BBA - Molecular Basis of Disease 1869 (2023) 166660

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

Tumor progression locus 2 (TPL2): A Cot-plicated progression from inflammation to chronic liver disease

Alejandro H. Gutierrez [a], Marina S. Mazariegos [a], Susana Alemany [b,c], Yulia A. Nevzorova [a,d,e], Francisco Javier Cubero [a,d,e], Carlos Sanz-García [a,*]

[a] Department of Immunology, Ophthalmology and ENT, Complutense University School of Medicine, 28040 Madrid, Spain
[b] Department of Metabolism and Cell Signaling, Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, 28049 Madrid, Spain
[c] Biomedicine Unit (Unidad Asociada al CSIC), Universidad de Las Palmas de Gran Canaria, 35001 Las Palmas, Spain
[d] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), 28029 Madrid, Spain
[e] Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), 28007 Madrid, Spain

ARTICLE INFO

Keywords:
MAPK
Tumor progression locus 2
Cancer Osaka thyroid
Inflammation
Chronic liver disease
cancer

ABSTRACT

The cytoplasmic protein tumor progression locus 2 (TPL2), also known as cancer Osaka thyroid (Cot), or MAP3K8, is thought to have a significant role in a variety of cancers and illnesses and it is a key component in the activation pathway for the expression of inflammatory mediators. Despite the tight connection between inflammation and TPL2, its function has not been extensively studied in chronic liver disease (CLD), a major cause of morbidity and mortality worldwide. Here, we analyze more in detail the significance of TPL2 in CLD to shed light on the pathological and molecular transduction pattern of TPL2 during the progression of CLD. This might result in important advancements and enable progress in the diagnosis and treatment of CLD.

1. Introduction

Chronic liver disease (CLD) is one of the major causes of morbidity and mortality worldwide. It consists of a wide range of liver pathologies ranging from inflammation (chronic hepatitis) to liver fibrosis and cirrhosis, which finally can develop an end-stage of hepatocellular carcinoma (HCC). Risk factors such as alcohol consumption, viral hepatitis, drugs and obesity and/or diabetes leading to metabolic syndrome make occident the largest affected area of liver disease in the world [1].

Most of inflammatory diseases, including CLD, are characterized by the activation of mitogen-activated protein kinase (MAPK) pathway and the phosphorylation and activation of the nuclear factor-κB (NF-κB) leading to the expression of several genes involved in many processes, which play a key role in the development of inflammation and progression of different diseases and cancers [2] (Fig. 1).

The mitogen-activated protein kinase (MAPK) cascades are among the most important signaling pathways in the cell. They perform a wide range of functions, but there are still questions regarding the true mechanism behind the signal transduction, which remain unanswered. MAPK cascade is an evolutionarily conserved signaling pathway in

Abbreviations: AA, Amino Acids; Acrp30, Adiponectin; ADH, Alcohol dehydrogenase; AHD4, ABIN2 homeodomain 4; ALDH, Aldehyde dehydrogenase; APAP, Acetaminophen; ArLD, Alcohol related liver disease; BMDM, Bone marrow-derived macrophages; C1, Compound 1; CLD, Chronic liver disease; ConA, Concanavalin A; Cot, Cancer Osaka thyroid; COX2, Ciclo-oxygenase 2; C-terminus, Carboxy-terminus; DC, Dendritic cell; DD, Death domain; DILI, Drug induced liver injury; ERK, Extracellular-signal-regulated kinases; FAK, Focal adhesion kinase; FAs, Fatty acids; GSH, Glutathione; HCC, Hepatocellular carcinoma; HSC, Hepatic stellate cells; IL, Interleukin; IL-1-R, Interleukin 1 receptor; JNK, C-jun N-terminal kinase; KC, Kupffer cell; kDa, kilo Dalton; KD, Kinase domain; LPS, Lipopolysaccharides; MAPK, Mitogen-activated protein kinase; MCD, Methionine-choline–deficient; MCMV, Murine cytomegalovirus; MDSC, Myeloid derived suppressor cells; MK5, Mitogen-activated protein kinase-activated protein kinase-5; MMP-1, Matrix metalloproteinase-1; MMTV, Mouse mammary tumor viral; MoMuLV, Moloney murine leukemia virus; NAFLD, Non-alcoholic fatty liver disease; NAPQI, *N*-acetyl-p-benzoquinone imine; NASH, Non-alcoholic steatohepatitis; NFAT, Nuclear factor of activated T cells; NF-κB, Nuclear factor κB; NK, Natural killer; NSADs, Non-steroidal anti-inflammatory medication; NSCLC, Non-small cell lung cancer; N-terminus, Amino-terminus; PAMP, Pathogen-associated molecular patterns; PAR1, Proteinase-activated receptor 1; PBC, Primary biliary cholangitis; PGE2, Prostaglandin E2; PLD, Phospholipase D; PRR, Pattern recognition receptors; ROS, Reactive oxygen species; SAPK, Stress-activated protein kinases; TCR, T- cell receptor; TLR, Toll-like receptor; TNFα, Tumor necrosis factor α; TNFR, Tumor necrosis factor receptor; TPL2, Tumor progression locus 2.

* Corresponding author.
E-mail address: csanz17@ucm.es (C. Sanz-García).

https://doi.org/10.1016/j.bbadis.2023.166660
Received 26 October 2022; Received in revised form 24 January 2023; Accepted 30 January 2023
Available online 8 February 2023

eukaryotic cells, as it is found in all eukaryotic organisms performing crucial tasks, including controlling cell proliferation, survival and cell death [3]. In response to a variety of extracellular signals such as growth factors, cytokines and physical/chemical stressors, MAPKs can also control DNA transcription without the need of enzymes [4,5]. There are three main core kinases in each cascade, which are MAP3K, MAP2K, and MAPK, frequently accompanied by additional upstream and downstream elements (MAP4K and MAPKAPK). The signal is sent within each of the cascades by successive phosphorylations in serine/threonine residues and activation of the sequential kinases, resulting in the phosphorylation of the target regulatory proteins by the MAPK and MAPK-activated protein kinases (MAPKAPK) components [6]. In detail, the signal transduction through its receptor allows the phosphorylation of the MAP3K and its activation; activated MAP3K is able to phosphorylate MAP2K (MEK) and finally, MEK will phosphorylate MAPK [7]. ERK, c-jun N-terminal kinase/stress-activated protein kinases (JNK or SAPK) and MAPK14 (p38) are the three main subfamilies of MAPK cascades. Although there are quite established activation pathways upon different stimuli and situations, MAP3K may activate different MAP2Ks, leading to various MAPKs phosphorylation [8–10]. There are a number of atypical MAPKs such as ERK3, ERK4, ERK7, ERK8 and nemo-like kinase (NLK) which meet at different MAPKAPKs, such as mitogen-activated protein kinase-activated protein kinase-5 (MK5) [5,8].

Lately, the Tpl2-MEK1/2-Erk1/2 axis has been described as an activator of inflammation in different liver pathologies and cancer [5]. Concretely, Tpl2, a MAP3K, induces the expression of pro-inflammatory mediators which lead to further stages of CLD such as fibrosis, cirrhosis and HCC. Thus, the potential therapeutic use of TPL2 could mitigate the symptomatology of inflammation in chronic hepatic patients as well as the progression of liver disease, opening a new door to novel treatment strategies in liver research. In this review, we focus on the innovative advances in the role of TPL2 and its activation cascade in the different stages of CLD and the end-stage of HCC.

2. Tumor progression locus 2 (TPL2): structure and function

Tumor progression locus 2 (TPL2) is also known as cancer Osaka thyroid (Cot) or MAP3K8. TPL2 is a cytoplasmic protein which was first described as an oncogene and a target for provirus integration in mice with T cell lymphomas caused by the mouse mammary tumor viral (MMTV) and mammary carcinomas caused by the Moloney murine leukemia virus (MoMuLV) [11–13]. Its structure consists of 467 amino acids (AA), and three different parts can be found: the amino-terminus (N-terminus), the kinase domain (138AA–388AA) and finally, the carboxy-terminus (C-terminus), which contains a degron sequence (435AA-457AA) to control the stability of the protein, specifically in the binding region of TPL2 to NF-κB1 (p105). When the C-terminus domain (398-467AA) of TPL2 interacts with p105, the access to the active site of TPL2 is blocked, and the protein remains stabilized in its inactive form [14,15]. TPL2 is highly expressed in several cell types including splenocytes, fibroblasts, peritoneal macrophages, bone marrow-derived macrophages (BMDM) and differentiated adipocytes. It is also highly expressed in the neonatal digestive system, thymus, spleen and finally, in the adult submandibular gland [16,17].

