Invited Review

Integrated molecular signaling involving mitochondrial dysfunction and alteration of cell metabolism induced by tyrosine kinase inhibitors in cancer

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ABSTRACT

Cancer cells have unlimited replicative potential, insensitivity to growth-inhibitory signals, evasion of apoptosis, cellular stress, and sustained angiogenesis, invasiveness and metastatic potential. Cancer cells adequately adapt cell metabolism and integrate several intracellular and redox signaling to promote cell survival in an inflammatory and hypoxic microenvironment in order to maintain/expand tumor phenotype. The administration of tyrosine kinase inhibitor (TKI) constitutes the recommended therapeutic strategy in different malignancies at advanced stages.

There are important interrelationships between cell stress, redox status, mitochondrial function, metabolism and cellular signaling pathways leading to cell survival/death. The induction of apoptosis and cell cycle arrest widely related to the antitumoral properties of TKIs result from tightly controlled events involving different cellular compartments and signaling pathways. The aim of the present review is to update the most relevant studies dealing with the impact of TKI treatment on cell function. The induction of endoplasmic reticulum (ER) stress and Ca^{2+} disturbances, leading to alteration of mitochondrial function, redox status and phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt)-mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) signaling pathways that involve cell metabolism reprogramming in cancer cells will be covered. Emphasis will be given to studies that identify key components of the integrated molecular pattern including receptor tyrosine kinase (RTK) downstream signaling, cell death and mitochondria-related events that appear to be involved in the resistance of cancer cells to TKI treatments.

1. TK inhibition in cancer treatment

The activation of receptor tyrosine kinase (RTK) and non-receptor tyrosine kinase (NRTK) transmits downstream signaling events related to cell proliferation, growth, migration, angiogenesis or cell dedifferentiation [1]. The genetic alterations of RTKs involve different molecular mechanisms such as gain-of-function mutation, genomic amplifications, chromosomal translocations and autocrine activation are related to transforming-related abilities in cancer and resistance to treatments [2].

Chemotherapy and radiotherapy exert their antitumoral activity using common mechanisms in normal and tumor cells leading to noxious side effects in the surrounding tissues. The traditional anti-cancer chemotherapy targets dividing cells inducing DNA damage that leads to

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Abbreviations

AIF	Apoptosis-inducing factor
AML	Acute myeloid leukemia
ALL	Acute lymphocytic leukemia
AMPK	AMP-activated protein kinase
ALK	Anaplastic lymphoma kinase
APE1	Apurinic/apyrimidinic endonuclease 1
BNIP3	BCL2 Interacting Protein 3
BiP	Binding immunoglobulin protein
NIX	BNIP3-like
CAMKK2	Calcium/calmodulin-dependent protein kinase kinase 2
CHOP	C/EBP homologous protein
c-Met	Mesenchymal-epithelial transition factor receptor
CML	Chronic myeloid leukemia
CLL	Chronic lymphocytic leukemia
JNK	c-Jun N-terminal kinase
CSF-1R	CSF1R Colony-stimulating factor receptor 1
CRC	Colon and rectum carcinoma
COX-2	Cyclooxygenase-2
ER	Endoplasmic reticulum
ENO2	Enolase 2
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal-regulated kinases
eIF2α	Eukaryotic Initiation Factor 2α
FGFR	Fibroblast growth factor receptor
Flt3	FMS-like tyrosine kinase 3
Grp78	Glucose-regulated protein 78
FoxM1	Forkhead Box M1
GIST	Gastrointestinal stromal tumor
GLUT1	Glucose transporter I
GLUT3	Glucose transporter 3
Grx1	Glutaredoxin 1
HNSCC	Head and neck squamous cell carcinoma
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HKII	Hexokinase II
H_2O_2	Hydrogen peroxide
HIF-1	Hypoxia-inducible factor-1
IRE1α	Inositol-requiring enzyme-1α, IRE1
JAK	Janus kinase
mTOR	Mammalian target of rapamycin
MMP	Matrix metalloproteinases
MITF	Melanocyte lineage-specification transcription factor
MAPK	Mitogen-activated protein kinase
MEK	MAPK/ERK
Mcl-1	Myeloid cell leukemia-1
SIRT1	NAD-dependent deacetylase sirtuin-1
NOX	NADPH oxidase
NRTK	Non-receptor tyrosine kinase
NSCLC	Non-small cell lung cancer
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf2	Nuclear transcription factor erythroid 2-related factor 2
LDH	Lactate dehydrogenase
LKB1	Liver kinase B1
PUMA	p53 upregulated modulator of apoptosis
PPP	Pentose phosphate pathway
Prdx2	Peroxiredoxin 2
Prdx6	Peroxiredoxin 6
PGC-1α	Peroxisome proliferator-activated receptor-coactivator 1α
PI3K	Phosphatidylinositol 3-kinase
PTEN	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and tensin homolog
PFK1	6-Phosphofructo-1-kinase
PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2
PDK-1	Phosphoinositide-dependent protein kinase-1
PDGFR	Platelet derived growth factor receptor
PARP-1	Poly (ADP-ribose) polymerase 1
PKA	Protein kinase A
Akt	Protein kinase B
PERK	Protein kinase RNA-like endoplasmic reticulum kinase
PPA2	Protein phosphatase A2
PTPB1	Protein tyrosine phosphatase B1
PDHA1	Pyruvate dehydrogenase E1 alpha 1
PKM2	Pyruvate kinase isoenzyme type M2
RHEB	Ras homolog enriched in brain
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
RCC	Renal cell carcinoma
ROS1	ROS proto-oncogene 1
SWH	Salvador-Warts-Hippo
STAT3	Signal transducer and activator of transcription 3
S6K1	S6 kinase 1
SHP-1	Src homology region 2 domain-containing phosphatase-1
SREBP1	Sterol regulatory element-binding transcription factor 1
$O_2^{\cdot-}$	Superoxide anion
Trx1	Thioredoxin 1
TrxR1	Thioredoxin reductase 1
TGF-β	Transforming growth factor-β
TCA	Tricarboxylic acid
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
TSC	Tuberous sclerosis complex
ULK1/2	Unc51-like kinases
UPR	Unfolded protein response
VEGFR	Vascular endothelial growth factor receptor
XBP-1	X-Box binding protein 1
XIAP	X-linked inhibitor of apoptosis protein

DNA damage response, leading to potential activation of DNA repair mechanisms, suppression of global general translation, cell cycle arrest and, ultimately, either cell survival or cell death [3,4]. Tyrosine kinase inhibitors (TKIs) research has gradually been replacing these conventional anti-tumoral therapies in order to achieve more specific targets with the promise to enhance positive results. TKIs target specific oncogenic signaling in tumor cells minimizing side effects in healthy cells [5]. The degree of efficacy and selectivity is variable among TKI treatments, and they can be differentially beneficial depending on the target disease in terms of preventing tumor cell dedifferentiation, proliferation and oncogenic signaling. Some of the advantages of TKIs over traditional chemotherapy are their high selectivity, few side effects and good oral administration, with an absorption grade that differs among

TKI molecules [6]. Currently, more than 20 TKI drugs have been approved both as first- and second-line therapies in clinical oncology for the treatment of different cancer diseases (Table 1). Even TKIs employment have resulted in a breakthrough in the area of cancer treatment, the acquired resistance of tumoral cells is still a crucial barrier that avoids better results in the cure of cancer [7].

TKIs are low-weight molecules that act as receptor antagonists through interfering with ATP-γ-phosphate for the ATP binding site within the kinase catalytic domain preventing the autophosphorylation, dimerization and activation of the downstream cascade, thereby reducing tyrosine kinase (TK) phosphorylation [1]. TKIs can also occupy an adjacent site to their ATP binding domain, allowing both the inhibitor and ATP to bind to the kinase [8]. There are various TKIs that vary in

Table 1

Tyrosine kinase inhibitors including targets, and their use as the recommended treatment in cancer. AML: Acute myeloid leukemia, ALL: Acute lymphocytic leukemia, CML: Chronic myeloid leukemia, CRC: Colon and rectum carcinoma, DTC: Differential thyroid carcinoma, GIST: Gastrointestinal stromal tumor, HCC: Hepatocellular carcinoma, MTC: Medullary thyroid carcinoma, c-Met: Mesenchymal-epithelial transition factor receptor, NSCLC: Non-small cell lung cancer, RCC: Renal cell carcinoma, STS: Soft tissue sarcoma.

