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TAK-ing aim at chemoresistance: The emerging role of MAP3K7 as a target for cancer therapy

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ABSTRACT

Cellular drug resistance remains the main obstacle to the clinical efficacy of cancer chemotherapy. Alterations in key pathways regulating cell cycle checkpoints, apoptosis and Epithelial to Mesenchymal Transition (EMT), such as the Mitogen-activated protein kinase (MAPK) pathway, appear to be closely associated to cancer chemoresistance.

Transforming growth factor-β (TGF-β)- activated kinase 1 (TAK1, also known as MAP3K7) is a serine/threonine kinase in the mitogen-activated protein kinase (MAP3K) family. It represents the cellular hub to which IL1, TGF-β and Wnt signaling pathways converge. By regulating the phosphorylation status and activities of transcription factors including Activated Protein-1 (AP-1) and nuclear factor κ-B (NF-κB), TAK1 mediates inflammatory and pro-survival responses. The interest towards the therapeutic targeting of TAK1 is due to its identification as one of the main mediators of both chemoresistance and EMT in several types of tumors, and as the possible target for a subset of treatment-refractory colon cancers exhibiting mutated KRAS or activated WNT pathways. For these reasons, many efforts have been made to design inhibitors of TAK1 kinase activity, which could be used to reverse TAK1-mediated chemoresistance. The activity of these inhibitors, in combination with the most commonly used chemotherapeutic drugs, has been tested in preclinical studies, proving the efficacy of TAK1 inhibition in reducing tumor growth and survival following chemotherapy administration. In the first part of this review, we describe the mechanisms underlying TAK1 regulation such as phosphorylation, ubiquitination and targeting by microRNAs. We then focus on the development of therapeutic small molecule inhibitors of TAK1 kinase activity, as well as preclinical studies supporting the role of TAK1 as a potential target for enhancing the response of tumors to anticancer therapies.

Background

The main obstacle to the clinical efficacy of cancer chemotherapy is the pre-existence or the development of cellular drug resistance (Gonen and Assaraf, 2012; Gottesman et al., 2016; Li et al., 2016; Livney and Assaraf, 2013; Shapira et al., 2011; Szakacs et al., 2014; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016). The ability of certain cancers to resist the cytotoxic effects of cancer chemotherapy appears to be closely associated with alterations in key pathways involved in cell-cycle checkpoint control and, most importantly, apoptosis (Melisi et al., 2013). Recent data suggest a critical role for tumor microenvironment in the development and maintenance of chemoresistance. In particular, cancer-related inflammation, one of the main features of the tumor microenvironment, is now accepted as enabling some of the most relevant characteristics of cancer, including chemoresistance (Khalafalla and Khan, 2017).

Several autocrine and/or paracrine pro-inflammatory factors as well as therapeutic approaches – including chemotherapy and radiotherapy – lead to the activation of different transcription factors involved in regulation of apoptosis. Nuclear Factor κB (NF-κB) is the most relevant of these transcription factors by representing a key mechanistic link between inflammation and cancer chemoresistance (Hoesel and Schmid, 2013; Melisi and Chiao, 2007). The activation of NF-κB suppresses the potential of pro-apoptotic stimuli by driving the expression of several antiapoptotic genes, thereby suppressing the cytotoxicity of chemotherapeutic agents. Unfortunately, direct targeting of NF-κB for cancer therapeutics still faces enormous challenges (Carbone and