The majority of total cellular p105 (NF-κB1) (>95 % in macrophages) is not complexed with TPL2, but rather likely linked to Rel proteins, even though all detectable cellular TPL2 in unstimulated cells is interacting with p105. It is also remarkable that TPL2 has two translation initiation sites, M1 and M30, which produce two different isoforms, 58-kDa (p58) and 52-kDa (p52) proteins at equimolar quantities. Both isoforms separately bind to p105 and ABIN2 (NF-κB2) to create a ternary complex that renders TPL2 inactive [18]. The kinase domain (KD) binds to the p105 death domain (DD), and the TPL2 C-terminus binds to the ABIN2 homeodomain 4 (AHD4), forming a stable complex with the other two proteins. This is critical in order to maintain stability and a steady state level, as these connections prevent the hydrolysis of the NF-κB precursor protein p105, which prevents TPL2 from being released from any of the complexes [19,20]. It is noteworthy that p38MAPKγ/δ, which is likewise activated by MKK3/6, has just come to light as also being crucial for preserving a steady state of TPL2 [21,22].

For the activation of TPL2 it is necessary a stimulatory signal. The critical first step is the pattern recognition receptors (PRR) identification of pathogen-associated molecular patterns (PAMP) or damage-associated molecular patterns (DAMP), which through the toll-like receptor (TLR), interleukin (IL) 1 receptor (IL-1-R), T- cell receptor (TCR), tumor necrosis factor receptor (TNFR) and CD40L receptors, will lead to the activation of the IKK complex (IKKα, IKKβ and IKKγ (NEMO)), by TAK1 [11,23,24]. This complex will be in charge of phosphorylating p105 at S927 and S932, creating a binding site for $SCF^{\beta TrCP}$ ubiquitin E3 ligase complex which links to IκBα. This will provoke p105 complete

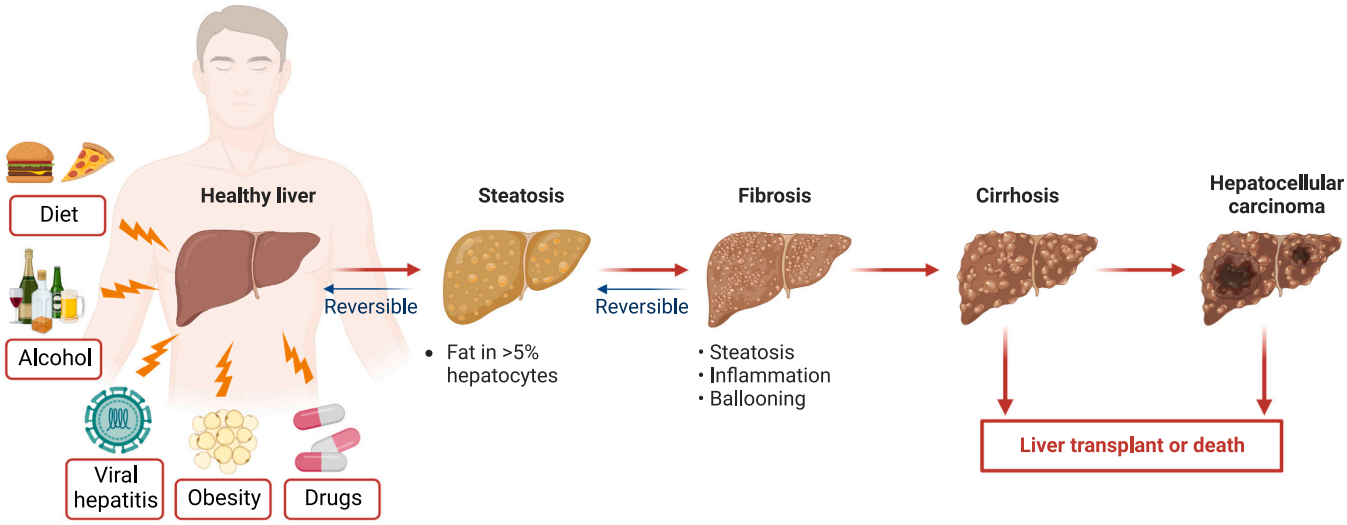

Fig. 1. The progression of CLD. Different factors can alter the liver, such as high-fat diet, alcohol intake, viral hepatitis, obesity or drug consumption. In the progression of CLD there are different stages, starting with a reversible stage of steatosis (>5 % fat in hepatocytes), followed by a still reversible stage of fibrosis associated with ballooning and inflammation and finally reaching the irreversible stages of cirrhosis and HCC, where a liver transplantation is required. Made by Biorender®.

degradation by the 26S proteasome, releasing TPL2 from the complex [11,12,14,25]. Similar to how NF-κB dimers are activated in the traditional route, IKK-induced proteolysis of p105 releases associated NF-κB dimers (C-Rel, Rel-A, p50), which subsequently are ready to be phosphorylated by a MAPK and translocate to the nucleus to start their transcriptional program. After p105 is degraded, the TPL2 complex also releases ABIN-2, which has unclear signaling properties but interacts with different proteins, such as A20, a known ubiquitination regulator protein, seen to have a role in the NF-κB inhibition [26]. Once TPL2 is released from the complex, it is phosphorylated in several sites, causing a different activation (site-dependent) and also, degradation via proteasome. T290 and S400 autophosphorylation contributes to the kinase activity, activating then the ERK MAP kinase signaling cascade [18,27–30] (Fig. 2).

TPL2, Ras and Raf-1 work together to activate MAPK in this system when TPL2 is present. Consequently, TPL2 activation may be inhibited by the activation of RasN17, a dominant negative mutant of c-Ha-Ras, and Raf1S621A, a dominant negative mutant of Raf-1, due to the activation of MEK-1, same substrate target as TPL2. This inhibition has been seen as reversible, since mutant TPL2 (TPL2K167M) partially blocks MAPK activation induced by v-Ha-Ras or by v-Raf [31–34]. The inactivation of TPL2 has been also achieved with different pharmacologic inhibitors, which have been demonstrated to have a potential therapeutic benefit. A clear example is a cell-permeable naphthyridine-cyclohexyl [35] or compound 1 (C1) [36]. Most of the inhibitors act blocking TPL2 phosphorylation and, consequently, its activation. In vitro experiments performed with isolated macrophages from human monocytes showed the inhibition of ERK1/2 after adiponectin (Acrp30) stimulation or the production of tumor necrosis factor α (TNFα) [37,38]. In vivo experiments also showed the reduction of TNFα expression after the inhibitor stimulation in a lipopolysaccharides (LPS)-induced rat model [39,40].

3. TPL2 and immunity: a synergic hub for inflammation

Different cell types work together to coordinate the innate immune response, the body's initial line of defense against infections, which includes the activity of macrophages, dendritic cells (DC), natural killer cells (NK), and neutrophils, among others. In this defense barrier, TPL2 has been understood to be closely related to it, as the TPL2-MEK-ERK pathway in macrophages has been described to control the generation of cytokines [41–46]. TPL2-MEK-ERK axis also regulates another essential molecule that acts in the innate immune response, which is the prostaglandin E2 (PGE2) and its regulatory enzyme cyclooxygenase 2 (COX2) in monocytes [47–51]. Recently, some processes in the innate immune response have been associated to the action of TPL2. The first one is the contribution of TPL2 to neutrophil functions. It has been described that, in the absence of TPL2, there is an impairment of the neutrophil recruitment and their killing capacity in response to an infection. Considering this, TPL2 can be contemplated as a promotor of neutrophil traffic and inflammatory cytokine secretion, implicating TPL2 in one of the first defense mechanisms in the innate immune system. Another step is the implication of TPL2-MEK-ERK cascade in the first line of innate response, TLRs stimulation. In macrophages, TPL2 regulates many processes, not only cytokine production but also cellular responses; and in bone marrow-derived dendritic cells, it regulates the correct activation of p38 MAPK during the stimulation of by LPS or CpG [5,48,52–54]. As a result, this may conclude that TPL2 causes innate immune cells to transduce a wider inflammatory signal (Fig. 3).

On the other hand, in the adaptive immune system, we find two main types of cells, T and B lymphocytes and, in both, TPL2 was observed to have a role [55–57]. In B lymphocytes, the activation via CD40-CD40L (T-dependent) of ERK via TRAF6, requires TPL2. This transduction pathway leads to an important event, the immunoglobulin isotype switching, where CD40-TPL2-ERK signal contributes to IgE production by B cells. Also, in T lymphocytes, TPL2 has been seen to play different roles, such as the induction of IL-2 by the activation of the nuclear factor of activated T cells (NFAT) or the differentiation of Th1/Th2 via INF-γ and IL-17 expression [5,55,58–60] (Fig. 3).

Finally, the relation between MAPK and different immune diseases has recently been described in many cases, as MAPK was seen to have an important function in them. A clear example would be MAP4K3, whose overexpression induces Th17-mediated autoimmune diseases [61]. Another autoimmune disease with MAPK pathways implication is primary biliary cholangitis (PBC) where several MAPK such as MAP2K1 or MAP2K2 are overexpressed [62]. Therefore, we can conclude the potential of MAPK as a therapeutic target.