TKI	Target	Diseases
Alectinib	ALK	NSCLC
Afatinib	EGFR	NSCLC
Axitinib	VEGFR, PDGFR, c-Kit	RCC
Brigatinib	ALK	NSCLC
Bosutinib	Abl, Src	CML, MTC
Cabozantinib	VEGFR, c-Met, RET, Flt3, c-Kit, Axl, Tie-2	HCC, MTC
Canertinib	EGFR	Breast cancer
Capmatinib	EGFR, c-Met	NSCLC
Ceritinib	ALK	NSCLC
Crizotinib	ALK, c-Met	NSCLC
Dasatinib	Abl, Src, PDGFR, c-Kit	CML
Dovitinib	VEGFR, FGFR, PDGFR, c-Kit, Flt3, CSF-1R	RCC
Erlotinib	EGFR	NSCLC
Gefitinib	EGFR	NSCLC
Herceptin	Her-2/neu	Breast Cancer
Imatinib	Abl, PDGFR, c-Kit	ALL, CML, CLL, GIST
Lapatinib	EGFR, ErbB2	Breast cancer
Leflunomide	PDGFR	Prostate cancer
Lenvatinib	VEGFR, PDGFR, FGFR, RET, c-Kit	DTC, HCC
Neratinib	HER2	Breast Cancer
Nilotinib	Bcr, Abl, PDGFR	CML
Osimertinib	EGFR	NSCLC
Pazopanib	VEGFR, PDGFR, FGFR, c-Kit	RCC, STS, NSCLC
Ponatinib	Bcr, Abl	CML, ALL
Regorafenib	VEGFR, PDGFR, FGFR, c-Kit, RET, Raf, Tie2	HCC, CCR, GIST
Ruxolitinib	JAK1, JAK2	Myelofibrosis
Semaxinib	VEGFR, c-Kit, Flt3	AML
Sorafenib	Raf, VEGFR, PDGFR, c-Kit, Flt3	RCC, HCC, Melanoma
Sunitinib	VEGFR, PDGFR, c-Kit, Flt3	GIST, RCC
Sutent	Flt3	AML
Vandetanib	VEGFR, EGFR	MTC
Vatalanib	VEGFR	CCR, Prostate cancer, RCC
Vemurafenib	B-Raf	Melanoma

their pharmacological effects, as well as in their side effects and target kinases, and the factors that define the effectiveness of inhibitors [9].

2. Alteration of ER stress and Ca^{2+} homeostasis by TKIs

The endoplasmic reticulum (ER) plays a crucial role in proteostasis, handling translocation during translation and folding of secretory proteins [10]. The accumulation of misfolded proteins in the lumen induces ER stress and triggers the unfolded protein response (UPR) to avoid cellular damage. Several situations including starvation, reduced glycosylation, drugs, alteration of redox status or mutant proteins might boost ER stress [11]. In mammals, inositol-requiring enzyme-1α (IRE1α), protein kinase RNA-like endoplasmic reticulum kinase (PERK) and ATF6 act as stress sensors governing restoration of homeostasis by attenuating translation, regulating ER lumen capacity and activating gene expression to reduce misfolding (Fig. 1).

2.1. Impact of TKI on ER stress

The administration of TKI induces ER stress with different functional repercussions in cancer cells. Sorafenib inhibits RTKs such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), NRTK such as c-kit and FMS-like tyrosine kinase (Flt3), as well as serine-threonine Raf kinase (Table 1), which increases markers of ER stress, including IRE1α, eukaryotic

initiation factor 2α (eIF2α) and binding immunoglobulin protein (BiP)/glucose-regulated protein 78 (BiP/Grp78) in hepatic tissue from patients submitted to liver resection for hepatocellular carcinoma (HCC) [12]. In addition, the administration of Sorafenib (10 μM) has been related to the induction of ER stress, Ca^{2+} release, generation of reactive oxygen species (ROS), and apoptosis in human leukemia cells [13]. In this study, cell death is related to the activation of PERK and subsequent phosphorylation of eIF2α, as well as induction of IRE1α and X-Box Binding Protein 1 (XBP-1) mRNA processing, independent of the Raf/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) or MEK pathway [13]. We have recently showed that Sorafenib induces early (3–12 h) ER stress characterized by an increase of PERK and IRE1α signaling, but a decrease of ATF6 expression, temporally associated with the activation of c-Jun N-terminal kinase (JNK) and AMP-activated protein kinase (AMPK), and reduction of mammalian target of rapamycin (mTOR) and protein translation [14]. The downregulation of ER signaling using siRNA strategies has proved to reduce autophagy markers and increased apoptosis in Sorafenib-treated HepG2 cells [14]. The downregulation of ATF6 and autophagy mediated by Sorafenib [13,14] might be related to the disruption of the secretory pathway measured by Golgi fragmentation and phosphorylation of ATPase p97/VCP as the initiator of autophagy [15]. The induction of apoptosis by Sorafenib in renal cell carcinoma (RCC) has been related to the upregulation of PERK-related induction of ATF4, C/EBP homologous protein (CHOP) and p53 upregulated modulator of apoptosis (PUMA) [16].

Lenvatinib targets VEGFR, PDGFR, fibroblast growth factor receptor (FGFR), RET and c-Kit (Table 1), inducing an elevation of ER stress markers in nasopharyngeal cancer HK-1 cell line. Its combined treatment with iodine-131 potentiates ER stress and cell death, as well as reduces migration and invasiveness [17]. Differently, proapoptotic and antiproliferative properties induced by antiangiogenic drug Sunitinib with similar targets as Sorafenib (Table 1), are related to reduced expression of BiP/Grp78 and downregulation of PERK/eIF2α signaling in RCC [18]. The study supports the survival properties of ER stress in the model. In this sense, the knockdown of GRP78 inhibits cancer cell survival and induces apoptosis in cultured RCC [18]. Other study has shown that Sunitinib-related resistance is associated with IRE1α-dependent nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway [19].

The administration of Dasatinib, another TKI that targets mutated Abl, Src, PDGFR and c-Kit (Table 1), induces AMPK activation, epidermal growth factor receptor (EGFR) degradation and ER stress downregulation that lead to apoptosis in sensitive Ca9-22 and HSC3 cell lines [20]. Combined treatment of Dasatinib with metformin has a synergistic effect by boosting AMPK activation, ER stress and EGFR downregulation in order to overcome resistance to Dasatinib in head and neck squamous cell carcinoma cells (HNSCC) [20]. The inhibition of protein translation induced by ER stress and AMPK-mTOR inhibition might be an important anti-tumor mechanism in Dasatinib and metformin [20]. Correlative evidence suggests that the upregulation of EGFR limits the effectiveness of TKIs in advanced non-small cell lung cancer cells (NSCLC) [21]. In fact, EGFR-TKIs acquired resistance limits therapy in advanced NSCLC. To overcome this resistance, a combined treatment based on EGFR targeted Gefinitib or Erlotinib (Table 1) and phosphoinositide-dependent protein kinase-1 (PDK-1) inhibitor OSU-03012 could reduce protein kinase B (Akt) and increased pro-apoptotic ER signaling through upregulation of CHOP, without concomitant induction of cytoprotective chaperones like BiP/Grp78 nor Grp94 [22]. As sustained treatment with Erlotinib promotes pro-survival autophagy signaling contributing to tumor cell resistance, the inhibition of the autophagic flux during Erlotinib therapy modulates ER response and contributes to cell death [23]. Ca^{2+} signaling might play a crucial role in the adaptive resistance to EGFR inhibitors. In this sense, Afatinib (Table 1), shows alterations in the proteome and phosphoproteome associated with increased Ca^{2+}-dependent adhesions and Ca^{2+}
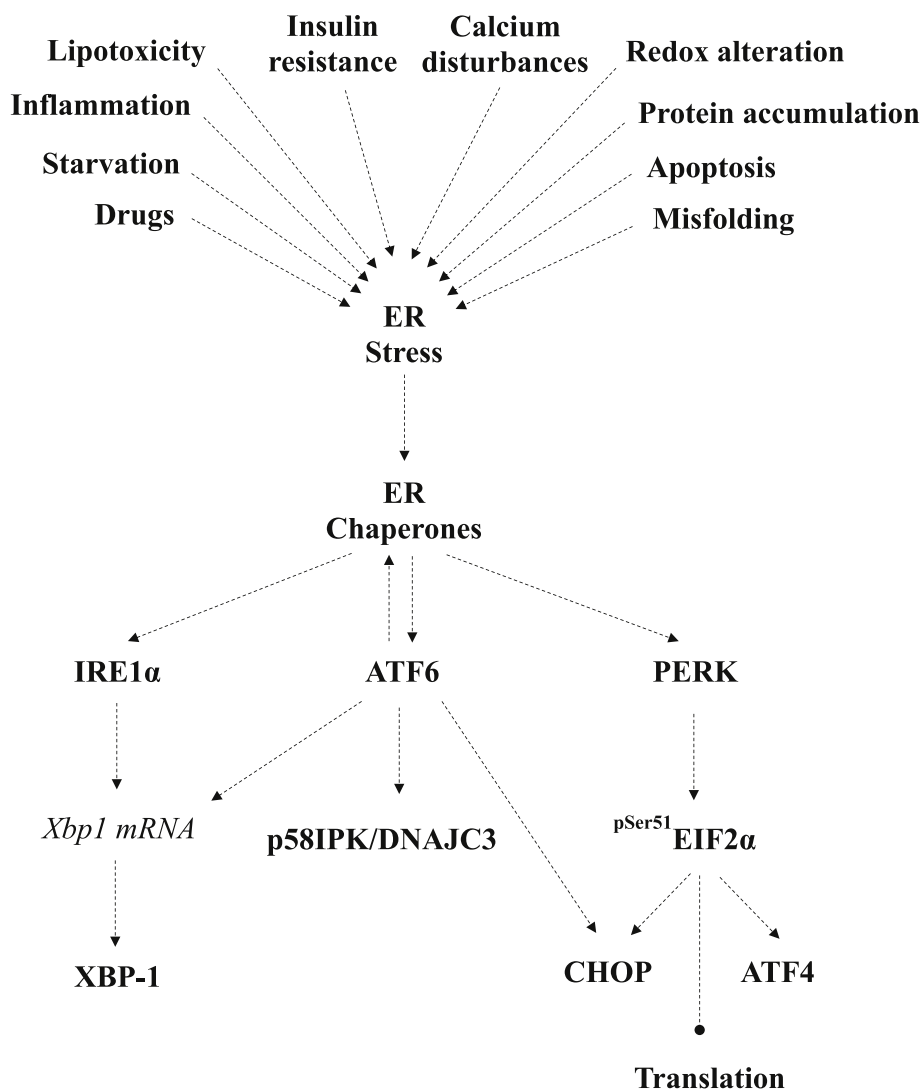
Lipotoxicity

