86). However, the molecular mechanism between them remains further elucidated.

In multiple myeloma cell lines, DEP-domain containing mTOR-interacting protein (DEPTOR), another endogenous

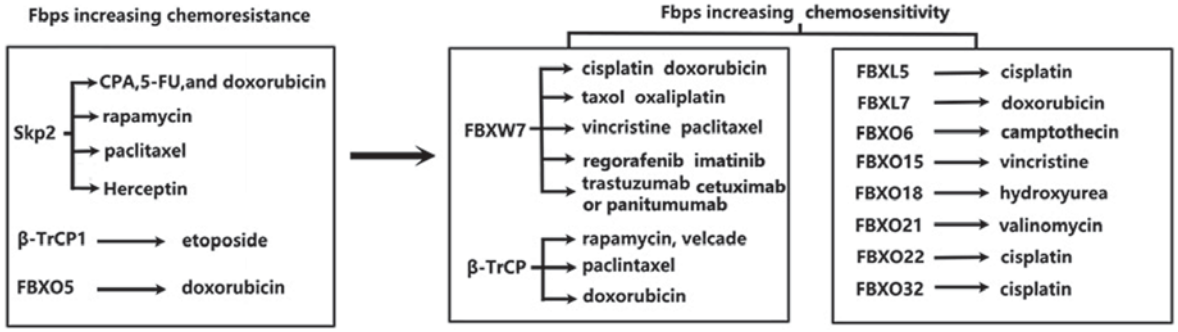

Figure 3. Schematic representation of Fbps involved in cancer chemoresistance. Fbps conferring chemoresistance such as CPA, 5FU and doxorubicin are shown in the left box, and Fbps responsible for enhancing drug response such as paclitaxel, CPT, oxaliplatin, vincristine, hydroxyurea, trastuzumab, imatinib are shown in the right two boxes.

mTOR inhibitor, is inversely correlated with cell's responsiveness to anticancer drugs, such as rapamycin, velcade, paclintaxel, via modifying the mTOR pathway. The degradation of DEPTOR is mainly controlled by β-TrCP, which gives us a clue that the dysregulation of β-TrCP directly affects the response of patients to chemotherapeutic agents (86). Sp1, specificity protein 1, is another agent enhances temozolomide resistance in glioblastoma (87). Doxorubixin stimulus causes the high expression of β-TrCP in breast cancer cell line MCF-7, which promoted Sp1 degradation. Therefore, upregulation of β-TrCP is likely to increase doxorubicin-induced cell apoptosis (88). The role of β-TrCP in determining chemoresistance is mainly through its diverse substrates which are involved cell death.

FBXL5 and FBXL7. FBXL5, a critical regulator of iron homeostasis, also plays crucial roles in cancer. Although little is known about its role in chemoresistance, Wu *et al* (89) explored the effects of expression of FBXL5 on anticancer drug sensitivity. In contrast, Rho GTPase dissociate inhibitors 2 (RhoGDI2), is known to be associated with cisplatin resistance, which is mainly infuenced by upregulation of Bcl-2 expression and reduction of cell apoptosis in gastric cancer cells (90). It has also been observed that Cho group use immunoprecipitation assay is highly efficient in elucidating the interaction between FBXL5 and RhoGDI2. The exogenous overexpression of FBXL5 increases the sensitivity of cisplatin through Erk and p38 pathway in RhoGDI2 high-expressed gastric cancer cells (88). Furthermore, single nucleotide polymorphisms (SNPs) in the FBXL7 gene are also associated with the increased breast cancer risk (91). This can be correlated with the fact that FBXL7 has been shown to induce the ubiquitylation of Aurora kinase A (92) and survivin (93) in a cell cycle-independent manner. Notably, Kamran *et al* (94) found that overexpression of Aurora kinase A negatively regulated FBXL7, leading to anti-apoptotic protein survivin accumulation and doxorubicin resistance in gastric cancer.

FBXO5, FBXO6, FBXO15, FBXO18, FBXO21, FBXO22 and FBXO32. Overexpression of FBXO5 is frequently considered as a potential oncogenic factor (95,96). Shimizu *et al* used small interfering RNA knockdown method to further explore the mechanism of doxorubicin resistance on FBXO5 accumulation. The results thus obtained indicated that the downregulation of FBXO5 enhanced the induction of apoptosis by doxorubicin, but not taxol. However, no synergistic effect of FBXO5 knockdown in combination with doxorubicin treatment was found in normal cells. Therefore, inhibition of FBXO5 function can be considered useful for enhancing sensitivity of cancer cells to chemotherapeutic drugs and ionizing radiations (97).