4. The role of TPL2 in chronic liver disease

Inflammation implies a complicated series of interactions involving soluble substances and cells, and it can occur in any tissue [63]. TPL2 plays a key role in the recruitment, differentiation and activation of immune cells by transmitting numerous intracellular and extracellular stimuli to effector proteins that control the release of pro-inflammatory cytokines, chemokines, enzymes and growth factors [5,11–13]. A massive response upon different risk factors such as alcohol consumption, viral hepatitis, drugs and obesity/diabetes leading to metabolic syndrome may cause an unresolved inflammation progressing to other stages such as fibrosis, cirrhosis and end-stage liver cancer [64]. These stages are included in CLD, a major group of diseases which, in our modern society, represents roughly 2 million deaths each year around the world [65].

4.1. Hepatitis: liver inflammation

Hepatitis is characterized as liver inflammation that can be provoked by a number of factors, including excessive alcohol use, autoimmune conditions, viral infections, medication intake or exposure to pollutants. Depending on how long the liver damage lasts, hepatitis can be further divided into acute and chronic forms; acute hepatitis lasts less than six months, whereas chronic hepatitis can endure more than six months. Normally, acute hepatitis is resolved on its own but, in some cases, it can finally result in fulminating liver failure. Chronic hepatitis can harm the liver and result in severe morbidity and death, caused by hepatic fibrosis, cirrhosis, hepatocellular carcinoma and characteristics of portal hypertension [66–68].

Several studies have utilized viral or bacterial infection with murine cytomegalovirus (MCMV) or *P. acnes*, and also via antigen injection like concavaline A (ConA) and liver homogenates with adjuvants as LPS, to induce hepatitis [69–71]. In a study analyzing the mechanism of TPL2 in hepatocytes and in myeloid derived suppressor cells (MDSC), TPL2 deficient mice which were stimulated with *P. acnes*, were seen to facilitate the recruitment of MDSC to reduce Th1-mediated local inflammation, via IL-25-induced CXCL1/2 chemokines, which in turn, improved fatal hepatitis. This study concluded that TPL2 significantly reduced the degree of acute liver damage and improved hepatitis survival [69]. Another recently conducted study using a murine mild hepatitis model discovered that genetic deletion of *Tpl2* in mice resulted in a good prognosis for liver injury and had an impact on NKT cells activation, seen as a reduction in the levels of early activation markers such as CD69 in the liver, but without affecting the formation of these cells in the thymus [70].

Even though viral hepatitis has still not been related to TPL2 directly, some virus causing this disease have been found interacting with several MAPK, such as hepatitis C virus, which is capable of inducing p38α autophosphorylation [72,73], or hepatitis B virus, which enhances the proliferation, invasion and migration of hepatocytes via p53 [74]. In spite of all these data, more studies should be performed, in order to observe all the implications of MAPK in hepatitis (Table 1).

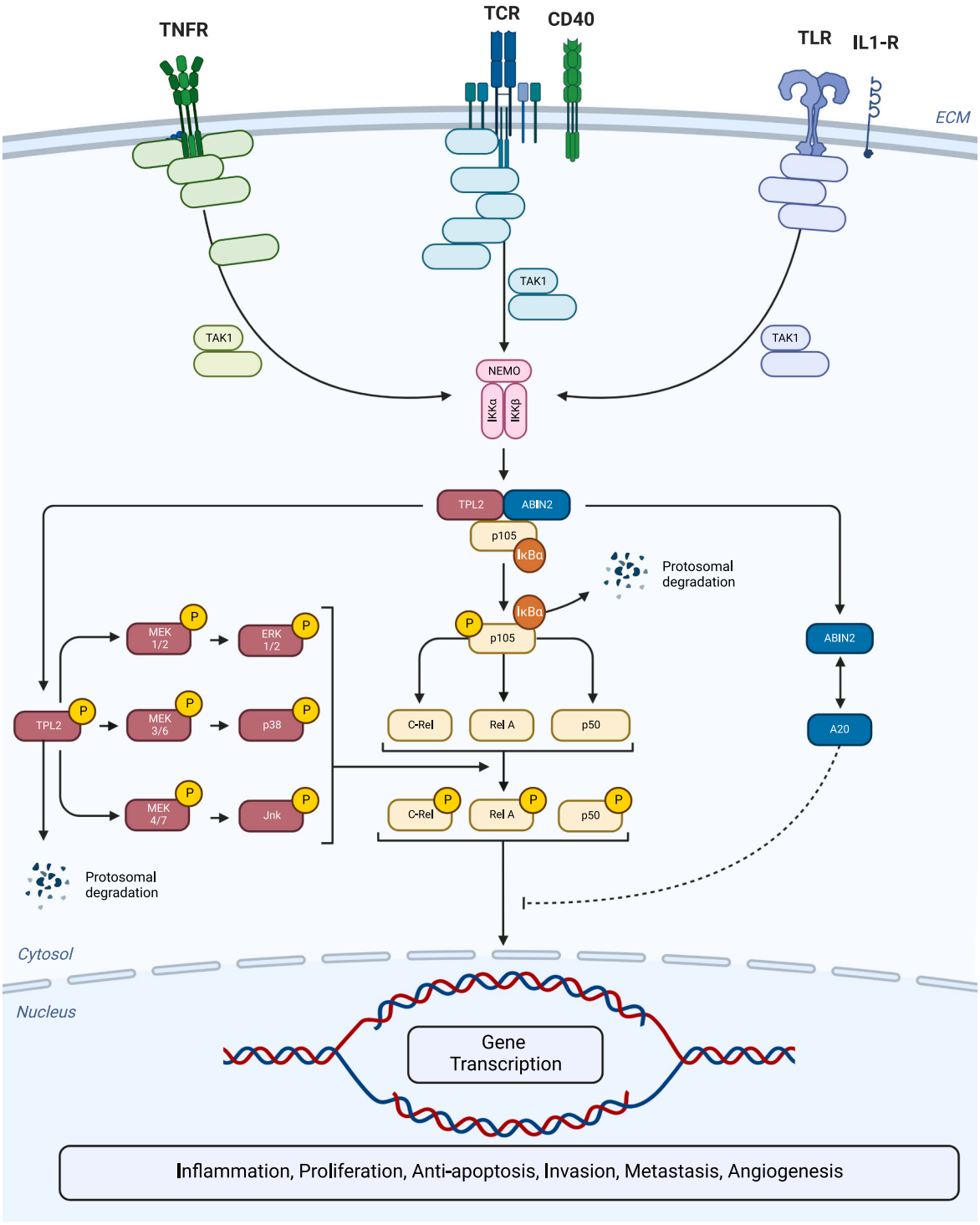

Fig. 2. TPL2 signaling. TPL2 is activated firstly by the recognition of PAMPs and DAMPs by several receptors such as TNFR, TCR, TLR and IL-1R. This signal may translocate to the cytoplasm and activate the IKK complex, formed by IKKα, IKKβ and NEMO (IKKγ). This complex of kinases will phosphorylate the inactive complex of TPL2, p105 and ABIN2, causing the release of the different proteins. TPL2 once gets phosphorylated and activated: 1- will activate the MEK 1/2, MEK 3/6 and MEK 4/7 routes, causing this the activation of ERK1/2, p38 and JNK MAPKs and 2- will be marked for degradation via proteasome. After partial degradation of the complex p105, ERK1/2, p38 and JNK will phosphorylate and activate C-Rel, Rel A and p50, which leads to the translocation to the nucleus and expression of their target genes. NF-κB activation will incite inflammation, proliferation, metastasis, invasion or anti-apoptosis action. Finally, regarding ABIN2 pathway, once it is activated, it will inhibit the NF-κB and MAPK routes via the activation of the deubiquitinase A20. ECM: extra cellular matrix. Made by Biorender®.