Inflammation

Starvation

Drugs

Insulin resistance

Calcium disturbances

Redox alteration

Protein accumulation

Apoptosis

Misfolding

ER Stress

ER Chaperones

IRE1α   **ATF6**   **PERK**

Xbp1 mRNA   **p58IPK/DNAJC3** ^{pSer51}**EIF2α**

XBP-1   **CHOP**   **ATF4**

Translation

Fig. 1. Schematic representation of ER stress induction and downstream signaling events. Several factors might activate ER sensor chaperones inositol-requiring enzyme-1α (IRE1α), ATF6 and/or protein kinase RNA-like endoplasmic reticulum kinase (PERK), resulting in the inhibition of translation and induction of ER stress pathways. EIF2α: Eukaryotic initiation factor 2α, XBP-1: X-Box Binding Protein 1; CHOP: C/EBP homologous protein.

transporters in NSCLC PC9 cell line [24]. Ca^{+2} homeostasis could also be involved in resistant chronic myeloid leukemia (CML)-T1 cells to drugs that target Abl, PDGFR and c-Kit such as Imatinib (Table 1) [25].

3. Induction of mitochondrial dysfunction and ROS production by TKIs

ROS, mainly superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2), are generated during normal mitochondrial function playing a relevant role in both physiological functions and tumor development [26]. Exacerbated ROS levels are widely associated with mitochondrial dysfunction, which can lead to damage of different cellular constituents like proteins, DNA and lipids. Unrepaired damage to mitochondrial DNA leads to defective complexes I or III which can result in increased electron uncoupling and translocation of electrons to oxygen leading $O_2^{\cdot-}$ generation [27].

The administration of TKIs has been reported to induce cytotoxicity in different cancer cell lines [28–30]. Mitochondrial damage is usually considered as a drug's "off-target" effect contributing to adverse reactions, and appears to be commonly shared by many drugs and toxins [31,32]. Ponatinib (Bcr-Abl), Sorafenib and Regorafenib (VEGFR, PDGFR, FGFR, c-Kit, RET, Raf, Tie2), but not Crizotinib (mesenchymal-epithelial transition factor receptor or c-Met, and anaplastic lymphoma kinase or ALK) and Pazopanib (VEGFR, PDGFR, FGFR and c-Kit), were able to induce relevant mitochondrial dysfunction, uncoupling components of electron transport chain and promoting ROS generation [28,29,33–35].

The mitochondrial dysfunction is also associated with the occurrence of several complications or side effects related to diarrhea, fatigue, hand-foot skin reaction and hypertension that have been related to effectiveness of the treatment in the case of patients in advanced stage of HCC [36]. In close connection with TKI-induced ROS generation and Ca^{2+} disturbances by TKI administration, generation of cardiotoxicity is a major health problem despite antitumor effectiveness [37,38]. Sorafenib induces mitochondrial dysfunction related to the impairment of complexes I, III and V in the electronic respiratory chain and mitochondrial membrane depolarization [28,35,39] (Fig. 2). The generation of ROS by Sorafenib has been observed in different studies [28,40]. In addition, the presence of oxidative stress and ERK down-regulation in peripheral blood mononuclear cells has been considered a good predictor of the evolution of patients with HCC treated with Sorafenib [41]. The induction of oxidative stress and depletion of antioxidant status by Sorafenib was related to Ca^{2+} disturbances that lead to its mitochondrial Ca^{2+} overload, which initiate lethal apoptotic
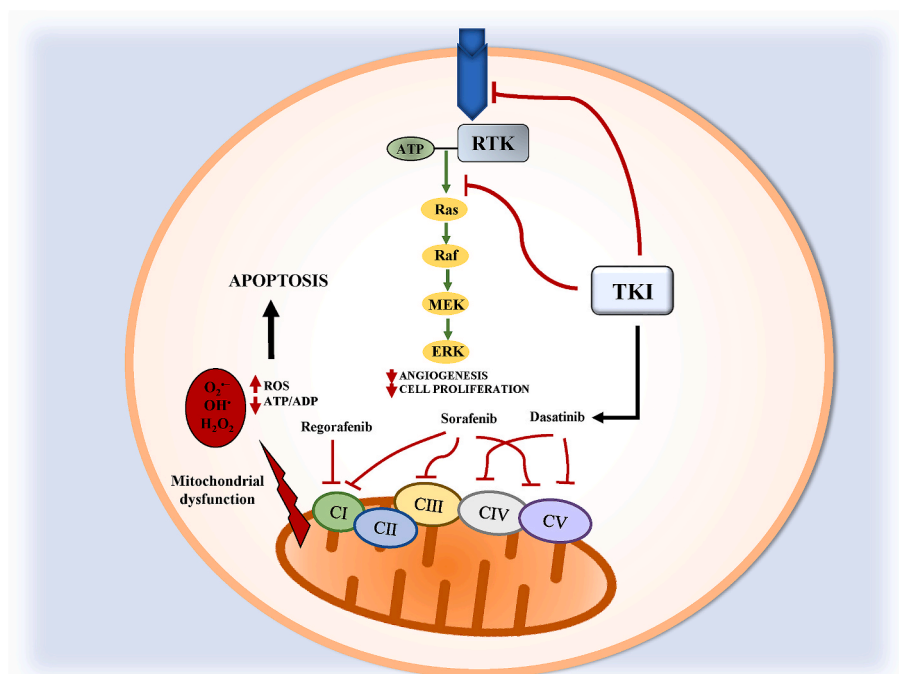
Fig. 2. Induction of mitochondrial dysfunction and reactive oxygen species (ROS) production by tyrosine kinase inhibitors (TKIs). TKIs act at the receptor tyrosine kinase (RTK), preventing Ras downstream events such as activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) (MEK) and ERK phosphorylation that leads reduction of angiogenesis and tumor progression. TKIs might also induce mitochondrial dysfunction. Regorafenib impairs the activity of complex I of the respiratory chain. Dasatinib inhibits complexes IV and V. Sorafenib was demonstrated to behave as a mitochondrial uncoupler, and inhibits complexes I, III, V. The resulting ROS and products of the oxidative stress might be the cause and/or consequence of the mitochondrial dysfunction. Scheme extracted from elsewhere (190).

events [42]. Regorafenib also directly uncouples oxidative phosphorylation and promotes Ca^{2+} accumulation and swelling of mitochondria [34]. Moreover, Regorafenib produces impairment of the respiratory chain that affects the maximal capacity of complex I [28] (Fig. 2). In this context, Dasatinib inhibits complexes IV and V of the electron transport chain in H9c2 rat cardiomyoblasts [29] (Fig. 2). Interestingly, the antitumoral properties of the antiangiogenic Sunitinib are related to the reduction of kidney toxicity, recovery of GSH levels and lipid peroxidation reduction induced by cisplatin in subcutaneous implantation of Ehrlich ascites carcinoma cells in mice [43].

The antitumoral properties of Crizotinib, a TKI targeting ALK, ROS proto-oncogene 1 (ROS1) and c-Met [44], are related to cell death and ROS production in hepatocytes [45], cardiomyocytes [46], and alveolar rhabdomyosarcoma cells [47]. Gefitinib and Erlotinib, which target EGFR, have been also recently associated with the generation of oxidative stress [48]. The cytotoxicity of Erlotinib also involves NADPH oxidase (NOX) 4-induced oxidative stress in HNSCC cell lines [49]. The activity of Lapatinib, targeting a sub-class of EGFR 1 and/or 2 (ErbB1, ErbB2) [50], is also associated with ROS generation in inflammatory breast cancer models [51]. In concordance with the action of these TKIs, Imatinib that targets Abl, PDGFR and c-Kit [52], and is the recommended treatment for acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), CML and gastrointestinal stromal tumors (GIST), the induction of apoptosis is associated with ROS production and loss of the mitochondrial membrane potential [53].