FBXO6 has been suggested as a potential biomarker for predicting anticancer drugs responsiveness. Checkpoint kinase 1 (Chk1), one of key components of the replication checkpoint response to DNA damage response, which was found to be inversely correlated with FBXO6 in human breast tumor tissues. Zhang *et al* (98) proposed that FBXO6 promotes the degradation of Chk1 and a defect in this mechanism may be responsible for increasing tumor cell resistance to certain anticancer drugs CPT. It was further suggested that the forced expression of FBXO6, but not Skp2, in the CPT-resistant cells promotes the degradation of endogenous levels of Chk1. Such cells exhibited strong staining for the caspase-3 cleavage product after CPT treatment. In contrast, depletion of FBXO6 decreased the CPT sensitivity in lung cancer cell line A549, which was completely restored by depletion of Chk1.

P-glycoprotein (P-gp), a multidrug resistance transporter that effluxes chemotherapeutic drugs, is a major cause of chemotherapy failure. FBXO15 knockdown causing P-gp accumulation enhanced vincristine resistance (99). CD44 can increase P-gp protein stability and promote drug resistance. Ravindranath *et al* (100) reported the mechanism between them. CD44 can protect P-gp from FBXO21 mediated degradation, thus leading to inducing resistance against valinomycin. In addition, CD147 and type I transmembrane glycoprotein have positive regulatory effects on P-gp expression. FBXO22 mediates the polyubiquitination and degradation of CD147, thus involving drug resistance. Low level of FBXO22 contributes to the accumulation of CD147, thereby inducing cisplatin resistance in non-small-cell lung carcinoma cell line A549/DDP cells (101).

FBXO32 is also well recognized since its upregulation during skeletal muscle atrophy (102), which is known to negatively regulate epithelial to mesenchymal transition in platinum resistant-urothelial carcinoma cells (103). Furthermore, FBXO32 enhances chemosensitivity to cisplatin by inducing

apoptosis in ovarian cancer cells (104). Although many FBXO family proteins involved in chemoresistance, for example, FBXO15 and FBXO21, can regulate P-gp ubiquitination, the question that remains is that 'which one of them is the most prominent determiner of chemoresistance?' Hence, further investigation that are intended towards accurate determination of the possible roles of FBPs in chemoresistance are warranted.

6. Conclusions and perspectives

The present article presents an unprecedented immaculate review of multiple facets of dysregulated expression of FBPs in human cancer cells, their possible roles in regulation of substrate turnover, their possible implications in inducing chemoresistance against anticancer drugs, such as cisplatin, doxorubicin, paclitaxel, CPT, oxaliplatin, vincristine, hydroxyurea, rapamycin, trastuzumab and imatinib (Fig. 3). Analyses of the results of multiple number of studies indicated that reconstitution of the function of FBPs could restore the sensitivity of tumor cells to the given chemotherapeutic agents. Organoids models have been used for testing FBXW7-associated drug response (105). FBXO31, which is considered as a potential tumor suppressor protein in both liver cancer and gastric cancer (106,107), is known to induce DNA damage and promote cyclin D1 degradation. Contrary to the results obtained from studies conducted on liver cancer and gastric cancer, FBXO31 in esophageal cancer is known to be overexpressed (100). Notably, studies conducted in our laboratory have demonstrated that FBXO31 is tightly correlated with incurring drug resistance in esophageal cancer. The data generated by us have showed that high expression of FBXO31 in esophageal cancer cell lines promotes cisplatin resistance through MAPK signal pathway (108). Therefore, FBPs can be considered as possible targets for reversing the occurrence and effects of chemoresistance. It is expected that these findings may contribute to study of chemoresistance in individualized cancer treatment methods. Although some progress has been made, further investigations are urgently warranted.

Notably, until now, no compounds that can directly target FBPs have been reported. Among the 69 FBPs that have been identified, most studies centered on FBXW7, SKP2 and β-TrCP. Bortezomib is a proteasome inhibitor which has been approved by the FDA and successfully used in the treatment of hematologic malignancies (109,110). It is proposed that it can be used to design the disease-specific components of UPS inhibitors. FBPs, such as the ones described in the preceding sections, are beginning to show therapeutic potential in the field of chemosensitivity. However, there are still many important questions that need to be addressed in future studies. For example, many FBPs have opposite functions in different cancer types. FBXO31 acts as a tumor suppressor in breast cancer or gastric cancer, but have oncogenic activity in esophageal cancer. Owing to the vast diversity of the substrates it interacts with, it is not uncommon that FBPs have multiple implications in cancer drug resistance. Although many of these substrates have been identified, the ones that are specifically related to drug resistance are yet to be elucidated. Furthermore, such diversity of substrates also raises questions on whether a given F-box protein can exert both chemoresistant and chemosensitive roles in the same tissue? Despite extensive studies, our understanding on the impact of FBPs in drug resistance is still limited. It is therefore recommended that in-depth investigation on this must be conducted so that critical players that are involved in mediating drug resistance can be identified.

Acknowledgements

JG, YQZ, DLL and JRH are grateful for the Fundamental Research Funds from the Science And Technology Plan Of Hunan Province (grant no. 2013SK3033).