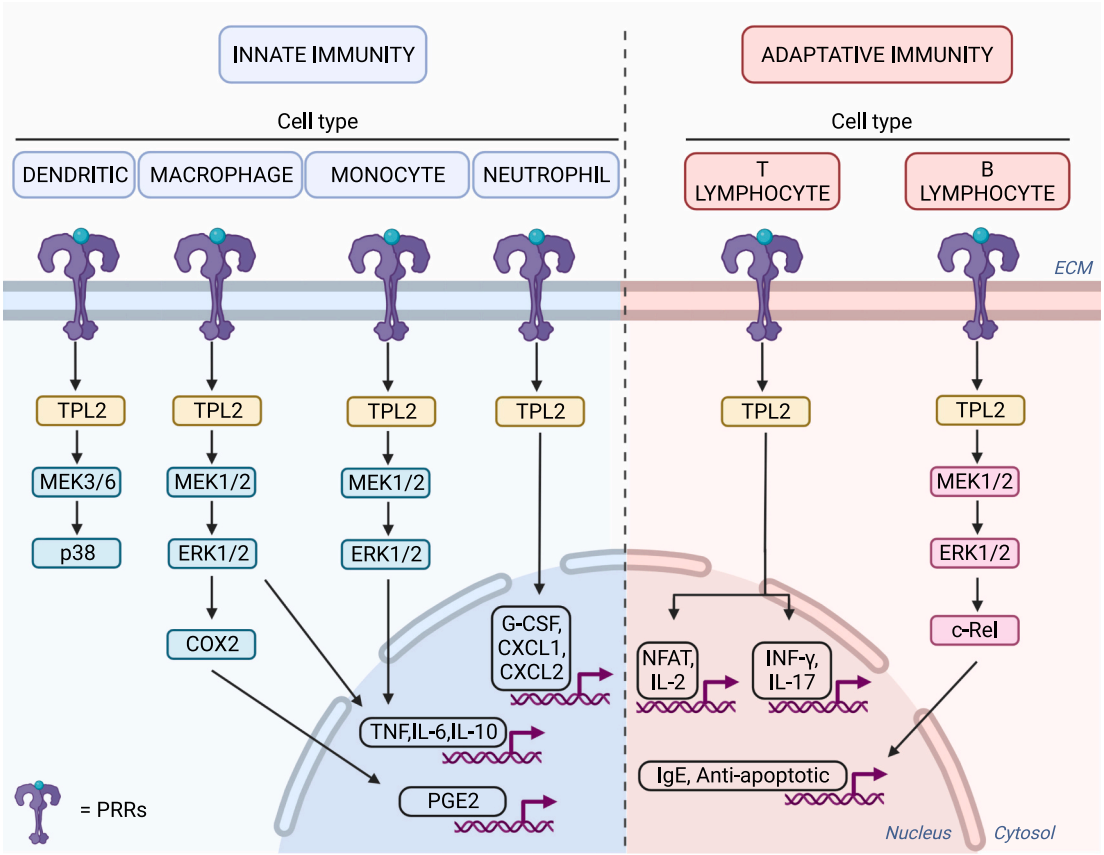

Fig. 3. TPL2 action in the innate and adaptive immunity. In the innate immunity, TPL2 is expressed in macrophages, monocytes and neutrophils, where it mediates the expression of different genes such as PGE, TNF, IL-6, IL-10, G-CSF, CXCL1 and CXCL2. It is also expressed in dendritic cells, where it mediates the expression of p38. Finally, in the adaptive immunity, TPL2 can be detected in T lymphocytes, where it was seen promoting the expression of NFAT, IL-2, INF-γ and IL-17. It is also expressed in B lymphocytes where it takes part in the immunoglobulin isotypes switching and phosphorylation and expression of c-Rel. ECM: extra cellular matrix; PRRs: pattern recognition receptors. Made by Biorender®.

Table 1
TPL2 functionality in CLD.

Pathology	Functionality	Genic expression	References
DILI	Enhancement of liver necrosis ALT/AST release	IL-18 IL-1β	[75,83–86]
ArLD	Enhancement of inflammation	TNF IL-6 IL-1 F4/88	[101,109,110]
NAFLD	Increase of steatosis Enhancement of inflammation	PEPCK G6pase TIMP1 IL1β	[70,116–120]
Hepatitis	Enhancement of Th1 local inflammation	IL25 CXCL1/2	[69,70,72–74]
HCC	Enhancement of nflammation Increase of endoplasmic reticulum stress	IL1β IL18 TNF	[129,131–134]

4.2. Drug induced liver injury (DILI)

The liver, a vital metabolic organ, is extremely vulnerable to drug damage. One of the most popular analgesics and antipyretics in the United States and Western Europe is the acetaminophen (*N*-acetyl-para-aminophenol, paracetamol, APAP), which is also responsible for 50 % of all occurrences of acute liver failure in Western Europe [75–77].

In the past, APAP was first classified as a non-steroidal anti-inflammatory medication (NSADs). However, APAP has been proved as an inefficient anti-inflammatory medication in peripherical tissues, since NSADs block the COX-dependent synthesis of prostaglandins [78], while APAP pharmacological action site is in the central nervous system, producing the inhibition of COX in the brain, being absent in peripherical organs like muscles [79].

When APAP is administered in excess, more APAP metabolism is diverted into the CYP450 pathway, increasing the synthesis of *N*-acetyl-p-benzoquinone imine (NAPQI) [80,81]. Depletion of glutathione (GSH) reserves, both the cytosolic and mitochondrial pools, is one of the initial symptoms of APAP intoxication and excessive NAPQI production [82].

In the last decade, several studies tried to address the role of TPL2 in APAP-induced liver injury. Imaeda et al. observed that TLR9 KO mice had resistance to APAP toxicity. APAP-induced cell death allowed free DNA to activate TLR9, associated with liver injury and expression of pro-IL-1β and pro-IL-18 genes. However, in TLR9 KO, mice were protected against DILI [83]. Another study discovered that TPL2 participated in inflammation mediated by APAP administration. TPL2 KO mice showed lower blood levels of both alanine and aspartate aminotransferases following acetaminophen exposure, decreased liver necrosis and enhanced survival in comparison to WT mice. This study clarified that TPL2 is not a DAMP but is necessary for the activation of ERK1/2 and JNK and the expression of pro-inflammatory genes after inflammation [75]. JNK was seen to aggravate liver injury [84], but also in some investigations was proposed to play a protective role in DILI, where, in hepatocyte and total KO mice, it seems to have combined effects in protecting mice from ibuprofen and acetaminophen-induced liver injury [85,86] (Table 1).

4.3. Alcohol related liver disease (ArLD)

3.3 million people (5.9 % of all fatalities) die each year due to alcohol related liver disease [87]. In the liver, there are two alcohol metabolism processes, one oxidative and the other one non-oxidative. The oxidative process consists in two phases: the first step is the enzyme alcohol dehydrogenase (ADH) action, which transforms alcohol to acetaldehyde by oxidization. In case of excessive alcohol use, CYP2E1 is the enzyme whose expression and activity are increased, instead of ADH. Reactive oxygen species (ROS) are created when CYP2E1 is activated, which encourages the creation of acetaldehyde [88–91]. The second phase occurs when the aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate, which will be metabolized into carbon dioxide (CO2), fatty acids (FAs) and water [92,93]. On the other hand, the non-oxidative process takes place when alcohol is coupled with different endogenous metabolites by various enzymes, such as the phospholipase D (PLD) [94,95]. The metabolites that remain once the metabolism is completed are the ones that will cause the liver damage, as it happens with the acetaldehyde [96,97].

Hepatic steatosis (fatty liver) and alcoholic steatohepatitis are the first two symptoms of ArLD, both of which are caused by LPS entering the bloodstream from the gut and activating Kupffer cells (KCs) (via TLR4) and starting the pro-inflammatory process. If alcohol intake is sustained, then the disease condition can advance to the irreversible phases of fibrosis and cirrhosis, increasing the risk for HCC [98–100].

JNK plays an essential role in alcohol-related inflammation, as Stice and colleagues discovered. Their study demonstrated that the lack of TPL2 reduces the activation of JNK and consequently, the expression of inflammatory cytokines (TNF, IL-6, and IL-1) and macrophage marker (F4/80) mRNA, and provokes a reduction in the prevalence of hepatic inflammatory foci [101].

There is a close relationship between the liver and the gut, where nutrients and microbiota help to maintain a healthy metabolism and liver. It is generally established that gut microbiota contributes to critical human functions including digestion, immunomodulation and angiogenesis stimulation, as well as physiological and pathological aspects of human health [102,103]. Regarding the liver, the microbiota is believed to play a relevant role [104–106]. Drinking alcohol can also alter the composition of the gut microbiota by releasing bacterial products into the bloodstream and activating the immune system. This may trigger several pathogenic mechanisms such as the expression of inflammatory mediators (cytokines and chemokines) that cause immune cells to invade the liver, the production of ROS due to alcohol metabolism, which causes oxidative stress and inflammation, and several other factors [107].

Recently, TPL2 has been linked to *Clostridium difficile* infection, an important bacterium, which takes part in the gut liver axis. It was observed that an inhibition in TPL2 could be a potential therapy for the treatment of the infection [108]. In addition, in a model of colorectal cancer, a worse prognosis has been recently correlated with the overexpression of TPL2 and a recovery with its inhibition [109–111]. These data conclude that TPL2 has also an important function in the intestine and the gut-liver axis (Table 1).