4. Involvement of redox regulation in cancer

Oxidative stress, generated from ROS and antioxidant imbalance, is present in a large number of serious diseases including cancer [54]. A wide variety of stimuli derived from different signal molecules (growth factors, cytokines …) have been associated with H_2O_2 generation that can play a dual role, either in signaling or in oxidative stress, according to the local intracellular concentration attained [55]. During normal

cell growth, levels of $O_2^{.-}$ and H_2O_2 are kept under tight control by the intracellular redox regulatory mechanisms. In fact, several evidences support that the effect of intracellular ROS on oncogenesis is dependent on the ratio between intracellular $O_2^{.-}$ and H_2O_2 in that a predominant increase in $O_2^{.-}$ supports cell survival and promotes oncogenesis, and by contrast H_2O_2 prevents carcinogenesis by facilitating cell death signaling [56]. Alterations in redox regulatory mechanisms have been observed in different types of cancer together with the main prevalent genetic mutations related to telomerase, Wnt-β-catenin, PI3K/Akt/mTOR, p53 and MAPK signaling [57].

Despite the high production of ROS, cancer cells proliferate thanks to the induction of antioxidant defense systems through the activation of the nuclear transcription factor erythroid 2-related factor 2 (Nrf2) [58]. In these cells, the high rate of proliferation and apoptosis evasion may be achieved through the constitutive activation of redox-sensitive signal-transduction at the level of kinases such as MAPK family [59], phosphatidylinositol 3-kinase (PI3K)/Akt [60] and redox-sensitive transcription factors as NF-κB, Nrf2 and signal transducer and activator of transcription 3 (STAT3) [61], and inactivation of phosphatases as protein tyrosine phosphatase B1 (PTPB1) [62,63], protein phosphatase A2 (PPA2) [64] and phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and tensin homolog (PTEN) [65]. In this sense, and among other repercussions, the antitumoral activity of PPA2 [66] is reduced during oxidative and nitrosative stress when Tyr289 nitration within the B56ζ subunit of PP2A occurs, preventing the recruitment of its catalytic core, and consequently stabilizing the antiapoptotic properties of Bcl-2 [67].

A number of these signaling proteins that undergo redox changes are targets of redoxins, including thioredoxin 1 (Trx1) and glutaredoxin 1 (Grx1). In addition, it has been shown that peroxiredoxin 6 (Prdx6), Trx1 and thioredoxin reductase 1 (TrxR1) are often overexpressed in tumor cells and that high levels of Trx1 could be linked to drug resistance during cancer treatment [68,69]. As a matter of fact, it has been described that ROS production and NF-κB activation promote HCC progression [70] and that NF-κB DNA-binding activity is regulated by Trx1 [71,72].

STAT3 is an oncoprotein constitutively activated in several human

cancers, what makes it a potential target for the development of cancer drugs [73]. STAT3 is activated by tyrosine phosphorylation which is influenced by its redox state. It has been described that STAT3 transcriptional activity can be modulated by S-glutathionylation [74] and it has also been found that its activity depends on its thiol redox state, which is influenced by H_2O_2 and peroxiredoxin 2 (Prdx2) levels and by the thioredoxin system activity [75]. The formation of Trx1-STAT3 disulfide exchange intermediates has been observed, suggesting that Trx1 may be a direct mediator of STAT3 disulfide reduction. Peroxiredoxin 6 (Prdx6) also promotes growth of lung tumors in mice through activation of Janus Kinase (JAK)2/STAT3 signaling [76].

Epithelial-mesenchymal transition (EMT) is an important de-differentiation process that occurs in normal development but also takes place in tumor cells and constitutes the first step towards metastasis during disease progression [77]. There are several proteins involved in EMT signaling pathways whose activity is ROS-dependent such as Smad, Snail, E-Cadherin, β-catenin and matrix metalloproteinases (MMP). It has also been described that transforming growth factor-β (TGFB) provokes an increase in the production of ROS, that results in the phosphorylation of Smad2, p38MAPK and ERK1/2 [78]. In addition, ROS may regulate EMT through a mechanism that involves NF-κB in close collaboration with hypoxia-inducible factor-1 (HIF-1) and cyclooxygenase-2 (COX-2) [79]. A critical molecular event of EMT is down-regulation of the cell adhesion molecule E-cadherin and its replacement by N-cadherin. It has been described by several authors that activation of Akt leads to a significant reduction in E-cadherin expression and nuclear localization of Snail, suggesting a role for the PI3K/Akt signaling pathway in the transient shift from E-cadherin to N-cadherin, and EMT progression in cancer [80]. The hyperactivation of PI3K/Akt signaling mediated by ROS and its relationship with tumor cell survival, apoptosis inhibition and resistance to chemotherapy has been described [81].

4.1. The role of redox in the resistance to TKIs

Given the role of redox status in tumorigenesis, we addressed how several studies have demonstrated a direct or indirect involvement of ROS in TKI-acquired resistance, usually through redox activation of the PI3K-Akt signaling pathways [1]. Akt is thought to be responsible for mediating the acquired resistance to Sorafenib via mTOR, but independent of PP2A, in HCC cells [82]. The overexpression of apurinic/apyrimidinic endonuclease 1 (APE1), a multifunctional enzyme that is involved in DNA repair and the redox regulation of transcription factors, significantly contributed to Gefitinib and Erlotinib resistance and Akt activation through a redox-dependent mechanism [83]. In addition, the combined treatment of Sorafenib and tetrandrine drastically increased apoptosis through ROS/Akt signaling in HCC cells [84].

The high basal levels of ROS found in TKI-resistant cancer cells are mainly due to elevated NOX expression [85] although mitochondrial ROS production cannot be discarded (Fig. 3). CML and glioblastoma cancer cell resistance to Imatinib and Dasatinib might be associated to overexpression of components of the NOX2/Egr-1/Fyn signaling axis, which prompts the search for inhibitors of p47phox, the organizer subunit of NOX2, to treat TKI-resistant cancers [85]. In Erlotinib-resistant NSCLC cells, effective cell death induction is achieved by combined treatment with Erlotinib and ampelopsin, concomitant with ROS accumulation through upregulation of NOX2 expression [86]. Recently, it has been found that TKI-resistant lung cancer cells exhibit poly (ADP-ribose) polymerase 1 (PARP-1) dependence for survival through restriction of NOX-mediated cytotoxic ROS production [87].

The combined treatment of Gefitinib- and Erlotinib-resistant k-Ras mutated NSCLC cells with Vorinostat has anti-proliferative and pro-apoptotic effects as well as increased ROS accumulation, Nrf2 down-regulation and Keap1 upregulation [88]. Dysfunctional mutations in
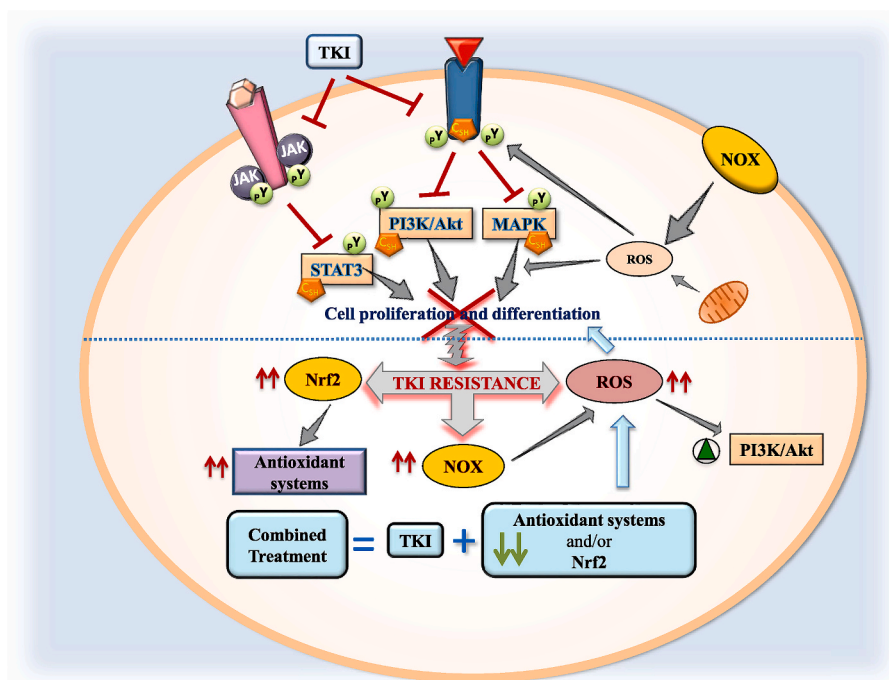