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
2. Huang Z, Huang Y, He H and Ni J: Podocalyxin promotes cisplatin chemoresistance in osteosarcoma cells through phosphatidylinositide 3-kinase signaling. Mol Med Rep 12: 3916-3922, 2015.
3. Lippert TH, Ruoff HJ and Volm M: Intrinsic and acquired drug resistance in malignant tumors. The main reason for therapeutic failure. Arzneimittelforschung 58: 261-264, 2008.
4. Fletcher JI, Haber M, Henderson MJ and Norris MD: ABC transporters in cancer: More than just drug efflux pumps. Nat Rev Cancer 10: 147-156, 2010.
5. Burger H, Loos WJ, Eechoute K, Verweij J, Mathijssen RH and Wiemer EA: Drug transporters of platinum-based anticancer agents and their clinical significance. Drug Resist Updat 14: 22-34, 2011.
6. Singh A and Settleman J: EMT, cancer stem cells and drug resistance: An emerging axis of evil in the war on cancer. Oncogene 29: 4741-4751, 2010.
7. Li RJ, Zhang GS, Chen YH, Zhu JF, Lu QJ, Gong FJ and Kuang WY: Down-regulation of mitochondrial ATPase by hypermethylation mechanism in chronic myeloid leukemia is associated with multidrug resistance. Ann Oncol 21: 1506-1514, 2010.
8. Li SS, Yang S, Wang S, Yang XM, Tang QL and Wang SH: Latent membrane protein 1 mediates the resistance of nasopharyngeal carcinoma cells to TRAIL-induced apoptosis by activation of the PI3K/Akt signaling pathway. Oncol Rep 26: 1573-1579, 2011.
9. Marin JJ, Castaño B, Blazquez AG, Rosales R, Efferth T and Monte MJ: Strategies for overcoming chemotherapy resistance in enterohepatic tumours. Curr Mol Med 10: 467-485, 2010.
10. Dean M, Fojo T and Bates S: Tumour stem cells and drug resistance. Nat Rev Cancer 5: 275-284, 2005.
11. Fang Y, Fang D and Hu J: MicroRNA and its roles in esophageal cancer. Med Sci Monit 18: RA22-RA30, 2012.
12. Sarkar FH, Li Y, Wang Z, Kong D and Ali S: Implication of microRNAs in drug resistance for designing novel cancer therapy. Drug Resist Updat 13: 57-66, 2010.
13. Shapira A, Livney YD, Broxterman HJ and Assaraf YG: Nanomedicine for targeted cancer therapy: Towards the overcoming of drug resistance. Drug Resist Updat 14: 150-163, 2011.
14. Hershko DD: Oncogenic properties and prognostic implications of the ubiquitin ligase Skp2 in cancer. Cancer 112: 1415-1424, 2008.
15. Gao M and Karin M: Regulating the regulators: Control of protein ubiquitinationand ubiquitin-like modifications by extracellular stimuli. Mol Cell 19: 581-593, 2005.
16. Thrower JS, Hoffman L, Rechsteiner M and Pickart CM: Recognition of the polyubiquitin proteolytic signal. EMBO J 19: 94-102, 2000.
17. Lee TY, Chen SA, Hung HY and Ou YY: Incorporating distant sequence features and radial basis function networks to identify ubiquitin conjugation sites. PLoS One 6: e17331, 2011.
18. Bielskienė K, Bagdonienė L, Mozūraitienė J, Kazbarienė B and Janulionis E: E3 ubiquitin ligases as drug targets and prognostic biomarkers in melanoma. Medicina 51: 1-9, 2015.
19. Gong J, Cao J, Liu G and Huo JR: Function and mechanism of F-box proteins in gastric cancer (Review). Int J Oncol 47: 43-50, 2015.
20. Zhao Y and Sun Y: Cullin-RING Ligases as attractive anti-cancer targets. Curr Pharm Des 19: 3215-3225, 2013.