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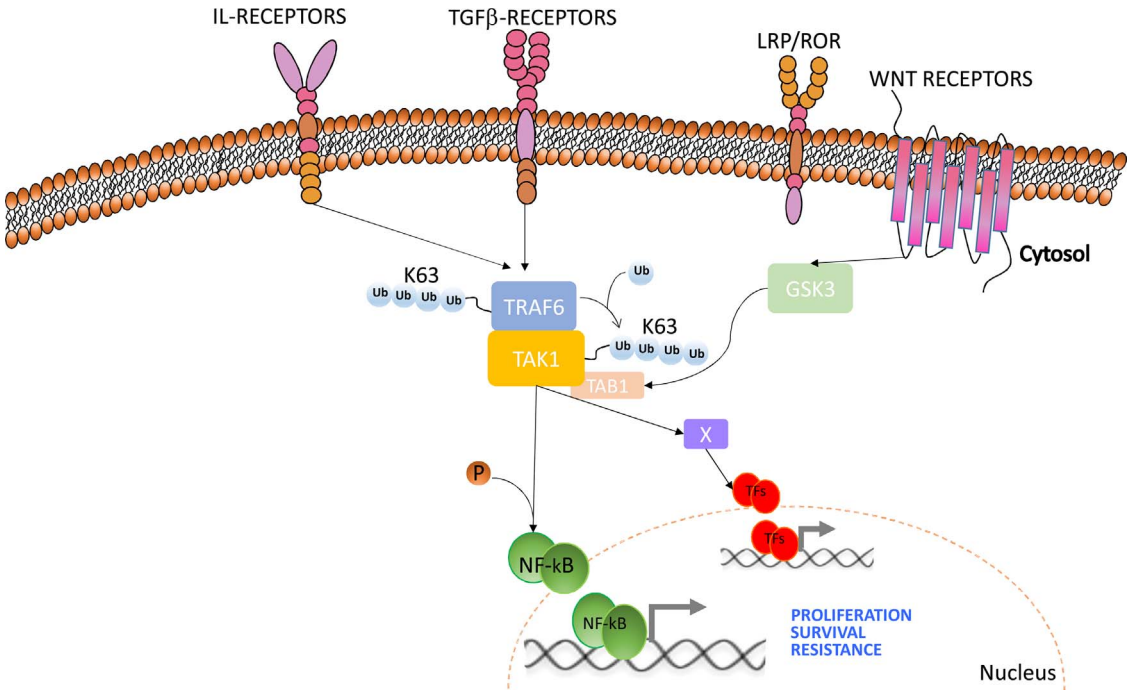

Fig. 1. TAK1 is the central hub for diverse signaling pathways. Following stimulation by their ligands, IL and TGFβ receptors trigger the activation of the E3 ubiquitin ligase TRAF6, which mediates the activating K63-linked polyubiquitination of TAK1. Instead, WNT receptors regulate the activity of GSK3 that in turn stabilizes the TAB1-TAK1 complex, thus activating TAK1. Active TAK1 mediates the transcriptional reprogramming of cancer cells towards proliferation, survival and resistance to chemotherapy by: (i) boosting NF-κB phosphorylation and transcriptional activity; (ii) triggering additional signaling pathways mediated by several proteins such as p38, JNK, NLK (indicated as X) and acting on different transcription factors (TFs).

Melisi, 2012; Darvishi et al., 2017; Durand and Baldwin, 2017).

Transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1, also known as MAP3K7) is a serine/threonine kinase in the mitogen-activated protein kinase (MAP3K) family. In the past decade, TAK1 has been clearly demonstrated as a key player in inflammatory responses and regulation of cell survival, as it integrates signals from various cytokines – including interleukin-1 (IL-1), TGF-β, and toll-like receptors (TLR) – controlling, in turn, the activation of different transcription factors, such as activator protein-1 (AP-1), and NF-κB (Sakurai, 2012) (Fig. 1). In this respect, TAK1 represents the possible missing link between the proinflammatory tumor microenvironment and the resistance of cancer cells to the proapoptotic activity of chemotherapeutic agents. Targeting TAK1 as a non-redundant cytosolic mediator of the activation of NF-κB might represent a novel approach to modulate the intrinsic and acquired chemoresistance of more refractory tumors addicted to the activity of this transcription factor.

In this review, we describe and discuss the most recent and compelling evidence supporting the role of TAK1 as a potential druggable target for cancer treatment.