Fig. 3. Redox regulation by tyrosine kinase inhibitors (TKIs). Two receptor tyrosine kinase (RTK) are drawn inserted in the cell membrane with their respective bound ligands. The phosphorylated Tyr (pY) sites are also shown in RTK including redox sensitive intermediates (C_{SH}, redox sensitive Cys in reduced state). The pathways inhibited by TKI are indicated with a red crossed line. Reactive oxygen species (ROS) generation by NADPH oxidase (NOX) and mitochondria impacts on redox sensitive sites in different targets showed with straight grey arrows. Transition from TKI-induced inhibition of cell proliferation and differentiation to resistance to TKI is indicated by a curly grey arrow and doted blue line. Events that accompany TKI resistance are displayed with vertical fine red arrows showing increased levels of nuclear transcription factor erythroid 2-related factor 2 (Nrf2)-dependent rise of antioxidant status, NOX and ROS, and activation of phosphatidylinositol 3-kinase (PI3K)/protein Kinase B (Akt) (green triangle inside a green circle). Grey arrows indicate an action. The lower part of the illustration reflects the contention that a combination of TKI treatment and down-regulation of antioxidant systems could counteract the development of TKI resistance in cancer cells (blue arrows). Janus kinase, JAK. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Keap1 gene provoke constitutive activation of Nrf2 leading to TKI resistance in NSCLC cells [89]. From these studies, Nrf2, a transcriptional factor playing a pivotal role in cellular antioxidant defense, emerges as a candidate target for anticancer therapy (Fig. 3).

4.2. The effectiveness of combined treatment with TKI and redoxin inhibitors

Reversible redox modification of key Cys residues constitutes a regulatory mechanism of protein function [90]. H_2O_2 acting as a second messenger modulates signaling cascades by reversible oxidation of redox sensitive cysteine residues in receptors and transduction proteins, including those using tyrosine phosphorylation signals like EGFR, MAPKs, PTEN, PI3K/Akt and STAT3 [91,92]. In particular, oxidation of Cys797 at the tyrosine kinase active site of EGFR enhances its activity [93] and coincidentally, mutation of C797S in EGFR has been described as a novel mechanism of acquired resistance to third-generation TKIs [94]. Peroxiredoxins may catalyze the oxidative modification of these cysteines while Trx and Grx are responsible for their reduction, as mentioned above. Hence, a role for redoxins in regulating cell signaling is to be expected.

Combination of TKI with down-regulation or inhibition of Grx/GSH or Trx/TrxR systems has been explored to treat TKI resistance. In a study carried out in Gefitinib-resistant NSCLC cells, Grx1 was upregulated and its inhibition enhanced the effects of Gefitinib on apoptosis an cell cycle arrest via the EGFR/Forkhead Box M1 (FoxM1) signaling pathway [95]. Trx1 has been shown to be overexpressed in a wide variety of cancers and its expression is associated with aggressive tumor growth, resistance to standard therapy and therefore decreased patient survival [96]. Recently, treatment with TKI has been combined with Trx1 inhibitors or downregulation of its levels to increase the effectiveness in TKI-resistant cancer cells [97]. In this study [97], the resistance of breast cancer cells to Trastuzumab, an antibody against Her2, appears to be related to the high levels of reduced Trx1

affecting the activity of the PTEN inhibitor. The combined treatment of Trastuzumab and a Trx1-inhibitor reduced cell viability, Akt phosphorylation and Bcl2 levels, as well as increased the levels of ROS, phosphorylated JNK, G1 arrest and apoptosis [97]. The downregulation of Trx1 could be a promising approach to improve the response to chemotherapy in HCC [98]. Our group has studied the role of Trx1 system in the sensitivity of three HCC cell lines (HepG2, SNU423 and SNU475) with different degrees of EMT to Sorafenib treatment. Basal Trx1/TrxR1 levels are markedly higher in poorly-differentiated SNU475 cells [99]. In these cells, Sorafenib treatment combined with Trx1 down-regulation using siRNA strategies dramatically induces inactivation of TGFβ and activation of tumor-suppressor Salvador-Warts-Hippo (SWH) signaling, as well as thiol oxidative changes in STAT3 [99]. In another study, the combination of Sorafenib with metformin decreases tumor invasiveness and cell motility associated with Trx1 downregulation [100]. Therefore, combination of Sorafenib with Trx1 inhibitors should be a good approach in the design of anticancer therapies. The panorama is not clear so far regarding the mechanisms of TKI resistance with the involvement of a varied panoply of signaling elements in different types of cancers. However, redox imbalance appears as a recurrent phenomenon in the majority, if not all cases studied so far. Consequently, combined therapy with TKI and other treatments aimed at either weakening the antioxidant defenses or stimulating ROS producing mechanisms can be envisaged as a promising therapeutic approach (Fig. 3).

5. Regulation of AMPK and mTOR during treatment with TKIs

The PI3K/Akt/mTOR pathway is one of the key pathways altered in cancer cells regulating relevant processes such as protein synthesis, cell growth, cell survival and, motility, as well as autophagy or angiogenesis. Several genes, such as PIK3K gene, are either overexpressed by amplification or activated by somatic point mutations in cancer [101]. The oncosuppressor PTEN is also frequently mutated [102] that leads to downstream
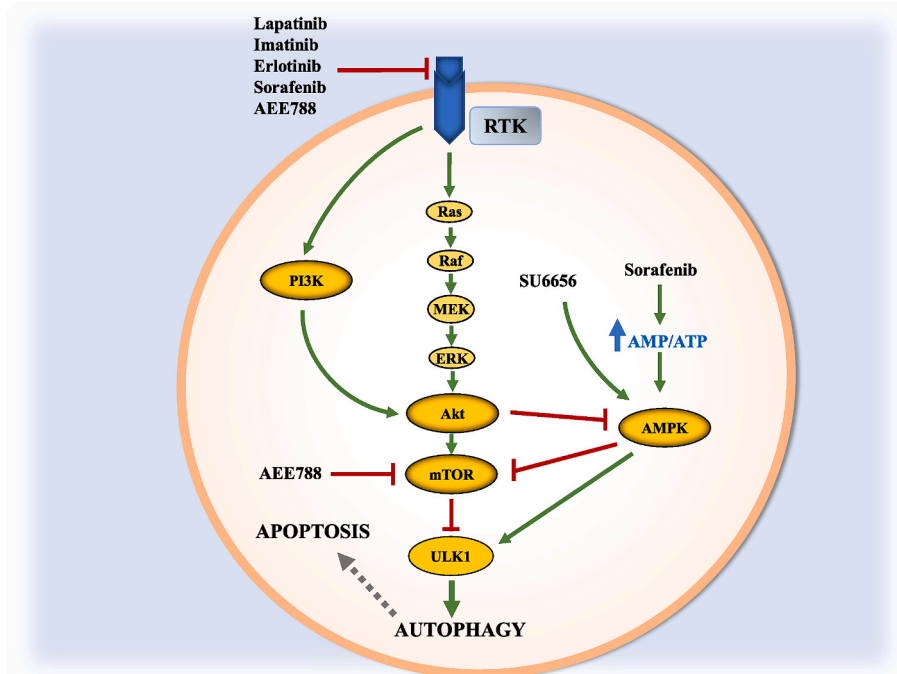

Fig. 4. Regulation of AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) during the treatment with tyrosine kinase inhibitors (TKIs). Regulation of cell proliferation, differentiation, angiogenesis and tumorigenesis signaling pathways by TKIs are closely related to the regulation of AMPK and mTOR. The binding of a mitogen to a receptor tyrosine kinase (RTK) stimulates the Ras/Raf/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) (MEK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling that target mTOR pathways. Among other downstream events, mTOR phosphorylates Unc51-like kinase (ULK) and inhibits autophagy. Akt negatively regulates AMPK, a protein involved in mTOR inhibition and ULK phosphorylation that promotes autophagy. Different TKIs are able to activate (green line) or inhibit (red line) specific pathways involved in downregulation of survival pathways. The activation of AMPK and inhibition of mTOR by TKIs induce autophagy and/or apoptosis that leads to the blockage of tumorigenesis and cell proliferation processes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Akt activation which, in turn, is often found to be somatically overexpressed and mutated [103]. The hyperactivation of PI3K/Akt/mTOR signaling is usually associated with resistance to different targeted-mediated therapies [104]. In this sense, mTOR can be regulated by different routes, being of special interest its inhibition by the AMPK, an energy sensor that regulates cellular metabolism while maintaining homeostasis, and which is involved in autophagy activation [105]. AMPK is activated in situations involving a rise of the AMP/ATP ratio, that might occur in stress induced by glucose deprivation, hypoxia, tissue ischemia, or during exercise. Thus, AMPK exerts stimulatory effects on glucose uptake, glycolysis, and fatty acid oxidation, while inhibits ATP-consuming cellular events, such as protein synthesis or fatty acid synthesis [106]. Liver kinase B1 (LKB1) is the upstream kinase activating AMPK by phosphorylating its Thr172 site, whereas calcium/cal-modulin-dependent protein kinase kinase 2 (CAMKK2) activates AMPK in response to calcium increase [107]. Although AMPK has been shown to promote ^{Ser15}p53 phosphorylation inducing cell cycle arrest, AMPKβ1 sub-unit is also upregulated by two downstream targets of p53 sestrin 1 and sestrin 2 [108]. The antitumoral properties of AMPK activation and mTOR inhibition have been related to antiproliferative and proapoptotic properties in leukemia [109]. Moreover, anti-apoptotic effects of AMPK have also been observed in other malignancies [110].