21. Reed SI: Ratchets and clocks: The cell cycle, ubiquitylation and protein turnover. Nat Rev Mol Cell Biol 4: 855-864, 2003.
22. Peters JM: The anaphase promoting complex/cyclosome: A machine designed to destroy. Nat Rev Mol Cell Biol 7: 644-656, 2006.
23. Kipreos ET and Pagano M: The F-box protein family. Genome Biol 1: REVIEWS3002, 2000. Epub 2000 Nov 10.
24. Xie CM, Wei W and Sun Y: Role of SKP1-CUL1-F-box-protein (SCF) E3 ubiquitin ligases in skin cancer. J Genet Genomics 40: 97-106, 2013.
25. Wang Z, Liu P, Inuzuka H and Wei W: Roles of F-box proteins in cancer. Nat Rev Cancer 14: 233-247, 2014.
26. Gong J, Lv L and Huo J: Roles of F-box proteins in human digestive system tumors (Review). Int J Oncol 45: 2199-2207, 2014.
27. Gong J and Huo J: New insights into the mechanism of F-box proteins in colorectal cancer (Review). Oncol Rep 33: 2113-2120, 2015.
28. Hartwell LH, Mortimer RK, Culotti J and Culotti M: Genetic control of the cell division cycle in yeast: V. Genetic analysis of *cdc* mutants. Genetics 74: 267-286, 1973.
29. Akhoondi S, Sun D, von der Lehr N, Apostolidou S, Klotz K, Maljukova A, Cepeda D, Fiegl H, Dafou D, Marth C, *et al*: FBXW7/hCDC4 is a general tumor suppressor in human cancer. Cancer Res 67: 9006-9012, 2007.
30. Bedford L, Lowe J, Dick LR, Mayer RJ and Brownell JE: Ubiquitin-like protein conjugation and the ubiquitin-proteasome system as drug targets. Nat Rev Drug Discov 10: 29-46, 2011.
31. Minella AC, Welcker M and Clurman BE: Ras activity regulates cyclin E degradation by the Fbw7 pathway. Proc Natl Acad Sci USA 102: 9649-9654, 2005.
32. Yada M, Hatakeyama S, Kamura T, Nishiyama M, Tsunematsu R, Imaki H, Ishida N, Okumura F, Nakayama K and Nakayama KI: Phosphorylation-dependent degradation of c-Myc is mediated by the F-box protein Fbw7. Embo J 23: 2116-2125, 2004.
33. Hoeck JD, Jandke A, Blake SM, Nye E, Spencer-Dene B, Brandner S and Behrens A: Fbw7 controls neural stem cell differentiation and progenitor apoptosis via Notch and c-Jun. Nat Neurosci 13: 1365-1372, 2010.
34. Rocher-Ros V, Marco S, Mao JH, Gines S, Metzger D, Chambon P, Balmain A and Saura CA: Presenilin modulates EGFR signaling and cell transformation by regulating the ubiquitin ligase Fbw7. Oncogene 29: 2950-2961, 2010.
35. Inuzuka H, Shaik S, Onoyama I, Gao D, Tseng A, Maser RS, Zhai B, Wan L, Gutierrez A, Lau AW, *et al*: SCF^{FBW7} regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction. Nature 471: 104-109, 2011.
36. Inuzuka H, Fukushima H, Shaik S, Liu P, Lau AW and Wei W: Mcl-1 ubiquitination and destruction. Oncotarget 2: 239-244, 2011.
37. Wertz IE, Kusam S, Lam C, Okamoto T, Sandoval W, Anderson DJ, Helgason E, Ernst JA, Eby M, Liu J, *et al*: Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. Nature 471: 110-114, 2011.
38. Tong J, Tan S, Zou F, Yu J and Zhang L: FBW7 mutations mediate resistance of colorectal cancer to targeted therapies by blocking Mcl-1 degradation. Oncogene 36: 787-796, 2017.
39. Tong J, Wang P, Tan S, Chen D, Nikolovska-Coleska Z, Zou F, Yu J and Zhang L: Mcl-1 degradation is required for targeted therapeutics to eradicate colon cancer cells. Cancer Res 77: 2512-2521, 2017.
40. Song Y, Zhou X, Bai W and Ma X: FBW7 increases drug sensitivity to cisplatin in human nasopharyngeal carcinoma by downregulating the expression of multidrug resistance-associated protein. Tumour Biol 36: 4197-4202, 2015.
41. Fang L, Yang Z, Zhou J, Tung JY, Hsiao CD, Wang L, Deng Y, Wang P, Wang J and Lee MH: Circadian clock gene CRY2 degradation is involved in chemoresistance of colorectal cancer. Mol Cancer Ther 14: 1476-1487, 2015.
42. Thompson BJ, Buonamici S, Sulis ML, Palomero T, Vilimas T, Basso G, Ferrando A and Aifantis I: The SCF^{FBW7} ubiquitin ligase complex as a tumor suppressor in T cell leukemia. J Exp Med 204: 1825-1835, 2007.
43. O'Neil J, Grim J, Strack P, Rao S, Tibbitts D, Winter C, Hardwick J, Welcker M, Meijerink JP, Pieters R, *et al*: *FBW7* mutations in leukemic cells mediate NOTCH pathway activation and resistance to γ-secretase inhibitors. J Exp Med 204: 1813-1824, 2007.
44. Ding XQ, Zhao S, Yang L, Zhao X, Zhao GF, Zhao SP, Li ZJ and Zheng HC: The nucleocytoplasmic translocation and up-regulation of ING5 protein in breast cancer: A potential target for gene therapy. Oncotarget 8: 81953-81966, 2017.