Molecular mechanisms regulating TAK1 signaling

Following stress conditions and stimulation by proinflammatory cytokines, TAK1 undergoes multiple post translational modifications, such as phosphorylation/dephosphorylation and ubiquitination (Mihaly et al., 2014; Sakurai, 2012). IL-1 treatment has been shown to induce activation of TAK1 by means of phosphorylation of Thr-178 and Thr-184 residues residing in its kinase activation loop (Bertelsen and Sanfridson, 2007; Mendoza et al., 2008), as well as by inducing the TNF receptor-associated factor 6 (TRAF6) mediated K63-linked ubiquitination of TAK1 on Lys-209 (Singh et al., 2012; Sorrentino et al., 2008; Waters et al., 2013). This translates into the activation of the transcription factor NF-κB (Adhikari et al., 2007), thus making IL-1 an important mediator of immune and inflammatory responses. In particular, we demonstrated that an IL1α feedforward loop is responsible for the activation of NF-κB by KrasG12D, and is required for the development of pancreatic cancer through the expression of several inflammation-related signaling pathways, including TAK1 (Ling et al., 2012). Along the same line, IL-17 induces a Mitogen-Activated Protein Kinase 8 (TPL2)-mediated phosphorylation of TAK1, thereby activating JNK, p38 and NF-κB and promoting autoimmune neuroinflammation (Xiao et al., 2014).

TGF-β principally exerts its effects through the canonical Smad pathway. However, attention is also being focused on the non-canonical pathway, which triggers MAPKs and NF-κB activation. The binding of TGF-β to TGF-β receptors type 1 and 2 (TβRI and TβRII) increases their association with TRAF6, which undergoes auto-ubiquitination and causes K63-linked poly-ubiquitination of TAK1, leading to p38 phosphorylation and sustainment of pro-survival pathways, such as NF-κB (Sorrentino et al., 2008; Wi et al., 2014; Yamashita et al., 2008). In addition to TRAF6, the E3 ubiquitin ligase XIAP has been shown to mediate TAK1 ubiquitination and activation, thus inducing NF-κB (Augeri et al., 2016; Lu et al., 2007; Melvin et al., 2011). All these proteins activate TAK1 through K63-linked ubiquitination, implying that ubiquitination is the key mechanism for TAK1 regulation. TAK1 can be polyubiquitinated with K48-linked chains by E3 ubiquitin ligases like Itch/AIP4 and de-ubiquitinated by deubiquitinating enzymes such as CYLD (Guo et al., 2016; Nikolaou et al., 2012; Sakurai, 2012), USP4 that is activated upon TNFα stimulation to prevent NF-κB activation (Fan et al., 2011; He et al., 2016; Liang et al., 2013), and USP18 that promotes Th17 differentiation of T cells through de-ubiquitination of TAK1 and consequent inactivation of NF-κB (An et al., 2017; Liu et al., 2013; Yang et al., 2015).

The Wnt signaling pathway regulates proliferation and differentiation of cells and its deregulation can cause aberrant proliferation and cancer (Nusse and Clevers, 2017). Different studies also demonstrated a role for TAK1 in mediating non-canonical WNT signaling (Kanei-Ishii et al., 2008; Song et al., 2013; Sugimura and Li, 2010; Winkel et al., 2008; Yumoto et al., 2013). Wnt1 stimulation resulted in autophosphorylation and activation of TAK1 in a TAB1-dependent fashion,

resulting in the activation of a Nemo-like kinase (NLK)-MAPK cascade, and phosphorylation of TCF/LEF that antagonized the interaction of the β-catenin/TCF complex with DNA (Kanei-Ishii et al., 2008; Smit et al., 2004). In addition, GSK3 inhibition following WNT activation caused TAB1-dependent destabilization of TAK1 in KRAS mutant cells (Bang et al., 2013). The TAK1-NLK-MAPK cascade could be also activated by the non-canonical Wnt5a/Ca^{2+} pathway to counteract canonical β-catenin signaling. However, a kinase-inactive mutant of TAK1(K63W) only minimally reversed the inhibitory effect of Wnt5a on β-catenin activation (Ishitani et al., 2003; Winkel et al., 2008). In a different study, the expression of Wnt5A did not result in kinase activation of TAK1 or phosphorylation of TCF (Smit et al., 2004). More recently, TAK1 was proposed as a downstream effector of the non-canonical pathway triggered by Wnt2, by mediating metastasis-associated survival signals in circulating tumor cells from pancreatic carcinoma (Yu et al., 2012). Thus, the activation of TAK1 by the non-canonical Wnt signaling antagonizes the canonical Wnt pathway (Ishitani et al., 2003; Ishitani et al., 1999; Winkel et al., 2008).