Autophagy is a highly conserved catabolic process that functions as a quality control system, facilitating the degradation of organelles and other damaged intracellular components in situations of metabolic stress. mTOR complex 1 works as a negative regulator of autophagy, exerting its in-hibitory action by phosphorylating and inactivating Unc51-like kinases (ULK1/2) and Atg13 [111]. AMPK activation can subsequently trigger tu-berous sclerosis complex (TSC)2 to repress mTOR complex 1 and, therefore, upregulates autophagy [112]. AMPK could also directly phosphorylate multiple sites in ULK1 that promotes autophagy [113] (Fig. 4).

Controversial reports exist on the antitumoral properties of autop-hagy during TKI treatments. It has been suggested that normalization of autophagy may be relevant to avoid cellular resistance to cancer drugs [114]. However, the baseline apoptotic priming is a key determinant of the reliable cell killing during TKI treatment [115]. It appears that re-sponse to targeted therapies can be predicted with the dynamic BH3 profiling technique to measure early changes in net pro-apoptotic sig-naling at the mitochondrion ('priming') [116]. Autophagy has been considered to be the mechanism regulating the proximity of tumor cells to apoptotic cliff during drug administration. In this sense, the inhibi-tion of autophagy by drugs, that downregulates the expression of pro-apoptotic transcription regulators such as Foxo3a, reduces the threshold to the initiation of apoptosis [117].

Sorafenib and Regorafenib have been extensively demonstrated to induce autophagy [118]. We have recently observed that the early Sorafenib-induced ER stress and transitory upregulation of JNK and AMPK-dependent signaling are associated with the inhibition of mTOR and activation of autophagy [14]. The activation of AMPK by Sorafenib is related to inhibition of mitochondrial metabolism, and increase of AMP/ADP and ADP/ATP ratios [119]. The inhibition of PERK, IRE1α and ATF6 branches of ER stress reduces autophagy, which played a survival role in Sorafenib-treated HepG2 cells [14].

Imatinib induces AMPK activation and suppression of S6 kinase 1 (S6K1) and mTOR, that appears to be related to sensitization of CML cells [120]. However, it is known that activation of AMPK has antileukemic ef-fects, since even being an autophagy activator, it can lead to cell death when ATP concentrations are sufficiently low [121]. Lapatinib inhibits Akt/mTOR signaling and activates AMPK, being both aspects related to anticancer ef-fects in breast cancer cells [122]. SU6656, a Src kinase inhibitor, activates AMPK pathway by enhancing its phosphorylation by LKB1 independently of cellular energy state [119]. The inhibition of mTOR by AMPK activation induced by different TKI, such as Erlotinib, Imatinib, Lapatinib, Sorafenib, and other preclinical drugs such as SU6656 (Src) or AEE788 (VEGFR and ErbB2) is relevant for the antitumoral properties of the drugs. The anti-tumoral impact of mTOR inhibition in autophagy process is related to the cell type and drug target. All in all, targeting autophagy has also become an important drug discovery approach to increase cancer chemosensitivity (Fig. 4).

6. Regulation of PGC-1α during TKI

The peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) regulates the activity of transcription factors and nuclear receptors that targets genes involved in mitochondrial biogenesis, oxidative metabolism, thermogenesis, anabolic pathways, glucose and lipid metabo-lisms, muscle fiber regeneration and antioxidant status [123–126]. The expression of PGC-1α is upregulated by p53 and the oncogenic melanocyte lineage-specification transcription factor (MITF), and downregulated by c-Myc and HIF-1 [127]. The activity of PGC-1α can be regulated by phos-phorylation through AMPK, protein kinase A (PKA), Akt, and p38 MAPK, which modulates its transcription regulatory properties [128]. AMPK en-hances mitochondrial biogenesis inducing PGC-1α transcription, and its phosphorylation ^{Thr177,Ser538}PGC-1α which promotes its co-transcriptional activity [129]. p38 MAPK activates PGC-1α by phosphorylation at Thr262, Ser265 and Thr298, increasing its half-life in cytoplasm [130]. By contrast, Akt inhibits PGC-1α activity through inducing its phosphorylation at ^{Ser570}PGC-1α [131]. In conditions of low cellular energy status, NAD-de-pendent deacetylase sirtuin-1 (SIRT1) deacetylates and activates PGC-1α. However, when the energy cellular status is high, histone acetylase GCN5 induces PGC-1α acetylation, that inhibits its activity [126]. In the context of HCC, the overexpression of SIRT1 was correlated with microvascular in-vasion, metastasis and predicted poor outcomes [132].

Opposite reports have been published assessing the expression of PGC-1α expression in tumors [133–136]. Although mitochondrial dysfunction is generally associated with the activation of glycolysis, many cancer cells possess intact mitochondrial respiration being some cancers subtypes de-pendent on mitochondrial respiration [127]. Mitochondrial biogenesis and metabolic reprogramming influence the phenotype of cancer cells and re-sistance to targeted therapy [137]. Interestingly, Hirpara et al. [138] showed that resistance to Gefitinib is associated with the upregulation of PGC1α and TFAM expression, and increased formation of supercomplexes I and II, oxygen consumption rate and mitochondrial mass in NSCLC cell line. Ve-murafenib, an inhibitor of mutated serine/threonine kinase B-Raf, increases the MITF/PGC-1α signaling axis resulting in metabolic reprogramming to-wards oxidative phosphorylation and conferring cellular intrinsic resistance in melanoma cells [139]. Both studies identify OPB-51602 [138] and Gami-trinib [139] as targets of mitochondrial components to circumvent cellular resistance to TKI. The transient overexpression of SIRT1, as well as NAD re-pletion, decreases Sorafenib-induced apoptosis suggesting that SIRT1 could be an underlying mechanism of resistance to Sorafenib treatment in HCC [39].

7. Role of cell metabolism in cancer

The process of tumorigenesis and cancer progression involves al-teration of cellular metabolism. During the last decades, numerous works have reported how metabolic reprogramming supports the ana-bolic requirements for cancer cell proliferation in terms of energetic demand for cell proliferation, increased macromolecules biosynthesis, new biomass building and tumor progression. Both genetic and mi-croenvironmental factors are involved in the deregulation of tumor cells metabolism, which in turn are able to modulate the micro-environment inside the tumor driving cancer evolution, invasiveness or metastatic potential [140–142].

One of the hallmarks of cancer is the deregulation of cellular energetics towards aerobic glycolysis to generate ATP and metabolic intermediates even in presence of normal oxygen concentration, known as "Warburg ef-fect" [143]. This effect is supported by tightly regulated molecular pathways including MAPK, PI3K, HIF-1, p53, c-Myc or AMPK pathways. Despite this shift from oxidative phosphorylation to glycolys for ATP production, mi-tochondria are required for tumor development and their regulation is a promising field for combined anticancer therapies. The activation of RTK/NRTK regulates PI3K-Akt-TSC1/2-Ras homolog enriched in brain (RHEB)-

mTOR pathway in order to maintain a cellular balance between anabolism and catabolism. mTOR complex 1 regulates protein and nucleotide synthesis, lipogenesis and glycolysis. The stimulation of protein synthesis involves an increase of ribosome biogenesis and mRNA translation [144]. mTOR increases nucleotide synthesis by increasing ATF4-dependent expression of mitochondrial bifunctional enzyme methylenetetrahydrofolate dehydrogenase/cyclohydrolase, the key enzyme in mitochondrial tetrahydrofolate cycle, increasing the production of purine nucleotides [145]. mTOR augments lipogenesis in Sterol regulatory element-binding transcription factor 1 (SREBP1)-dependent pathway either through S6K1 phosphorylation [146] or by controlling the nuclear entry of lipin 1, a phosphatidic acid phosphatase, involved on SREBP1 gene regulation [147]. mTOR signaling also stimulates the expression of genes involved in nearly every step of glycolysis and pentose phosphate pathway (PPP) [146]. Several key enzymes of glucose metabolism, such as enolase 2 (ENO2), hexokinase II (HKII), lactate dehydrogenase (LDH) A, 6-phosphofructo-1-kinase (PFK1), and glucose transporter I (GLUT1) are described to be regulated by c-Myc [148], however, they are not upregulated in TSC-deficient cells [146].