45. Yu HG, Wei W, Xia LH, Han WL, Zhao P, Wu SJ, Li WD and Chen W: FBW7 upregulation enhances cisplatin cytotoxicity in non-small cell lung cancer cells. Asian Pac J Cancer Prev 14: 6321-6326, 2013.
46. Izumi D, Ishimoto T, Miyake K, Eto T, Arima K, Kiyozumi Y, Uchihara T, Kurashige J, Iwatsuki M, Baba Y, *et al*: Colorectal cancer stem cells acquire chemoresistance through the upregulation of F-Box/WD repeat-containing protein 7 and the consequent degradation of c-Myc. Stem Cells 35: 2027-2036, 2017.
47. Takeishi S and Nakayama KI: Role of Fbxw7 in the maintenance of normal stem cells and cancer-initiating cells. Br J Cancer 111: 1054-1059, 2014.
48. Yokobori T, Mimori K, Iwatsuki M, Ishii H, Onoyama I, Fukagawa T, Kuwano H, Nakayama KI and Mori M: *p53*-Altered *FBXW7* expression determines poor prognosis in gastric cancer cases. Cancer Res 69: 3788-3794, 2009.
49. Welcker M, Larimore EA, Frappier L and Clurman BE: Nucleolar targeting of the fbw7 ubiquitin ligase by a pseudosubstrate and glycogen synthase kinase 3. Mol Cell Biol 31: 1214-1224, 2011.
50. Balamurugan K, Wang JM, Tsai HH, Sharan S, Anver M, Leighty R and Sterneck E: The tumour suppressor C/EBPδ inhibits FBXW7 expression and promotes mammary tumour metastasis. EMBO J 29: 4106-4117, 2010.
51. Lerner M, Lundgren J, Akhoondi S, Jahn A, Ng HF, Akbari Moqadam F, Oude Vrielink JA, Agami R, Den Boer ML, Grandér D and Sangfelt O: MiRNA-27a controls FBW7/hCDC4-dependent cyclin E degradation and cell cycle progression. Cell Cycle 10: 2172-2183, 2011.
52. Xu Y, Sengupta T, Kukreja L and Minella AC: MicroRNA-223 regulates cyclin E activity by modulating expression of F-box and WD-40 domain protein 7. J Biol Chem 285: 34439-34446, 2010.
53. Zhou X, Jin W, Jia H, Yan J and Zhang G: MiR-223 promotes the cisplatin resistance of human gastric cancer cells via regulating cell cycle by targeting FBXW7. J Exp Clin Cancer Res 34: 28, 2015.
54. Li R, Wu S, Chen X, Xu H, Teng P and Li W: miR-223/FBW7 axis regulates doxorubicin sensitivity through epithelial mesenchymal transition in non-small cell lung cancer. Am J Transl Res 2016: 2512-2524, 2016.
55. Ye M, Zhang Y, Zhang X, Zhang J, Jing P, Cao L, Li N, Li X, Yao L, Zhang J and Zhang J: Targeting FBW7 as a strategy to overcome resistance to targeted therapy in non-small cell lung cancer. Cancer Res 77: 3527-3539, 2017.
56. Adua D, Di Fabio F, Ercolani G, Fiorentino M, Gruppioni E, Altimari A, Rojas Limpe FL, Normanno N, Pinna AD and Pinto C: Heterogeneity in the colorectal primary tumor and the synchronous resected liver metastases prior to and after treatment with an anti-EGFR monoclonal antibody. Mol Clin Oncol 7: 113-120, 2017.
57. Zheng M, Xu H, Liao XH, Chen CP, Zhang AL, Lu W, Wang L, Yang D, Wang J, Liu H, *et al*: Inhibition of the prolyl isomerase Pin1 enhances the ability of sorafenib to induce cell death and inhibit tumor growth in hepatocellular carcinoma. Oncotarget 8: 29771-29784, 2017.
58. Lupini L, Bassi C, Mlcochova J, Musa G, Russo M, Vychytilova-Faltejskova P, Svoboda M, Sabbioni S, Nemecek R, Slaby O and Negrini M: Prediction of response to anti-EGFR antibody-based therapies by multigene sequencing in colorectal cancer patients. BMC Cancer 15: 808, 2015.
59. Eto K, Iwatsuki M, Watanabe M, Ishimoto T, Ida S, Imamura Y, Iwagami S, Baba Y, Sakamoto Y, Miyamoto Y, *et al*: The sensitivity of gastric cancer to trastuzumab is regulated by the miR-223/FBXW7 pathway. Int J Cancer 136: 1537-1545, 2015.
60. Demetrick DJ, Zhang H and Beach DH: Chromosomal mapping of the genes for the human CDK2/cyclin A-associated proteins p19 (SKP1A and SKP1B) and p45 (SKP2). Cytogenet Cell Genet 73: 104-107, 1996.
61. Hershko D, Bornstein G, Ben-Izhak O, Carrano A, Pagano M, Krausz MM and Hershko A: Inverse relation between levels of $p27^{Kip1}$ and of its ubiquitin ligase subunit Skp2 in colorectal carcinomas. Cancer 91: 1745-1751, 2001.
62. Fukuchi M, Masuda N, Nakajima M, Fukai Y, Miyazaki T, Kato H and Kuwano H: Inverse correlation between expression levels of p27 and the ubiquitin ligase subunit Skp2 in early esophageal squamous cell carcinoma. Anticancer Res 24: 777-783, 2004.