Tumor Necrosis Factor alpha (TNFα) is produced by cancer cells and immune cells within the tumor microenvironment, to support cancer proliferation by establishing an inflammatory niche, but also to induce caspase-8-mediated apoptosis or Receptor Interacting Protein Kinase 3 (RIPK3)-dependent necrosis (Waters et al., 2013). In fibroblasts, the TNFα-induced formation of a macromolecular complex, containing RIPK1, RIPK3 and TAK1, causes RIPK3-mediated phosphorylation of TAK1. In turn, TAK1 inhibits caspase-8 activity, thereby impairing apoptosis and fostering RIPK3-dependent necrosis (Morioka et al., 2014). These observations depict a scenario in which TAK1 represents the cellular node for oncogenic signaling by the tumor environment.

In our previous study, we discovered that both TAK1 and its binding protein TAB1 are overexpressed in pancreatic cancer cell lines as well as tumor specimens from pancreatic cancer patients, and demonstrated that TAK1 stability and activity are regulated by TAB1. TAK1 and TAB1 can stabilize each other through physical interaction (Xia et al., In preparation). Knocking down TAB1 in pancreatic cancer cells with RNAi resulted in decrease of TAK1 expression and *vice versa*, and inhibition or knockdown of TAK1 induced cell apoptosis and significantly reduced the size of tumors in mice, suggesting that TAK1 and TAB1 play an important role in tumorigenesis of pancreatic cancer (Xia et al., In preparation). These findings provide a concept for the use of small molecules to disrupt the interaction between TAK1 and TAB1 as a novel approach of drug discovery.

In addition to post-translational modifications, micro-RNAs are emerging as novel regulators of TAK1 expression and activity. A negative correlation has been observed in pancreatic cancer patients between the tumor suppressor miR-143 and TAK1 expression, and molecular analyses have shown that miR-143 targets TAK1 directly by binding to its 3′UTR. TAK1 downregulation following miR-143 overexpression reduced cell proliferation and migration of pancreatic cancer cell lines, while inhibition of miR-143 induced NF-κB activation (Huang et al., 2017). Likewise, expression of miR-892b is reduced in breast cancer as compared to normal samples, and its levels are inversely correlated to clinical stage. Moreover, miR-892b downregulation sustained NF-κB activation by upregulating TAB3, TRAF2 and TAK1, resulting in increased cell proliferation and metastatic potential of breast cancer cell lines (Jiang et al., 2016). miR-377 has proven to be a direct regulator of TAK1, E2F3 and KRAS, and its overexpression in melanoma cell lines reduced the levels and DNA binding capacity of NF-κB in a TAK1-dependent manner, making it a possible candidate to inhibit both E2F3 and TAK1/NF-κB signaling in melanoma (Zehavi et al., 2015).

Clinical-translational advances

Tumor stroma contributes to tumor progression by influencing the development of pre-metastatic niches and inducing cancer cells towards metastatic genetic programs such as the Epithelial to Mesenchymal Transition or EMT (Smith and Bhowmick, 2016). In this regard, TAK1 triggers EMT by activating NF-κB and downregulating of the expression of the epithelial marker E-cadherin (Strippoli et al., 2010; Yao et al., 2007), thereby triggering EMT. In addition, inhibition of TAK1 reversed IL-1β and TGF-β1-induced EMT by reducing the transcriptional activity of Smad1-5-8 in mesothelial cells (Strippoli et al., 2012), by inhibition of Smad2/3 phosphorylation in retinal pigment epithelial (RPE) cells (Dvashi et al., 2015), and by impairing p38 phosphorylation in breast carcinoma cell lines (Pal et al., 2012; Wu et al., 2014). In addition, TAK1 activity sustains the highly metastatic potential of breast cancer cells by inducing NF-κB-mediated MMP9 expression upon TNFα stimulation and binding to the oncogenic RNA helicase DP103 (Shin et al., 2014). Of notice, in contrast to the abovementioned observations, TAK1 deficiency in skin squamous cell carcinoma cell lines promotes TGF-β1 induced EMT, as confirmed by a decrease in E-cadherin and increase in N-cadherin, vimentin and fibronectin, as well as upregulation of ZEB1 (Lam et al., 2013).