7.1. Impact of TKIs in cancer metabolic pathways

TKIs can deregulate glycolysis in malignant tissue through its impact on EGFR, VEGFR, c-Met, Bcr-Abl, HER2 or ALK signaling in many different cancer types [149]. The inhibition of PDGFR, c-Kit and Bcr-Abl by Imatinib leads pyruvate entering into the tricarboxylic acid (TCA) cycle providing these cells with an alternative mechanism of glucose metabolism to compensate for the inhibition of glycolysis [150], and reduced GLUT1 in leukemic cell [151]. Thus, Imatinib induces a shift in the glucose metabolism between anaerobic glycolysis to aerobic mitochondrial TCA cycle depending on dosage (Fig. 5). In this sense, combined adjuvant therapies based on targeting mitochondrial metabolism are relevant to prevent treatment-acquired resistance [138,139].

Different studies using Erlotinib and Gefitinib, which specifically target EGFR, have shown that these drugs reduce extracellular acidification rate, lactate production and glucose consumption in lung adenocarcinoma cell lines [152]. These effects might be the consequence of c-Myc down-regulation during EGFR inhibition [153]. Moreover, metabolomic analysis of TKI-treated cells shows a reduced presence of intermediate metabolites related to glucose metabolism [153].

The overexpression of EGFR and HER2 is associated with aggressive phenotypes and tumor progression in breast cancer. Lapatinib exerts a dual inhibition of EGFR and HER2, although its effects on HER2 appears to be more critical [154]. Among other interactions, Lapatinib blocks HER2 signaling inhibiting the phosphorylation of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 (PFKFB2) in different cancer cell lines, decreasing the amount of intermediate metabolites in PPP and blocking the glucose-dependent EGFR/HER2 signaling [155]. Consequently, current studies are trying to determine how HER2 expression could be considered as a predictive biomarker of clinical prognosis.

The inhibition of c-Met reduces intracellular NADPH content which plays an essential role during lipid and nucleic acid biosynthesis, as well as by enzymatic systems regulating oxidative system [149]. In addition, c-Met inhibition modulates glucose metabolism preventing the expression of different mitochondrial proteins [156]. The increased tumor growth activity of Cabozantinib, that targets VEGFR, c-Met, Tie2, Axl, RET, c-Kit and Flt3 (Table 1), compared to Regorafenib is related to decreased glycolysis in a colon and rectum carcinoma (CRC) xenograft mouse model [157]. Cabozantinib significantly reduces glucose uptake and PI3K/mTOR-dependent signaling pathway in CRC098 and CRC162 cells [157]. Crizotinib, which targets c-Met and ALK, reduces the expression of phosphorylated pyruvate kinase isoenzyme type M2 (PKM2), lactate release, phosphorylated LDH and glucose uptake in lymphoma cells [158].

The administration of Sorafenib induces a glycolytic cell reprogramming that may represent a cellular resistance strategy potentially
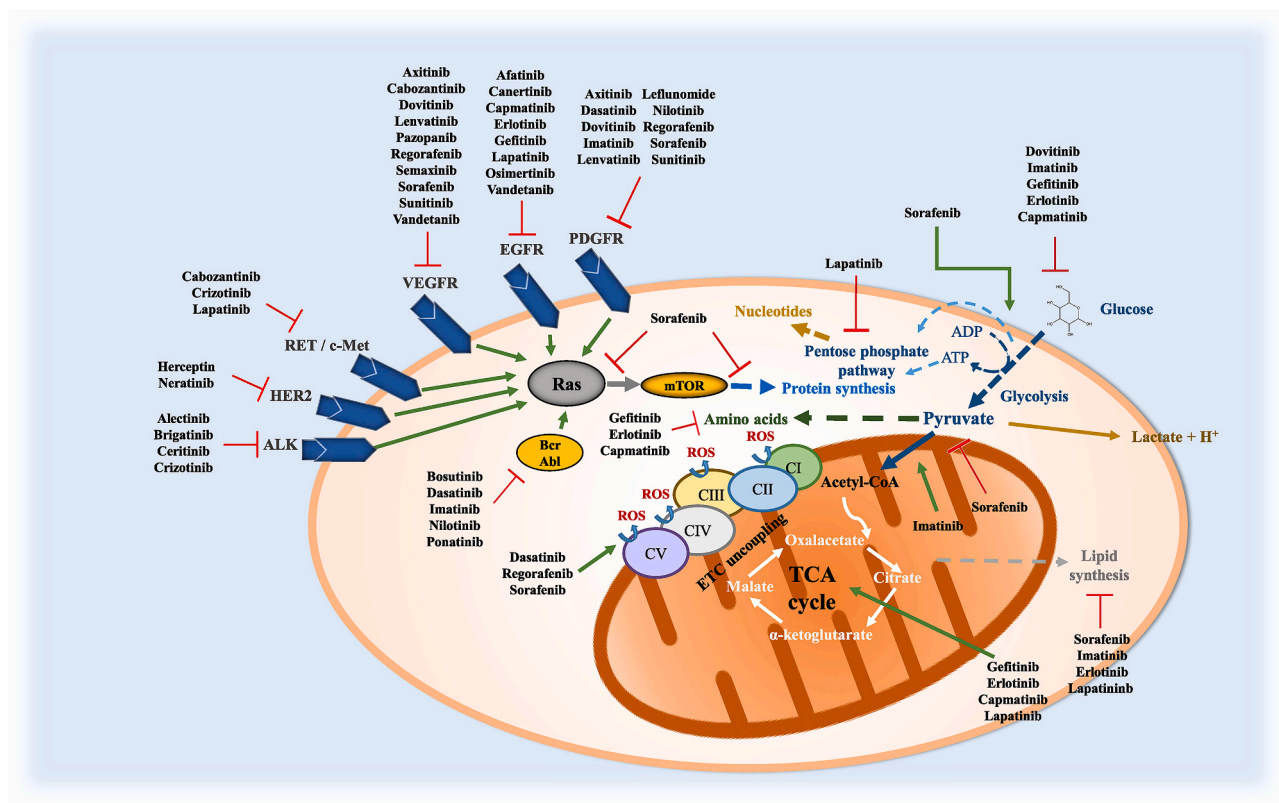

Fig. 5. Metabolic impact of tyrosine kinase inhibitor (TKI) administration. The inhibition of different receptor tyrosine kinase (RTK) alters all cancer hallmarks. Dovitinib, Imatinib, Gefitinib, Erlotinib and Capmatinib reduce glycolytic pathway, while Sorafenib promoted mitochondrial dysfunction. Lipid synthesis and protein synthesis were profoundly altered by TKIs. ETC; Electron transport chain.

targetable by combination therapies. Sorafenib induces the expression of glucose transport 3 (GLUT3), ENO2, and PFK1 that are related to increased uptake of glucose and lactate production as a response to mitochondrial dysfunction [159] (Fig. 5). In addition, Sorafenib downregulates the expression of the mitochondrial enzyme pyruvate dehydrogenase E1 alpha 1 (PDHA1) [159].

The resistance to Axitinib treatment, which targets VEGFR, PDGFR and c-Kit, has been related to upregulation of cell surface exposure of GLUT1 and extracellular acidification rate, both reflecting an increased glycolytic rate [160]. Dovitinib, targeting VEGFR, FGFR, PDGFR, c-Kit, Flt3 and colony-stimulating factor receptor 1 (CSF-1R), is able to hinder glucose metabolism with combined downregulation of Akt-mTOR pathway [161]. Imatinib shifts glycolysis to mitochondrial glucose metabolism inducing a reduction of glucose uptake and an increment of cell energetic state [162]. The inhibition of EGFR- and/or c-Met-related pathways by Capmatinib, Gefitinib and Erlotinib reverts aerobic glycolysis and reactivates mitochondrial oxidative phosphorylation in NSCLC through the concerted downregulation of HKII and phosphorylated PKM2, and upregulation of mitochondrial-dependent oxidative phosphorylation [163].

The contribution of reprogramming amino acids metabolism in malignant tissues is relevant for its requirement for protein synthesis. The impact of Sorafenib in mTOR and protein synthesis has also been already described [14]. Erlotinib, Gefitinb and Capmatinib have also been reported as negative regulators of amino acid levels [149]. Altered levels of lipids are widely related to carcinogenesis and cancer metastasis [164]. In fact, the levels of total cholesterol, triglycerides, HDL and LDL in plasma from breast cancer patients are significantly higher than those of control group [165]. Treatment of Bcr-Abl-positive cells with Imatinib decreases phosphocholine concentrations [162]. Erlotinib reduces the expression of fatty acid genes in MDA-MB-231 and Hs578T cells, while Capmatinib sensitizes MDA-MB-468 cells to knockdown of arachidonic and linoleic acid metabolism rate limiting enzymes [166]. The different response to TKI in sensitive or resistant cells is evidence that metabolic reprogramming is relevant to revert malignancy, and combined TKI-based strategies can be a very promising clinical tool for more effective targeted therapies to treat previously characterized subgroups of patients.