4.4. Non-alcoholic fatty liver disease (NAFLD)

More than one-third of the population suffers from non-alcoholic fatty liver disease (NAFLD), meaning that it is the most common CLD. NAFLD spectrum ranges from simple hepatic steatosis to the concurrent presence of inflammation and ballooning (NASH). Some NASH patients develop fibrosis, which eventually results in cirrhosis and HCC [112].

Fibrosis is a dynamic and reversible process, being the main indicator of the liver disease course. It usually appears as a consequence of chronic liver inflammation, but the main problem is that it remains asymptomatic in most cases, making it difficult to diagnose [113]. In a fibrotic liver, we can observe a continuous inflammation, steatosis with appearance of hepatocyte ballooning and transactivation of quiescent myofibroblasts deriving from hepatic stellate cells (HSC) [114,115].

There are several studies, which have evaluated the role of TPL2 in the liver and systemic metabolic dysfunction, specifically activating the downstream MKK7-JNK1/2 axis, controlling hepatic and systemic metabolic problems caused by persistent low-grade inflammation [70,116,117]. Perfield II et al. observed that TPL2 KO mice were protected against steatosis and inflammation due to a poor activation of ERK and JNK [118], which seemed to aggravate liver inflammation and fibrosis [119]. Moreover, studying the role of TPL2 in the fibrosis progression, a hepatocyte specific TPL2 KO was generated, being observed a reduction in the mRNA expression of PEPCK and G6pase, two essential enzymes for gluconeogenesis, and an increase in glycogen concentration [117]. Another study described that liver from TPL2 KO mice had a significant reduction in fibrogenesis induced by two different models: CCl_4 administration and a methionine-choline–deficient (MCD) diet. [120]. TPL2 appears to contribute to liver steatosis, fibrosis and NAFLD progression, and it is critical for TLR4 stimulation of ERK/JNK-dependent production of pro inflammatory genes. However, other studies did not relate TPL2 role to the progression of NAFLD. For example, Lancaster et al. determined that TPL2 KO mice did not present protection against inflammation and insulin resistance [121]. Other study with human samples demonstrated no differences between healthy subjects and obese patients with similar levels of adipose inflammation. This work also exhibited that TPL2 KO mice displayed higher levels of TNFα in adipose tissue without changes in ERK and NFκB activation, also with insulin resistance [122]. This controversy on the data already published evidence the necessity of further investigation on TPL2 function in NAFLD and the use of a knockout mouse specific for each cell type, to understand completely the mechanism and activation of TPL2 in every sub-cellular family (Table 1).

5. TPL2 as an oncogene in hepatocellular carcinoma (HCC)

Inflammation is frequently linked to the onset and spread of cancer, hence the increasing approach of targeting inflammation as a strategy to prevent and treat cancer. Cells that cause cancer-associated inflammation are genetically stable and do not quickly develop drug resistance [123]. Taking this into account, it is not altogether novel to think that TPL2-driven inflammation and cancer may be related, implying it could act as a cancer promotion adjuvant. Indeed, there are several studies which have described numerous human cancers, such as skin, prostate, breast, ovarian, colorectal, endometrial and gastric cancer, as well as EBV-related nasopharyngeal carcinoma, anaplastic large-cell lymphoma, colitis-associated carcinoma, bladder and cervical cancer, which are linked to poor prognosis and progression when TPL2 activity is elevated [11,13,109,124–128]. In line with this, TPL2 kinase activity has not only been related to cancer by the activation of inflammation it produces, but also to different phases of carcinogenesis, where we can find tumor initiation, promotion and progression, meaning TPL2 can also act as an oncogene [12,126].

Nevertheless, there are cancers such as non-small cell lung cancer (NSCLC) or skin cancer, where the overexpression of TPL2 is correlated with a good prognosis [129–131]. This discrepancy may signify that TPL2 prognostic functions vary based on the type or subtype of tumor [109].

Cancer is highly related to an accumulation of mutations which encourage clonal selection of cells with an aggressive phenotype [132]. Despite mutations in human *TPL2* gene are rare, a variety of them have been described in the components of the signaling pathway which activate the kinase, such as a mutation in MyD88 L265P, which causes an activation inside the Toll/interleukin 1 receptor (TIR) domain [13,133,134]. In addition, there are some evidences suggesting that the TPL2 signal amplification and constitutive kinase activity are caused by mutations occurring in different cancers, for instance in breast cancer and lung adenocarcinoma, denoting that the TPL2 C-terminal may be a

target for mutations in some cancers [12,46,132].

Likewise, TPL2 has been related to cancer metastasis, since both in fibroblasts and tumor cells, TPL2 transduces the proteinase-activated receptor 1 (PAR1). Once PAR1 is activated by thrombin and the matrix metalloproteinase-1 (MMP-1) proteinases, it can be triggered to induce angiogenesis, tumor metastasis, cell transformation, reorganization of the actin cytoskeleton and, finally, to promote the cell migration via ERK and JNK1 activation by the engagement of Rac1 and focal adhesion kinase (FAK) [135–139].

Specifically regarding the liver, we find HCC, whose prevalence is rising and strongly associated with CLD, and whose development is the main reason for screening and monitoring cirrhosis, the biggest risk factor for this malignancy [140]. Several studies have researched the role of TPL2 in HCC, observing that this kinase promotes the increase of pro-inflammatory cytokines such as interleukin IL-1β and IL-18, the activity of the inflammasome and, finally, endoplasmic reticulum stress, enhancing this way the development of HCC [13,125,141]. Additionally, other MAPK have been studied in HCC, such as JNK, which was considered to play a dual role in HCC by acting on hepatocytes to inhibit tumor growth as well as by encouraging an inflammatory hepatic environment that favors tumor formation [142].

6. Conclusion

TPL2 is a common kinase known to play an important role in different types of cancer and diseases, but in CLD it has not been deeply studied yet. Since the molecular mechanisms of CLD at different stages are still not fully understood, there is a limitation regarding the different treatments. Furthermore, the large number of cell types that reside into the liver makes very difficult to understand completely TPL2 role in the development of chronic liver disease. Even if short-term treatment or regular drug usage might reduce symptoms, they cannot stop the progress of the disease at some stages. In this review, we discuss the early impact TPL2 has in CLD, since it is expressed and, consequently, has an impact in the liver. To summarize, TPL2 is associated with the activation of ERK1/2 and JNK in the liver, affecting the expression of different inflammatory mediators.

Early activation of TPL2 in the liver may provoke an inflammation and further progression of the disease. Therefore, the elucidation of the pathological and molecular transduction pattern of TPL2 in the different stages of CLD could lead to significant advances and allow progress in the diagnosis and treatment of CLD. More studies should be conducted to clarify TPL2 role in the progression of liver disease, and particularly, cell-specific studies to understand the function of TPL2 in every cell type.

CRediT authorship contribution statement

A.H.G.; M.S.M.; S.A.; Y.A.N.; F.J.C. AND C.S.G participated in writing and reviewing this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work has received funding from the MICINN Retos PID2020-113299RA-I00, PID2020-11782RB-I00, PID2020-117941RB-I00, PID2020-116146RB-I00 all of which were cofinanced with Fondos FEDER. The European Horizon's research and innovation programme HORIZON-HLTH-2022-STAYHLTH-02 under agreement No 101095679 and COST Action CA17112. CSG is an Atracción de Talento (CAM) Researcher 2019-T1/BMD-13313.