63. Yang G, Ayala G, De Marzo A: Tian W, Frolov A, Wheeler TM, Thompson TC and Harper JW: Elevated Skp2 protein expression in human prostate cancer: Association with loss of the cyclin-dependent kinase inhibitor p27 and PTEN and with reduced recurrence-free survival. Clin Cancer Res 8: 3419-3426, 2002.
64. Traub F, Mengel M, Lück HJ, Kreipe HH and von Wasielewski R: Prognostic impact of Skp2 and p27 in human breast cancer. Breast Cancer Res Treat 99: 185-191, 2006.
65. Rose AE, Wang G, Hanniford D, Monni S, Tu T, Shapiro RL, Berman RS, Pavlick AC, Pagano M, Darvishian F, *et al*: Clinical relevance of SKP2 alterations in metastatic melanoma. Pigment Cell Melanoma Res 24: 197-206, 2011.
66. Xu HM, Liang Y, Chen Q, Wu QN, Guo YM, Shen GP, Zhang RH, He ZW, Zeng YX, Xie FY, *et al*: Correlation of Skp2 overexpression to prognosis of patients with nasopharyngeal carcinoma from South China. Chin J Cancer 30: 204-212, 2011.
67. Schüler S, Diersch S, Hamacher R, Schmid RM, Saur D and Schneider G: SKP2 confers resistance of pancreatic cancer cells towards TRAIL induced apoptosis. Int J Oncol 38: 219-225, 2011.
68. Wang Z, Fukushima H, Inuzuka H, Wan L, Liu P, Gao D, Sarkar FH and Wei W: Skp2 is a promising therapeutic target in breast cancer. Front Oncol 1: pii: 18702, 2012.
69. Shapira M, Ben-Izhak O, Linn S, Futerman B, Minkov I and Hershko DD: The prognostic impact of the ubiquitin ligase subunits Skp2 and Cks1 in colorectal carcinoma. Cancer 103: 1336-1346, 2005.
70. Blagosklonny MV: Review Why therapeutic response may not prolong the life of a cancer patient: Selection for oncogenic resistance. Cell Cycle 4: 1693-1698, 2005.
71. Zhuang K, Zhang L, Zhang X, Tang H, Zhang J, Yan Y, Han K and Guo H: Gastrin induces multidrug resistance via the degradation of $p27^{Kip1}$ in the gastric carcinoma cell line SGC7901. Int J Oncol 50: 2091-2100, 2017.
72. Huang T, Yang L, Wang G, Ding G, Peng B, Wen Y and Wang Z: Inhibition of Skp2 sensitizes lung cancer cells to paclitaxel. Onco Targets Ther 10: 439-446, 2017.
73. Davidovich S, Ben-Izhak O, Shapira M, Futerman B and Hershko DD: Over-expression of Skp2 is associated with resistance to preoperative doxorubicin-based chemotherapy in primary breast cancer. Breast Cancer Res 10: R63, 2008.
74. Schüler S, Diersch S, Hamacher R, Schmid RM, Saur D and Schneider G: SKP2 confers resistance of pancreatic cancer cells towards TRAIL-induced apoptosis. Int J Oncol 38: 219-225, 2011.
75. Totary-Jain H, Sanoudou D, Dautriche CN, Schneller H, Zambrana L and Marks AR: Rapamycin resistance is linked to defective regulation of Skp2. Cancer Res 72: 1836-1843, 2012.
76. Chan CH, Li CF, Yang WL, Gao Y, Lee SW, Feng Z, Huang HY, Tsai KK, Flores LG, Shao Y, *et al*: The Skp2-SCF E3 ligase regulates Akt ubiquitination, glycolysis, herceptin sensitivity, and tumorigenesis. Cell 149: 1098-1111, 2012.
77. Wang J, Han F, Wu J, Lee SW, Chan CH, Wu CY, Yang WL, Gao Y, Zhang X, Jeong YS, *et al*: The role of Skp2 in hematopoietic stem cell quiescence, pool size, and self-renewal. Blood 118: 5429-5438, 2011.
78. Guardavaccaro D, Kudo Y, Boulaire J, Barchi M, Busino L, Donzelli M, Margottin-Goguet F, Jackson PK, Yamasaki L and Pagano M: Control of meiotic and mitotic progression by the F box protein beta-Trcp1 in vivo. Dev Cell 4: 799-812, 2003.
79. Müerköster S, Arlt A, Sipos B, Witt M, Grossmann M, Klöppel G, Kalthoff H, Fölsch UR and Schäfer H: Increased expression of the E3-ubiquitin ligase receptor subunit betaTRCP1 relates to constitutive nuclear factor-kappaB activation and chemoresistance in pancreatic carcinoma cells. Cancer Res 65: 1316-1324, 2005.
80. Pan Y, Zhang F, Zhao Y, Shao D, Zheng X, Chen Y, He K, Li J and Chen L: Berberine enhances chemosensitivity and induces apoptosis through dose-orchestrated AMPK signaling in breast cancer. J Cancer 8: 1679-1689, 2017.
81. Wang N, Wang X, Tan HY, Li S, Tsang CM, Tsao SW and Feng Y: Berberine suppresses cyclin D1 expression through proteasomal degradation in human hepatoma cells. Int J Mol Sci 17: pii: E1899, 2016.
82. Harder B, Jiang T, Wu T, Tao S, Rojo de la Vega M, Tian W, Chapman E and Zhang DD: Molecular mechanisms of Nrf2 regulation and how these influence chemical modulation for disease intervention. Biochem Soc Trans 43: 680-686, 2015.