8. Induction of cell death by TKIs in cancer cells

The resistance to apoptosis is one of the main characteristics of tumor cells, characterized by their unlimited replicative potential, insensitivity to cellular stress, sustained angiogenesis, invasiveness and metastatic potential [167]. Apoptosis is a form of genetically programmed death process that can be mediated by ligand-dependent receptor activation (Type I) or mitochondrial outer membrane permeabilization (Type II), which could lead to an uncontrolled cell death process under limiting energy conditions termed necrosis, which involves cell swelling and sudden membrane rupture.

Sorafenib can induce apoptosis of cancer cells through regulation of multiple proapoptotic and antiapoptotic factors, including Bad, Bax, Bim, myeloid cell leukemia-1 (Mcl-1), and X-linked inhibitor of apoptosis protein (XIAP) [168]. The expression of these factors may be regulated at either transcriptional, translational, or posttranslational levels, and may involve mechanisms independent on ERK activity. The inhibition of Mcl-1 expression, which accounts for Sorafenib-induced apoptosis in multiple cancer types, has been found independent on Raf/MEK/ERK inhibition [169]. Recently, the proapoptotic factor Bim has been identified as an important factor in Sorafenib-induced apoptosis [14,170]. In fact, the progressive increase of ER stress and PERK-dependent CHOP expression, and reduction of ^{Thr308}Akt/Akt and ^{Ser473}Akt/Akt ratios are associated with the reduction of autophagic flux and an additional upregulation of BimEL expression and caspase-3 activity [14]. Small interfering-RNA (si-RNA) assays show that Bim, but not Bak and Bax, is involved in the induction of caspase-3 in Sorafenib-treated HepG2 cells [14]. The increase in Bad and decrease in Mcl-1 expression have also been shown to account for Sorafenib-induced apoptosis [171]. Bim exerts its proapoptotic activity through binding to several antiapoptotic Bcl-2 family members [172]. The mechanisms accounting for downregulation of Mcl-1 expression by Sorafenib may be cell type specific, and involve both ERK-dependent and ERK-independent mechanisms [173,174]. Sorafenib can also inhibit phosphorylation of eIF4B, which may lead to decreased translation of antiapoptotic factors such and Mcl-1 and cFLIP, and could also inhibit the
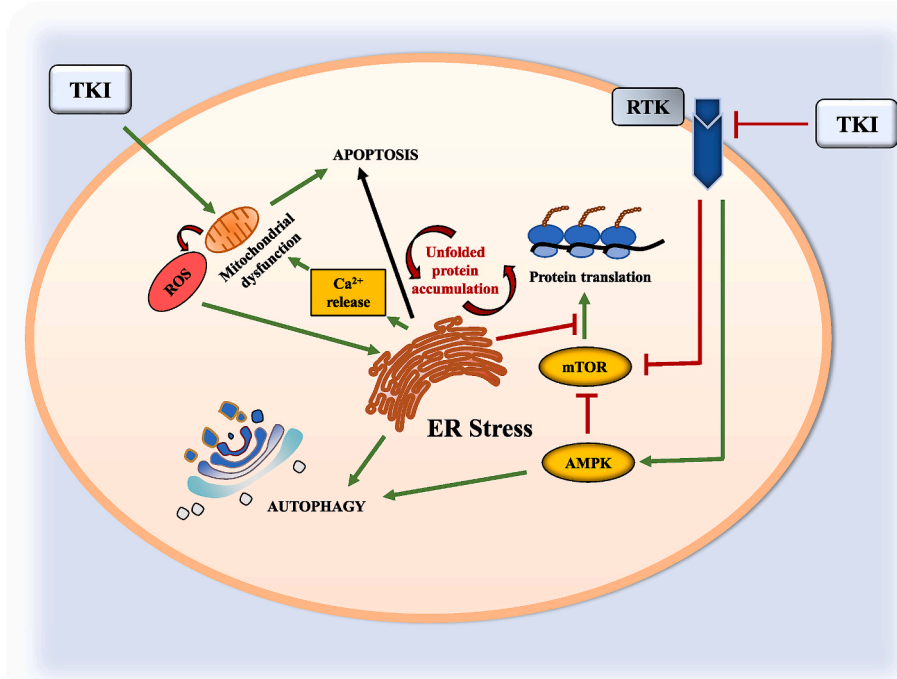

Fig. 6. Graphical Abstract. Tyrosine kinase inhibitor (TKI) induced endoplasmic reticulum (ER) stress promoting unfolded protein response (UPR), Ca²⁺ release, translation blockage, autophagy and apoptosis. Furthermore, other mechanisms of TKIs involve mitochondrial dysfunction, generation of reactive oxygen species (ROS), AMP-activated protein kinase (AMPK) activation and mammalian target of rapamycin (mTOR) inhibition. These cellular pathways are interconnected and result in the induction of autophagy and apoptosis.

nuclear translocation of the apoptosis-inducing factor (AIF) [175,176]. Beclin-1 contains a BH3 domain which binds to multiple antiapoptotic proteins belonging to the Bcl-2 family, such as Bcl-2, Bcl-xL, or Mcl-1 [177]. This interaction represses Beclin-1 activity and significantly reduces initiation of autophagy. When the BH3 domain is phosphorylated, there is a decrease in the binding affinity between these two proteins, resulting in Beclin-1 release and its subsequent activation [178]. Another significant signaling pathway related to reduced apoptotic cell death involves HIF-1α. HIF-1α levels are higher in Sorafenib-resistant HCC tissue samples than observed in Sorafenib-sensitive ones since, through HIF-1α resistant cells upregulate genes implicated in cell proliferation, angiogenesis, migration and autophagy [179]. Sorafenib reduces the expression of HIF-1α targets BCL2 Interacting Protein 3 (BNIP3) and BNIP3-like (NIX) that delay mitophagy, as revealed by their mitochondria and lysosomes colocalization and the autophagosome markers p62 and LC3-II [180].

The induction of apoptosis by Lenvatinib has also been related to reduction of tumor growth in a glioma-derived tumor bearing mice [181]. Lenvatinib significantly reduces Akt and ERK1/2 phosphorylation, cyclin D1 expression and cell proliferation, as well as increases the percentage of apoptotic cells in cultured anaplastic thyroid cancer cells [181]. The induction of ER stress has also been associated with the induction of apoptosis, reduced cell migration and invasiveness in Lenvatinib-treated nasopharyngeal carcinoma cells [17].

The reduction of phospho-ERK and phospho-JNK by Regorafenib have been associated with decreased cell proliferation and induction of apoptosis in cultured liver cancer cells [182]. The induction of apoptosis by Sorafenib [183] and Regorafenib [184] is related to the activation of Src homology region 2 domain-containing phosphatase-1 (SHP-1) and inhibition of STAT3 phosphorylation. Analysis of Bcl-2 family members reveals dose- and time-dependent depletion of anti-apoptotic Mcl-1 in Regorafenib-treated HCT116 cells. A delayed and/or attenuated Mcl-1 degradation is observed in resistant Regorafenib-treated CRC [185]. Cabozantinib reduces cell proliferation and promotes apoptosis *in vitro* and *in vivo* in breast, lung, and glioma tumor cells [186]. Cabozantinib blocks hepatocyte growth factor (HGF)-stimulated c-Met pathway, and inhibits cell migration and invasiveness in cultured liver cancer cells, as well as reduces tumor growth and angiogenesis, and promotes apoptosis in xenograft-mouse model [187]. The reduced phosphorylation of c-Met RET and AXL is related to downregulation of PI3K/mTOR-dependent signaling pathway and increased ATG3, LC3 and Beclin-1 expression upon Cabozantinib treatment in CRC patient-derived tumor xenograft models [157].

9. Concluding remarks

Downregulation of RTK and NRTK by TKIs administration drastically alters cancer hallmarks involving cell survival/death, cellular stress, and metabolism. The alteration of TK-related signaling by TKIs involves the activation of ER stress and UPR that affect the expression of key proteins involved in mitochondrial function, PI3K/TSC/mTOR and AMPK that impact cell metabolism and death (Fig. 6). The balance between $O_2^{.-}$ and H_2O_2 is tightly controlled, and proteins regulating redox status that change the activation/deactivation state of proteins involved in cellular signaling are altered during TKI treatment. The shift between pro- and antitumoral role of autophagy and mitochondria-related events can be involved in the resistance of cancer cells to treatments. In addition, the proximity of tumor cells to the apoptotic cliff promoted by TKI treatment can also limit the induction of cell death in cancer cells. In conclusion, the specific genetic pattern of cancer cells and the prevailing molecular signaling status upon drug pressure that drive resistance to cancer-related hallmarks, support the use of combined TKI treatments.

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