References

[1] L. Pimpin, et al., Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies, J. Hepatol. 69 (3) (2018) 718–735.
[2] A. Shah, C. Patel, A concise review of inflammatory biomarkers targeted cancer therapy, Folia Med. 64 (4) (2022) 572–580.
[3] S.F. Krens, H.P. Spaink, B.E. Snaar-Jagalska, Functions of the MAPK family in vertebrate-development, FEBS Lett. 580 (21) (2006) 4984–4990.
[4] J. Rodriguez, P. Crespo, Working without kinase activity: phosphotransfer-independent functions of extracellular signal-regulated kinases, Sci. Signal. 4 (196) (2011) re3.
[5] H.W. Lee, et al., Tumor progression locus 2 (Tpl2) kinase as a novel therapeutic target for cancer: double-sided effects of Tpl2 on cancer, Int. J. Mol. Sci. 16 (3) (2015) 4471–4491.
[6] A. Plotnikov, et al., The MAPK cascades: signaling components, nuclear roles and mechanisms of nuclear translocation, Biochim. Biophys. Acta 1813 (9) (2011) 1619–1633.
[7] D.R. Caffrey, L.A. O'Neill, D.C. Shields, The evolution of the MAP kinase pathways: coduplication of interacting proteins leads to new signaling cascades, J. Mol. Evol. 49 (5) (1999) 567–582.
[8] J.Y. Fang, B.C. Richardson, The MAPK signalling pathways and colorectal cancer, Lancet Oncol. 6 (5) (2005) 322–327.
[9] K.L. DeCicco-Skinner, M.M. Deshpande, J.S. Wiest, The Role of Tpl2 Protein Kinase in Carcinogenesis and Inflammation, 2012.
[10] A. Escos, et al., TPL2 kinase expression is regulated by the p38gamma/p38delta-dependent association of aconitase-1 with TPL2 mRNA, Proc. Natl. Acad. Sci. U. S. A. 119 (35) (2022), e2204752119.
[11] T. Gantke, S. Sriskantharajah, S.C. Ley, Regulation and function of TPL-2, an IkappaB kinase-regulated MAP kinase kinase kinase, Cell Res. 21 (1) (2011) 131–145.
[12] T. Gantke, et al., IkappaB kinase regulation of the TPL-2/ERK MAPK pathway, Immunol. Rev. 246 (1) (2012) 168–182.
[13] L.W. Njunge, et al., Tumor progression locus 2 (TPL2) in tumor-promoting inflammation,tumorigenesis and tumor immunity, Theranostics 10 (18) (2020) 8343–8364.
[14] D. Xu, et al., TPL2 kinase action and control of inflammation, Pharmacol. Res. 129 (2018) 188–193.
[15] M.L. Gandara, et al., The COOH-terminal domain of wild-type cot regulates its stability and kinase specific activity, Mol. Cell. Biol. 23 (20) (2003) 7377–7390.
[16] M.R. Waterfield, et al., NF-kappaB1/p105 regulates lipopolysaccharide-stimulated MAP kinase signaling by governing the stability and function of the Tpl2 kinase, Mol. Cell 11 (3) (2003) 685–694.
[17] J. Jager, et al., Tpl2 kinase is upregulated in adipose tissue in obesity and may mediate interleukin-1beta and tumor necrosis factor-{alpha} effects on extracellular signal-regulated kinase activation and lipolysis, Diabetes 59 (1) (2010) 61–70.
[18] J. Cho, P.N. Tsichlis, Phosphorylation at Thr-290 regulates Tpl2 binding to NF-kappaB1/p105 and Tpl2 activation and degradation by lipopolysaccharide, Proc. Natl. Acad. Sci. U. S. A. 102 (7) (2005) 2350–2355.
[19] H.T. Yang, et al., Coordinate regulation of TPL-2 and NF-kappaB signaling in macrophages by NF-kappaB1 p105, Mol. Cell. Biol. 32 (17) (2012) 3438–3451.
[20] M.H. Yan, et al., Advancement in TPL2-regulated innate immune response, Immunobiology 224 (3) (2019) 383–387.
[21] M.B. Menon, M. Gaestel, TPL2 meets p38MAPK: emergence of a novel positive feedback loop in inflammation, Biochem. J. 473 (19) (2016) 2995–2999.
[22] A. Risco, et al., p38gamma and p38delta kinases regulate the toll-like receptor 4 (TLR4)-induced cytokine production by controlling ERK1/2 protein kinase pathway activation, Proc. Natl. Acad. Sci. U. S. A. 109 (28) (2012) 11200–11205.
[23] B. Skaug, X. Jiang, Z.J. Chen, The role of ubiquitin in NF-kappaB regulatory pathways, Annu. Rev. Biochem. 78 (2009) 769–796.
[24] S. Vallabhapurapu, M. Karin, Regulation and function of NF-kappaB transcription factors in the immune system, Annu. Rev. Immunol. 27 (2009) 693–733.
[25] V. Lang, et al., ABIN-2 forms a ternary complex with TPL-2 and NF-kappa B1 p105 and is essential for TPL-2 protein stability, Mol. Cell. Biol. 24 (12) (2004) 5235–5248.
[26] L.V. Webb, S. Ventura, S.C. Ley, ABIN-2, of the TPL-2 signaling complex, modulates mammalian inflammation, Trends Immunol. 40 (9) (2019) 799–808.
[27] T.M. Black, et al., Characterization of phosphorylation sites on Tpl2 using IMAC enrichment and a linear ion trap mass spectrometer, J. Proteome Res. 6 (6) (2007) 2269–2276.
[28] M.J. Stafford, et al., Interleukin-1 stimulated activation of the COT catalytic subunit through the phosphorylation of Thr290 and Ser62, FEBS Lett. 580 (16) (2006) 4010–4014.
[29] S.I. Goktuna, IKBKE-driven TPL2 and MEK1 phosphorylations sustain constitutive ERK1/2 activation in tumor cells, EXCLI J. 21 (2022) 436–453.
[30] S. Rousseau, et al., Correction: TPL2-mediated activation of ERK1 and ERK2 regulates the processing of pre-TNFalpha in LPS-stimulated macrophages, J. Cell Sci. 135 (21) (2022).