83. Chowdhry S, Zhang Y, McMahon M, Sutherland C, Cuadrado A and Hayes JD: Nrf2 is controlled by two distinct β-TrCP recognition motifs in its Neh6 domain, one of which can be modulated by GSK-3 activity. Oncogene 32: 3765-3781, 2013.
84. Woo Y, Oh J and Kim JS: Suppression of Nrf2 activity by chestnut leaf extract increases chemosensitivity of breast cancer stem cells to paclitaxel. Nutrients 9: pii: E760, 2017.
85. Karathedath S, Rajamani BM, Musheer Aalam SM, Abraham A, Varatharajan S, Krishnamurthy P, Mathews V, Velayudhan SR and Balasubramanian P: Role of NF-E2 related factor 2 (Nrf2) on chemotherapy resistance in acute myeloid leukemia (AML) and the effect of pharmacological inhibition of Nrf2. PLoS One 12: e0177227, 2017.
86. Duong HQ, You KS, Oh S, Kwak SJ and Seong YS: Silencing of NRF2 reduces the expression of ALDH1A1 and ALDH3A1 and sensitizes to 5-FU in pancreatic cancer cells. Antioxidants 6: pii: E52, 2017.
87. Chang KY, Hsu TI, Hsu CC, Tsai SY, Liu JJ, Chou SW, Liu MS, Liou JP, Ko CY, Chen KY, *et al*: Specificity protein 1-modulated superoxide dismutase 2 enhances temozolomide resistance in glioblastoma, which is independent of O^6-methylguanine-DNA methyltransferase. Redox Biol 13: 655-664, 2017.
88. Liu WH and Chang LS: Fas/FasL-dependent and -independent activation of caspase-8 in doxorubicin-treated human breast cancer MCF-7 cells: ADAM10 down-regulation activates Fas/FasL signaling pathway. Int J Biochem Cell Biol 43: 1708-1719, 2011.
89. Wu WD, Wang M, Ding HH and Qiu ZJ: FBXL5 attenuates RhoGDI2-induced cisplatin resistance in gastric cancer cells. Eur Rev Med Pharmacol Sci 20: 2551-2557, 2016.
90. Cho HJ, Baek KE, Park SM, Kim IK, Nam IK, Choi YL, Park SH, Im MJ, Choi J, Ryu J, *et al*: RhoGDI2 confers gastric cancer cells resistance against cisplatin-induced apoptosis by upregulation of Bcl-2 expression. Cancer Lett 311: 48-56, 2011.
91. Wang X, Pankratz VS, Fredericksen Z, Tarrell R, Karaus M, McGuffog L, Pharaoh PD, Ponder BA, Dunning AM, Peock S, *et al*: Common variants associated with breast cancer in genome-wide association studies are modifiers of breast cancer risk in BRCA1 and BRCA2 mutation carriers. Hum Mol Genet 19: 2886-2897, 2010.
92. Coon TA, Glasser JR, Mallampalli RK and Chen BB: Novel E3 ligase component FBXL7 ubiquitinates and degrades Aurora A, causing mitotic arrest. Cell Cycle 11: 721-729, 2012.
93. Liu Y, Lear T, Iannone O, Shiva S, Corey C, Rajbhandari S, Jerome J, Chen BB and Mallampalli RK: The proapoptotic F-box protein Fbxl7 regulates mitochondrial function by mediating the ubiquitylation and proteasomal degradation of survivin. J Biol Chem 290: 11843-11852, 2015.
94. Kamran M, Long ZJ, Xu D, Lv SS, Liu B, Wang CL, Xu J, Lam EW and Liu Q: Aurora kinase A regulates Survivin stability through targeting FBXL7 in gastric cancer drug resistance and prognosis. Oncogenesis 6: e298, 2017.
95. Lehman NL, Tibshirani R, Hsu JY, Natkunam Y, Harris BT, West RB, Masek MA, Montgomery K, van de Rijn M and Jackson PK: Oncogenic regulators and substrates of the anaphase promoting complex/cyclosome are frequently overexpressed in malignant tumors. Am J Pathol 170: 1793-1805, 2007.
96. Gütgemann I, Lehman NL, Jackson PK and Longacre TA: Emi1 protein accumulation implicates misregulation of the anaphase promoting complex/cyclosome pathway in ovarian clear cell carcinoma. Mod Pathol 21: 445-454, 2008.
97. Shimizu N, Nakajima N, Tsunematsu T, Ogawa I, Kawai H, Hirayama R, Fujimori A, Yamada A, Okayasu R, Ishimaru N, *et al*: Selective enhancing effect of early mitotic inhibitor 1 (Emi1) depletion on the sensitivity of doxorubicin or X-ray treatment in human cancer cells. J Biol Chem 288: 17238-17252, 2013.
98. Zhang YW, Brognard J, Coughlin C, You Z, Dolled-Filhart M, Aslanian A, Manning G, Abraham RT and Hunter T: The F box protein Fbx6 regulates Chk1 stability and cellular sensitivity to replication stress. Mol Cell 35: 442-453, 2009.
99. Katayama K, Noguchi K and Sugimoto Y: FBXO15 regulates P-glycoprotein/ABCB1 expression through the ubiquitin-proteasome pathway in cancer cells. Cancer Sci 104: 694-702, 2013.
100. Ravindranath AK, Kaur S, Wernyj RP, Kumaran MN, Miletti-Gonzalez KE, Chan R, Lim E, Madura K and Rodriguez-Rodriguez L: CD44 promotes multi-drug resistance by protecting P-glycoprotein from FBXO21-mediated ubiquitination. Oncotarget 6: 26308-26321, 2015.