Deficiency of essential modulators of TAK1, such as Itch/AIP4 or CYLD, enhances tumor-associated macrophage-induced inflammation and metastasis (Ahmed et al., 2011) and the TAK1/NF-kB signaling is required for TGF-β induction of metastasis (Safina et al., 2008; Zhang et al., 2013). TAK1 promotes lymphatic invasion of breast cancer through increase in the expression of chemokine C-C motif receptor 7 (CCR7), whereas inhibition of its kinase activity by treatment with 5Z-7-Oxozeaenol (5Z-O) suppresses both lymphatic invasion and lung metastasis (Huang et al., 2015; Pan et al., 2009). Similar results are observed in ovarian cancer, where TAK1 enhances tumor growth and metastatic capacity (Cai et al., 2014), and in colon cancer, where TAK1 has been shown to induce cancer cell migration and lung metastasis upon TNF-α stimulation, by activating both JNK and p38 pathways (Choo et al., 2006; Kan et al., 2013).

In addition to these signaling pathways, TAK1 has been shown to play a key role in the DNA damage response. When DNA damage occurs, cells undergo either cell cycle arrest to repair the DNA damage and avoid the propagation of genomic mutations, or apoptosis if the extent of damage is too prominent. However, DNA damage triggers also pro-survival pathways in tumor cells, among which NF-κB is a crucial event and TAK1 seems to be responsible for its activation. However, as the duration and magnitude of TAK1 activation differs in response to different kinds of genotoxic stimuli (e.g. ionizing radiation and chemotherapy), diverse pathways operate towards TAK1 activation (Hinz et al., 2010; Wu et al., 2010). In addition, genotoxic stimuli induce the activation of the P21 activated kinase 1 (PAK1) (Li et al., 2012) that, in turn, has been shown to prevent gemcitabine-induced DNA damage in pancreatic cancer by activating the TAK1/NF-κB pathway through TAK1 phosphorylation at Ser412 (Jagadeeshan et al., 2016).

In a screen for kinases that differentially promote survival, TAK1 was identified as the most significantly required for tumor cell viability in KRAS-dependent versus KRAS-independent colon cancer cell lines. Notably, a canonical WNT signaling was significantly enriched in KRAS-dependent cells compared to KRAS-independent cells, and the induction of apoptosis by the inhibition of TAK1 in KRAS-dependent cells was linked to the suppression of hyper-activated WNT. Conversely, KRAS-independent cells were largely resistant to TAK1 inhibition, and TAK1 can act as a negative regulator of canonical Wnt signaling in these cells (Singh et al., 2012).

Being the hub between membrane receptors and nuclear transcription factors, TAK1 represents an ideal target for cancer therapy. For these reasons, efforts are being made to design chemical inhibitors for TAK1 to be used in the clinical setting however, so far, none has progressed into clinical development.

To date, the most extensively studied inhibitor of TAK1 is the natural compound 5(*Z*)-7-oxozeaenol, first identified by Ninomiya-Tsuji et al. in 2003, which binds irreversibly to Cys174 located in the ATP-binding pocket of TAK1 (Ninomiya-Tsuji et al., 2003). Since then, it has been used to treat various types of cancer cells. 5(*Z*)-7-oxozeaenol