[31] P.L. Channavajhala, et al., Identification of a novel human kinase supporter of Ras (hKSR-2) that functions as a negative regulator of Cot (Tpl2) signaling, J. Biol. Chem. 278 (47) (2003) 47089–47097.
[32] C.M. Johannessen, et al., COT drives resistance to RAF inhibition through MAP kinase pathway reactivation, Nature 468 (7326) (2010) 968–972.
[33] C. Patriotis, et al., Tpl-2 acts in concert with Ras and Raf-1 to activate mitogen-activated protein kinase, Proc. Natl. Acad. Sci. U. S. A. 91 (21) (1994) 9755–9759.
[34] A. Tubita, I. Tusa, E. Rovida, Playing the whack-A-mole game: ERK5 activation emerges among the resistance mechanisms to RAF-MEK1/2-ERK1/2- targeted therapy, Front. Cell Dev. Biol. 9 (2021), 647311.
[35] N. Kaila, et al., Identification of a novel class of selective Tpl2 kinase inhibitors: 4-alkylamino-[1,7]naphthyridine-3-carbonitriles, Bioorg. Med. Chem. 15 (19) (2007) 6425–6442.
[36] R. Glatthar, et al., Discovery of imidazoquinolines as a novel class of potent, selective, and in vivo efficacious cancer osaka thyroid (COT) kinase inhibitors, J. Med. Chem. 59 (16) (2016) 7544–7560.
[37] C. Sanz-Garcia, et al., Cot/tpl2 participates in the activation of macrophages by adiponectin, J. Leukoc. Biol. 95 (6) (2014) 917–930.
[38] L.K. Gavrin, et al., Inhibition of Tpl2 kinase and TNF-alpha production with 1,7-naphthyridine-3-carbonitriles: synthesis and structure-activity relationships, Bioorg. Med. Chem. Lett. 15 (23) (2005) 5288–5292.
[39] N. Green, et al., Inhibitors of tumor progression loci-2 (Tpl2) kinase and tumor necrosis factor alpha (TNF-alpha) production: selectivity and in vivo antiinflammatory activity of novel 8-substituted-4-anilino-6-aminoquinoline-3-carbonitriles, J. Med. Chem. 50 (19) (2007) 4728–4745.
[40] J. Wu, et al., Selective inhibitors of tumor progression loci-2 (Tpl2) kinase with potent inhibition of TNF-alpha production in human whole blood, Bioorg. Med. Chem. Lett. 19 (13) (2009) 3485–3488.
[41] M. Lopez-Pelaez, et al., Cot/tpl2-MKK1/2-Erk1/2 controls mTORC1-mediated mRNA translation in toll-like receptor-activated macrophages, Mol. Biol. Cell 23 (15) (2012) 2982–2992.
[42] D. Rubin, Integrative tumor board: metastatic renal cell carcinoma: naturopathic medicine, Integr. Cancer Ther. 3 (1) (2004) 34–41.
[43] L.D. Wilson, J.R. McCranie, The herpetofauna of the cloud forests of Honduras, Amphib. Reptile Conserv. 3 (1) (2004) 34–48.
[44] Z. Krcova, et al., Tpl-2/Cot and COX-2 in breast cancer, Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub. 152 (1) (2008) 21–25.
[45] A. Banerjee, et al., Diverse Toll-like receptors utilize Tpl2 to activate extracellular signal-regulated kinase (ERK) in hemopoietic cells, Proc. Natl. Acad. Sci. U. S. A. 103 (9) (2006) 3274–3279.
[46] G. Sourvinos, C. Tsatsanis, D.A. Spandidos, Overexpression of the Tpl-2/Cot oncogene in human breast cancer, Oncogene 18 (35) (1999) 4968–4973.
[47] S.H. Liu, et al., Calpain/SHP-1 interaction by honokiol dampening peritoneal dissemination of gastric cancer in nu/nu mice, PLoS One 7 (8) (2012), e43711.
[48] M. Lopez-Pelaez, et al., Cot/tpl2 activity is required for TLR-induced activation of the Akt p70 S6k pathway in macrophages: implications for NO synthase 2 expression, Eur. J. Immunol. 41 (6) (2011) 1733–1741.
[49] C. Rodriguez, et al., COX2 expression and Erk1/Erk2 activity mediate Cot-induced cell migration, Cell. Signal. 20 (9) (2008) 1625–1631.
[50] M. Malz, et al., Overexpression of far upstream element binding proteins: a mechanism regulating proliferation and migration in liver cancer cells, Hepatology 50 (4) (2009) 1130–1139.
[51] J.P. Hall, et al., Pharmacologic inhibition of tpl2 blocks inflammatory responses in primary human monocytes, synoviocytes, and blood, J. Biol. Chem. 282 (46) (2007) 33295–33304.
[52] P. Schulz, et al., Angiopoietin-2 drives lymphatic metastasis of pancreatic cancer, FASEB J. 25 (10) (2011) 3325–3335.
[53] F. Kaiser, et al., TPL-2 negatively regulates interferon-beta production in macrophages and myeloid dendritic cells, J. Exp. Med. 206 (9) (2009) 1863–1871.
[54] N.V. Acuff, et al., Tpl2 promotes neutrophil trafficking, oxidative burst, and bacterial killing, J. Leukoc. Biol. 101 (6) (2017) 1325–1333.
[55] A.G. Eliopoulos, et al., Tpl2 transduces CD40 and TNF signals that activate ERK and regulates IgE induction by CD40, EMBO J. 22 (15) (2003) 3855–3864.
[56] W.T. Watford, et al., Tpl2 kinase regulates T cell interferon-gamma production and host resistance to Toxoplasma gondii, J. Exp. Med. 205 (12) (2008) 2803–2812.
[57] C.D. Dumitru, et al., TNF-alpha induction by LPS is regulated posttranscriptionally via a Tpl2/ERK-dependent pathway, Cell 103 (7) (2000) 1071–1083.
[58] A. Banerjee, et al., NF-kappaB1 and c-Rel cooperate to promote the survival of TLR4-activated B cells by neutralizing Bim via distinct mechanisms, Blood 112 (13) (2008) 5063–5073.
[59] K. Sugimoto, et al., A serine/threonine kinase, Cot/Tpl2, modulates bacterial DNA-induced IL-12 production and th cell differentiation, J. Clin. Invest. 114 (6) (2004) 857–866.
[60] C. Tsatsanis, C. Patriotis, P.N. Tsichlis, Tpl-2 induces IL-2 expression in T-cell lines by triggering multiple signaling pathways that activate NFAT and NF-kappaB, Oncogene 17 (20) (1998) 2609–2618.
[61] H.C. Chuang, T.H. Tan, MAP4K3/GLK in autoimmune disease, cancer and aging, J. Biomed. Sci. 26 (1) (2019) 82.
[62] M.S. Al Suraih, et al., Senescent cholangiocytes release extracellular vesicles that alter target cell phenotype via the epidermal growth factor receptor, Liver Int. 40 (10) (2020) 2455–2468.
[63] I.T.S. Meliala, et al., The biological implications of Yin Yang 1 in the hallmarks of cancer, Theranostics 10 (9) (2020) 4183–4200.
[64] S.M. Alwahsh, R. Gebhardt, Dietary fructose as a risk factor for non-alcoholic fatty liver disease (NAFLD), Arch. Toxicol. 91 (4) (2017) 1545–1563.
[65] S.K. Asrani, et al., Burden of liver diseases in the world, J. Hepatol. 70 (1) (2019) 151–171.
[66] A.J. Zuckerman, Hepatitis viruses, in: th, S. Baron (Eds.), Medical Microbiology, 1996. Galveston (TX).
[67] N. Dakhil, O. Junaidi, A.S. Befeler, Chronic viral hepatitis, Mo. Med. 106 (5) (2009) 361–365.
[68] S.D. Ryder, I.J. Beckingham, ABC of diseases of liver, pancreas, and biliary system: acute hepatitis, BMJ 322 (7279) (2001) 151–153.
[69] J. Xu, et al., Tpl2 protects against fulminant hepatitis through mobilization of myeloid-derived suppressor cells, Front. Immunol. 10 (2019) 1980.
[70] D. Vyrla, et al., TPL2 kinase is a crucial signaling factor and mediator of NKT effector cytokine expression in immune-mediated liver injury, J. Immunol. 196 (10) (2016) 4298–4310.
[71] M. Yuksel, et al., Hepatitis mouse models: from acute-to-chronic autoimmune hepatitis, Int. J. Exp. Pathol. 95 (5) (2014) 309–320.
[72] Y. Cheng, et al., Virus-induced p38 MAPK activation facilitates viral infection, Theranostics 10 (26) (2020) 12223–12240.
[73] S.F. He, et al., Interferon alpha and ribavirin collaboratively regulate p38 mitogen-activated protein kinase signaling in hepatoma cells, Cytokine 61 (3) (2013) 801–807.
[74] C. Zhang, et al., C-terminal-truncated hepatitis B virus X protein promotes hepatocarcinogenesis by activating the MAPK pathway, Microb. Pathog. 159 (2021), 105136.
[75] C. Sanz-Garcia, et al., Sterile inflammation in acetaminophen-induced liver injury is mediated by Cot/tpl2, J. Biol. Chem. 288 (21) (2013) 15342–15351.
[76] D.W. Kaufman, et al., Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey, JAMA 287 (3) (2002) 337–344.
[77] D.G. Blazer, L.T. Wu, Nonprescription use of pain relievers by middle-aged and elderly community-living adults: National Survey on Drug Use and Health, J. Am. Geriatr. Soc. 57 (7) (2009) 1252–1257.
[78] J.R. Vane, Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs, Nat. New. Biol. 231 (25) (1971) 232–235.
[79] C.I. Ghanem, et al., Acetaminophen from liver to brain: new insights into drug pharmacological action and toxicity, Pharmacol. Res. 109 (2016) 119–131.
[80] H. Zaher, et al., Protection against acetaminophen toxicity in CYP1A2 and CYP2E1 double-null mice, Toxicol. Appl. Pharmacol. 152 (1) (1998) 193–199.
[81] J.L. Raucy, et al., Acetaminophen activation by human liver cytochromes P450IIE1 and P450IA2, Arch. Biochem. Biophys. 271 (2) (1989) 270–283.
[82] J.R. Mitchell, et al., Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione, J. Pharmacol. Exp. Ther. 187 (1) (1973) 211–217.
[83] A.B. Imaeda, et al., Acetaminophen-induced hepatotoxicity in mice is dependent on Tlr9 and the Nalp3 inflammasome, J. Clin. Invest. 119 (2) (2009) 305–314.
[84] J. Zhang, et al., The role of MAP2 kinases and p38 kinase in acute murine liver injury models, Cell Death Dis. 8 (6) (2017), e2903.
[85] F.J. Cubero, et al., Combined activities of JNK1 and JNK2 in hepatocytes protect against toxic liver injury, Gastroenterology 150 (4) (2016) 968–981.
[86] M.E. Zoubek, et al., Protective role of c-Jun N-terminal kinase-2 (JNK2) in ibuprofen-induced acute liver injury, J. Pathol. 247 (1) (2019) 110–122.
[87] H.K. Seitz, et al., Alcoholic liver disease, Nat. Rev. Dis. Primers 4 (1) (2018) 16.
[88] C.S. Lieber, Ethanol metabolism, cirrhosis and alcoholism, Clin. Chim. Acta 257 (1) (1997) 59–84.
[89] Y. Lu, A.I. Cederbaum, CYP2E1 and oxidative liver injury by alcohol, Free Radic. Biol. Med. 44 (5) (2008) 723–738.
[90] T.M. Leung, N. Nieto, CYP2E1 and oxidant stress in alcoholic and non-alcoholic fatty liver disease, J. Hepatol. 58 (2) (2013) 395–398.
[91] C. Wei, et al., LncRNA HOXA11-AS promotes glioma malignant phenotypes and reduces its sensitivity to ROS via Tpl2-MEK1/2-ERK1/2 pathway, Cell Death Dis. 13 (11) (2022) 942.
[92] A.I. Cederbaum, Alcohol metabolism, Clin. Liver Dis. 16 (4) (2012) 667–685.
[93] S. Zakhari, Overview: how is alcohol metabolized by the body? Alcohol Res. Health 29 (4) (2006) 245–254.
[94] T.M. Maenhout, M.L. De Buyzere, J.R. Delanghe, Non-oxidative ethanol metabolites as a measure of alcohol intake, Clin. Chim. Acta 415 (2013) 322–329.
[95] J. Hyun, et al., Pathophysiological aspects of alcohol metabolism in the liver, Int. J. Mol. Sci. 22 (11) (2021).
[96] D.J. Tuma, C.A. Casey, Dangerous byproducts of alcohol breakdown–focus on adducts, Alcohol Res. Health 27 (4) (2003) 285–290.
[97] Y. Israel, et al., Monoclonal and polyclonal antibodies against acetaldehyde-containing epitopes in acetaldehyde-protein adducts, Proc. Natl. Acad. Sci. U. S. A. 83 (20) (1986) 7923–7927.
[98] A.J. McCullough, J.F. O'Connor, Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology, Am. J. Gastroenterol. 93 (11) (1998) 2022–2036.
[99] T.R. Morgan, S. Mandayam, M.M. Jamal, Alcohol and hepatocellular carcinoma, Gastroenterology 127 (5 Suppl 1) (2004) S87–S96.
[100] L.E. Nagy, Molecular aspects of alcohol metabolism: transcription factors involved in early ethanol-induced liver injury, Annu. Rev. Nutr. 24 (2004) 55–78.
[101] C.P. Stice, et al., Deletion of tumor progression locus 2 attenuates alcohol-induced hepatic inflammation, Hepatobiliary Surg. Nutr. 5 (1) (2016) 29–37.
[102] G. Szabo, Gut-liver axis in alcoholic liver disease, Gastroenterology 148 (1) (2015) 30–36.