101. Wu B, Liu ZY, Cui J, Yang XM, Jing L, Zhou Y, Chen ZN and Jiang JL: F-box protein FBXO22 mediates polyubiquitination and degradation of CD147 to reverse cisplatin resistance of tumor cells. Int J Mol Sci 18: pii: E212, 2017.
102. Hanai J, Cao P, Tanksale P, Imamura S, Koshimizu E, Zhao J, Kishi S, Yamashita M, Phillips PS, Sukhatme VP and Lecker SH: The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. J Clin Invest 117: 3940-3951, 2007.
103. Tanaka N, Kosaka T, Miyazaki Y, Mikami S, Niwa N, Otsuka Y, Minamishima YA, Mizuno R, Kikuchi E, Miyajima A, *et al*: Acquired platinum resistance involves epithelial to mesenchymal transition through ubiquitin ligase FBXO32 dysregulation. JCI Insight 1: e83654, 2016.
104. Tan J, Yang X, Zhuang L, Jiang X, Chen W, Lee PL, Karuturi RK, Tan PB, Liu ET and Yu Q: Pharmacologic disruption of Polycomb-repressive complex 2-mediated gene repression selectively induces apoptosis in cancer cells. Genes Dev 21: 1050-1063, 2007.
105. Lorenzi F, Babaei-Jadidi R, Sheard J, Spencer-Dene B and Nateri AS: Fbxw7-associated drug resistance is reversed by induction of terminal differentiation in murine intestinal organoid culture. Mol Ther Methods Clin Dev 3: 16024, 2016.
106. Zhang X, Kong Y, Xu X, Xing H, Zhang Y, Han F, Li W, Yang Q, Zeng J, Jia J and Lui Z: F-box protein FBXO31 is down-regulated in gastric cancer and negatively regulated by miR-17 and miR-20a. Oncotarget 5: 6178-6190, 2014.
107. Huang HL, Zheng WL, Zhao R, Zhang B and Ma WL: FBXO31 is down-regulated and may function as a tumor suppressor in hepatocellular carcinoma. Oncol Rep 24: 715-720, 2010.
108. Liu J, Lv L, Gong J, Tan Y, Zhu Y, Dai Y, Pan X, Huen MS, Li B, Tsao SW, *et al*: Overexpression of F-box only protein 31 predicts poor prognosis and deregulates p38α- and JNK-mediated apoptosis in esophageal squamous cell carcinoma. Int J Cancer 142: 145-155, 2018.
109. Kogo R, Mimori K, Tanaka F, Komune S and Mori M: FBXO31 determines poor prognosis in esophageal squamous cell carcinoma. Int J Oncol 39: 155-159, 2011.
110. Guerrero-Garcia TA, Mogollon RJ and Castillo JJ: Bortezomib in plasmablastic lymphoma: A glimpse of hope for a hard-to-treat disease. Leuk Res 62: 12-16, 2017.