reduced the proliferation of triple-negative breast cancer cells (Zhang et al., 2017), induced cell cycle arrest, reactive oxygen species (ROS) production and caspase 7-mediated apoptosis in MDA-MB-231 breast cancer cells (Acuna et al., 2012a) and HeLa cervical adenocarcinoma cells (Acuna et al., 2012b). Along the same line, 5(*Z*)-7-oxozeaenol treatment in a panel of neuroblastoma cell lines showed sensitization to both doxorubicin and etoposide and enhanced the efficacy of chemotherapy in mouse xenografts (Fan et al., 2013). 5(*Z*)-7-oxozeaenol proved also effective in attenuating tumor growth and metastatic potential of ovarian cancer cells both *in vitro* and *in vivo* (Cai et al., 2014), and in sensitization of both ovarian and cervical cancer cells to chemotherapy-induced cell death (Bo et al., 2016; Guan et al., 2017). In addition, 5(*Z*)-7-oxozeaenol abrogated remarkably WNT-2-induced tumor spheres and suppressed Fibronectin 1 (FN1) expression in pancreatic cancer cells, thus reversing the pro-survival and pro-metastatic phenotype induced by WNT-2 (Yu et al., 2012). A synergistic pro-apoptotic effect of the proteasome inhibitor bortezomib and 5(*Z*)-7-oxozeaenol was observed in the Burkitt's lymphoma cell line Daudi (Zhang et al., 2016). Finally, treatment of esophageal adenocarcinoma cells with 5(*Z*)-7-oxozeaenol in combination with cisplatin and paclitaxel sensitized the cells to apoptosis, which seemed to be mediated by a TAK1-dependent reduction in the levels of the antiapoptotic BIRC3 protein (Piro et al., 2015). However, 5(*Z*)-7-oxozeaenol has not shown high selectivity for TAK1, proving to be also a potent inhibitor of other kinases, such as TβR and MEK1/2, thus excluding the possibility to use it for therapeutic purposes (Wu et al., 2013). As a consequence, 5(*Z*)-7-oxozeaenol analogues are being synthesized and tested for their specificity and activity (Fakhouri et al., 2015).

Treatment of pancreatic cancer cells with the orally active TAK1 inhibitor LYTAK1 reduced chemoresistance to oxaliplatin, gemcitabine and SN38, and it reduced tumor volume and prolonged survival in mice harboring pancreatic cancer xenografts and treated with the above-mentioned drugs (Melisi et al., 2011). In addition, LYTAK1 proved effective in reducing the growth of KRAS mutant colorectal carcinoma cell lines both *in vitro* and *in vivo* (Zhou et al., 2015), as well as proliferation and EMT in retinal pigment epithelium cells (Chen et al., 2016). Also ovarian cancer cell lines overexpressing TAK1 were impaired in their growth when treated with LYTAK1, and the combination of paclitaxel and LYTAK1 impaired the proliferation of SKOV3 cells in nude mice xenografts (Ying et al., 2015).

The ATP-competitive inhibitor of TAK1, AZ-TAK1, caused a TAK1-dependent inhibition of p38 phosphorylation and NF-κB nuclear translocation. Furthermore, AZ-TAK1 induced a downregulation of XIAP and increase in caspase 9-mediated apoptosis in primary lymphoma cells, which could be rescued by treatment with the caspase 9 inhibitor Z-LEHD-FMK (Buglio et al., 2012). Moreover, treatment with either AZ-TAK1 or 5(*Z*)-7-oxozeaenol increased apoptosis in acute myeloid leukemia (AML) $CD34^+$ cells, but not in normal $CD34^+$ cells, at least in part through activation of NF-κB (Bosman et al., 2014).

NG25 is a different ATP-competitive inhibitor of TAK1, designed using a pharmacophore model and identified through a kinome screen as a targeting agent of both TAK1 and GCK/MAP4K2 (Tan et al., 2015). NG25 used as a monotherapy drug showed a cytotoxic effect in breast cancer cell lines and it enhanced doxorubicin-induced apoptosis by inhibiting the TAK1/NF-κB axis (Wang et al., 2016). Unlike NG25 and other inhibitors, the newly designed aminobenzimidazole Takinib targets TAK1 with a 45-fold higher potency as compared to GCK and more than 15-fold as compared to IRAK1 and IRAK4, while it does not modulate p38 activity. Takinib proved effective in suppressing the TAK1-sustained prosurvival signaling triggered by TNF-α stimulation in breast cancer cells (Totzke et al., 2017).

IL1 receptor antagonist (IL1Ra) is a physiological inhibitor of IL1 signaling that competitively binds to IL1 receptors without transmitting an activation signal. Recombinant IL1Ra, also called anakinra (Kineret; Amgen/Biovitrum), is currently indicated for the management of signs and symptoms of rheumatoid arthritis and other autoinflammatory diseases. We recently demonstrated that anakinra could contribute to modulate the acquired resistance to anti-VEGF treatment (Carbone et al., 2016), and, it could reduce tumor growth when given with or without gemcitabine in pancreatic cancer models by modulating TAK1 activity (Zhuang et al., 2016).