[103] I. Milosevic, et al., Gut-liver axis, gut microbiota, and its modulation in the management of liver diseases: a review of the literature, Int. J. Mol. Sci. 20 (2) (2019).
[104] A. Albillos, A. de Gottardi, M. Rescigno, The gut-liver axis in liver disease: pathophysiological basis for therapy, J. Hepatol. 72 (3) (2020) 558–577.
[105] D.R. Triger, T.D. Boyer, J. Levin, Portal and systemic bacteraemia and endotoxaemia in liver disease, Gut 19 (10) (1978) 935–939.
[106] K. Tarao, et al., Detection of endotoxin in plasma and ascitic fluid of patients with cirrhosis: its clinical significance, Gastroenterology 73 (3) (1977) 539–542.
[107] E. Slevin, et al., Kupffer cells: inflammation pathways and cell-cell interactions in alcohol-associated liver disease, Am. J. Pathol. 190 (11) (2020) 2185–2193.
[108] Y. Wang, et al., TPL2 is a key regulator of intestinal inflammation in Clostridium difficile infection, Infect. Immun. 86 (8) (2018).
[109] J.S. Pyo, M.J. Park, C.N. Kim, TPL2 expression is correlated with distant metastasis and poor prognosis in colorectal cancer, Hum. Pathol. 79 (2018) 50–56.
[110] M. Roulis, et al., Intestinal myofibroblast-specific Tpl2-Cox-2-PGE2 pathway links innate sensing to epithelial homeostasis, Proc. Natl. Acad. Sci. U. S. A. 111 (43) (2014) E4658–E4667.
[111] V. Koliaraki, M. Roulis, G. Kollias, Tpl2 regulates intestinal myofibroblast HGF release to suppress colitis-associated tumorigenesis, J. Clin. Invest. 122 (11) (2012) 4231–4242.
[112] M. Eslam, L. Valenti, S. Romeo, Genetics and epigenetics of NAFLD and NASH: clinical impact, J. Hepatol. 68 (2) (2018) 268–279.
[113] L. Caballeria, P. Toran, J. Caballeria, Markers of hepatic fibrosis, Med. Clin. 150 (8) (2018) 310–316.
[114] R. Schierwagen, et al., Serum markers of the extracellular matrix remodeling reflect antifibrotic therapy in bile-duct ligated rats, Front. Physiol. 4 (2013) 195.
[115] M. Pinzani, PDGF and signal transduction in hepatic stellate cells, Front. Biosci. 7 (2002) d1720–d1726.
[116] K.C. Wu, et al., Tpl2 kinase regulates inflammation but not tumorigenesis in mice, Toxicol. Appl. Pharmacol. 418 (2021), 115494.
[117] J. Gong, et al., Tumor progression locus 2 in hepatocytes potentiates both liver and systemic metabolic disorders in mice, Hepatology 69 (2) (2019) 524–544.
[118] J.W. Perfield II, et al., Tumor progression locus 2 (TPL2) regulates obesity-associated inflammation and insulin resistance, Diabetes 60 (4) (2011) 1168–1176.
[119] E. Seki, D.A. Brenner, M. Karin, A liver full of JNK: signaling in regulation of cell function and disease pathogenesis, and clinical approaches, Gastroenterology 143 (2) (2012) 307–320.
[120] M.J. Perugorria, et al., Tumor progression locus 2/Cot is required for activation of extracellular regulated kinase in liver injury and toll-like receptor-induced TIMP-1 gene transcription in hepatic stellate cells in mice, Hepatology 57 (3) (2013) 1238–1249.
[121] G.I. Lancaster, et al., Tumor progression locus 2 (Tpl2) deficiency does not protect against obesity-induced metabolic disease, PLoS One 7 (6) (2012), e39100.
[122] D.B. Ballak, et al., MAP3K8 (TPL2/COT) affects obesity-induced adipose tissue inflammation without systemic effects in humans and in mice, PLoS One 9 (2) (2014), e89615.
[123] N. Singh, et al., Inflammation and cancer, Ann. Afr. Med. 18 (3) (2019) 121–126.
[124] H.W. Lee, et al., Tpl2 induces castration resistant prostate cancer progression and metastasis, Int. J. Cancer 136 (9) (2015) 2065–2077.
[125] X. Li, et al., Tumor progression locus 2 ablation suppressed hepatocellular carcinoma development by inhibiting hepatic inflammation and steatosis in mice, J. Exp. Clin. Cancer Res. 34 (2015) 138.
[126] M. Vougioukalaki, et al., Tpl2 kinase signal transduction in inflammation and cancer, Cancer Lett. 304 (2) (2011) 80–89.
[127] J.H. Jeong, et al., TPL2/COT/MAP3K8 (TPL2) activation promotes androgen depletion-independent (ADI) prostate cancer growth, PLoS One 6 (1) (2011), e16205.
[128] T. Gruosso, et al., MAP3K8/TPL-2/COT is a potential predictive marker for MEK inhibitor treatment in high-grade serous ovarian carcinomas, Nat. Commun. 6 (2015) 8583.
[129] L. Boldrini, et al., Role of microRNA-33a in regulating the expression of PD-1 in lung adenocarcinoma, Cancer Cell Int. 17 (2017) 105.
[130] K.L. Decicco-Skinner, et al., Tpl2 knockout keratinocytes have increased biomarkers for invasion and metastasis, Carcinogenesis 34 (12) (2013) 2789–2798.
[131] F. Balkwill, K.A. Charles, A. Mantovani, Smoldering and polarized inflammation in the initiation and promotion of malignant disease, Cancer Cell 7 (3) (2005) 211–217.
[132] A.M. Clark, et al., Mutational activation of the MAP3K8 protooncogene in lung cancer, Genes Chromosomes Cancer 41 (2) (2004) 99–108.
[133] G. Kim, et al., Interleukin-17 induces AP-1 activity and cellular transformation via upregulation of tumor progression locus 2 activity, Carcinogenesis 34 (2) (2013) 341–350.
[134] S. Rousseau, G. Martel, Gain-of-function mutations in the toll-like receptor pathway: TPL2-mediated ERK1/ERK2 MAPK activation, a path to tumorigenesis in lymphoid neoplasms? Front. Cell Dev. Biol. 4 (2016) 50.
[135] M. Hatziapostolou, et al., Proteinase-activated receptor-1-triggered activation of tumor progression locus-2 promotes actin cytoskeleton reorganization and cell migration, Cancer Res. 68 (6) (2008) 1851–1861.
[136] M. Hatziapostolou, et al., Tumor progression locus 2 mediates signal-induced increases in cytoplasmic calcium and cell migration, Sci. Signal. 4 (187) (2011) ra55.
[137] M.L. Nierodzik, S. Karpatkin, Thrombin induces tumor growth, metastasis, and angiogenesis: evidence for a thrombin-regulated dormant tumor phenotype, Cancer Cell 10 (5) (2006) 355–362.
[138] R.C. Chambers, et al., Thrombin stimulates fibroblast procollagen production via proteolytic activation of protease-activated receptor 1, Biochem. J. 333 (Pt 1) (1998) 121–127.
[139] K.E. Dawes, A.J. Gray, G.J. Laurent, Thrombin stimulates fibroblast chemotaxis and replication, Eur. J. Cell Biol. 61 (1) (1993) 126–130.
[140] W. Wang, C. Wei, Advances in the early diagnosis of hepatocellular carcinoma, Genes Dis. 7 (3) (2020) 308–319.
[141] Q. Wang, H. Dai, TPL2, a therapeutic potential target for cancer, Hum. Pathol. 83 (2019) 224.
[142] M. Das, et al., The role of JNK in the development of hepatocellular carcinoma, Genes Dev. 25 (6) (2011) 634–645.