Taken together, these reports point out that TAK1 inhibition could be widely used as an adjuvant therapy in many types of cancers. However, due to the low selectivity of the existing inhibitors towards TAK1 or the high concentrations to be used, structure-based development coupled to high-throughput screening for novel selective TAK1 inhibitors has been performed and several inhibitors with IC_{50} enzymatic activity in the nanomolar range have been designed (Hornberger et al., 2013a; Hornberger et al., 2013b; Tan et al., 2017).

Conclusions and future perspectives

Alterations in the TGF-β, IL1 and WNT signaling pathways are very common events in several types of cancers, and cancer-related inflammation in the tumor microenvironment has been shown to contribute to anticancer drug resistance (Gottesman et al., 2016; Khalafalla and Khan, 2017; Wijdeven et al., 2016). TAK1 has been clearly demonstrated as one of the main mediators of inflammatory response, as well as the central hub for triggering TGF-β, IL1 and WNT signaling towards cell survival and EMT, mostly by promoting the activity of transcription factors such as NF-κB (Chen et al., 2016; Martin et al., 2011; Piro et al., 2015; Singh et al., 2012). These characteristics make it an interesting target to turn off cancer cell survival and drug resistance mechanisms. However, although TAK1 could be an attractive molecular target, its pleiotropic activities in a wide range of key physiological processes including inflammation, immune system homeostasis, and neural development, increase the risk of adverse side effects related to the inhibition of its kinase activity. For instance, conditional TAK1 KO in liver parenchymal cells has been reported to cause hepatocyte dysplasia and liver carcinogenesis, with impaired NF-κB signaling, as well as spontaneous apoptosis of hepatocytes and cholangiocytes, fibrosis, inflammation and carcinogenesis (Bettermann et al., 2010; Inokuchi et al., 2010; Roh et al., 2014). In addition, epidermal-specific KO induced severe inflammatory skin condition and massive keratinocyte apoptosis, with impaired NF-κB and JNK signaling (Omori et al., 2006), while conditional KO of TAK1 in Hematopoietic Stem/Progenitor Cells (HSPC) caused massive apoptosis in spleen, thymus, liver and bone marrow, together with complete abrogation of both NF-κB and JNK signaling in bone marrow (Tang et al., 2008), In addition, besides potentiation of the cytotoxicity in combination with classic chemotherapeutic agents, TAK1 inhibition could therapeutically target both bacterial and viral infections. In this respect, the use of immunocompromised murine models kept under axenic conditions in the preclinical studies with TAK1 inhibitors could, indeed, underestimate the potential toxicities of these agents.

In order to reduce the risk of relevant side effects of TAK1 inhibition, but still taking advantage of the sensitization to chemotherapeutic agents, the intermittent administration of TAK1 inhibitors in combination with the continuous infusion of proapoptotic chemotherapeutic agents could be an appropriate strategy. Therefore, we believe that in the clinical development of this class of inhibitors, it will be of primary importance not only to define the recommended doses but, in particular, the development of adequate treatment schedules for combination strategies with TAK1 inhibitors and classic chemotherapeutic agents.

In addition, it is worth noting that recent reports show that the expression of Programmed death ligand 1 (PD-L1) immune checkpoint is induced by NF-κB in natural killer/T-cell lymphoma (Bi et al., 2016), melanoma (Gowrishankar et al., 2015) and ovarian cancer (Peng et al., 2015), and that the inflammatory MUC1-TAK1- NF-κB axis has been identified as the driver of PD-L1 expression in non-small cell lung cancer (Bouillez et al., 2017). These findings identify an additional

mode for TAK1 to sustain cancer cell survival by evading immune surveillance.

These findings confirm that additional studies are warranted to further dissect the different molecular pathways regulated by TAK1 that could be relevant in the pathogenesis of human tumors. Deciphering the role of TAK1 in processes such as tumor initiation and progression, metastasis, cancer cells' stemness, as well as adaptive immune resistance, will be of major relevance in order to develop the inhibition of this kinase for additional purposes, including post-resection adjuvant treatment and cancer chemoprevention.

Disclosure of potential conflicts of interest

Authors have no potential conflicts of interest to disclose.

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