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Review

MAP3K Family Review and Correlations with Patient Survival Outcomes in Various Cancer Types

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Abstract

The mitogen-activated protein kinase (MAPK) pathways are ubiquitous in cellular signaling and are essential for proper biological functions. Disruptions in this signaling axis can lead to diseases such as the development of cancer. In this review, we discuss members of the MAP3K family and correlate their mRNA expression levels to patient survival outcomes in different cancers. Furthermore, we highlight the importance of studying the MAP3K family due to their important roles in the larger, overall MAPK pathway, relationships with cancer progression, and the understudied status of these kinases.

Keywords: MAP kinases; MAPK; MAP3K; understudied kinase; Dark Kinome; Illuminating the Druggable Genome; cancer

1. Introduction

Mitogen-activated protein kinase (MAPK) pathways are crucial signaling networks that link extracellular signals to machinery that controls cellular processes such as growth, proliferation, differentiation, migration, and apoptosis. Once activated by a stimulus, MAPK pathways are characterized by three sequential phosphorylation of MAPK kinase kinases (MAP3K, MEK kinases, or MKKKs) to MAPK kinases (MAP2K, MEK, or MKKs) to MAPKs. The 4 well-known and conventional MAPK subfamilies are extracellular signal-regulated kinases 1 and 2 (ERK1/2), c- Jun amino-terminal kinases 1 to 3 (JNK1 to 3), p38 (α, β, γ, and δ), and ERK5 families [1].

MAP3Ks are serine/threonine kinases that act upstream of MAP2Ks and MAPKs. There are 24 characterized MAP3Ks, named from MAP3K1 to MAP3K21 plus B-Raf, C-Raf, and A-Raf [2].

Supplementary Table 1 contains the Uniprot number, synonyms, chromosome location, and HGNC ID for each MAP3K isoform. It has been well-described that MAPK signaling pathways can be dysregulated and some MAP3Ks become mutated in cancers [3]. Among the aforementioned MAP3Ks, the role of B-Raf in cancers is the most thoroughly characterized. Activating mutations in the *BRAF* oncogenes resulting in constitutive activation of MEK1/2 and subsequent activation of ERK1/2 are seen in some 70% of melanomas, some 10% of colorectal cancers, and some 30–70% of papillary thyroid carcinomas [4–7]. **Supplementary Table 2** contains a compilation of MAPK compound inhibitors and their investigations in different diseases, mechanisms of action, and stage of study [8]. However, except for B-Raf, the role of other MAP3Ks in cancers has not been fully investigated.

This review seeks to address the gap in knowledge of MAP3K family members and establish a foundation for elucidating functions of novel MAP3Ks. We approach this by discussing existing literature and by determining the correlations between the mRNA expression of 21 MAP3K isoforms and patient survival across 21 cancer types using Kaplan-Meier online plotter. Additionally, we also use the Pharos user interface to the Knowledge Management Center's (KMC) Illuminating the Druggable Genome (IDG) program funded by the National Institutes of Health (NIH) Common Fund to quantify the novelty of each MAP3K family member by assigning them each a PubMed and Novelty score. Lastly, we reference the NIH FOA RFA-RM-21-012, titled *Pilot Projects Investigating Understudied G Protein-Coupled Receptors, Ion Channels, and Protein Kinases*, to emphasize the importance and opportunities associated with studying these kinase family members. IDG-

eligible kinases are prioritized by this funding opportunity to support the generation of data and tools to study understudied kinases.

2. Method

2.1 The KM Plotter Online Tool was Used to Determine the mRNA Expression of MAP3Ks and Patient Survival

The KM plotter online tool was used to investigate the mRNA expression of 21 MAP3K isoforms and patient survival across 21 cancer types: bladder carcinoma, breast cancer, cervical squamous cell carcinoma, esophageal adenocarcinoma, esophageal squamous cell carcinoma, head-neck squamous cell carcinoma, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, ovarian cancer, pancreatic ductal adenocarcinoma, pheochromocytoma and paraganglioma, rectum adenocarcinoma, sarcoma, stomach adenocarcinoma, testicular germ cell tumor, thymoma, thyroid carcinoma, and uterine corpus endometrial carcinoma [9,10]. Parameters for cutoffs were $p < 0.05$ and Hazard Ratios excluding a value equal to 1.0. The results section of this manuscript and primary tables only discusses and displays data that are statistically significant. For complete analysis, including results with insignificant *p*-values, refer to **Supplementary Table 3**.

2.2 PubMed and Novelty Score Analysis

PubMed and Novelty scores were generated through Pharos (Pharos.NIH.gov), a user interface for the Knowledge Management Center (KMC) for the Illuminating the Druggable Genome (IDG) program funded by the National Institutes of Health (NIH) Common Fund. The PubMed score is described as: "Jensen Lab generated fractional counting score for the prevalence of this target in PubMed articles". The Novelty score is described as: "Tin-X metric for the relative scarcity of specific publications for this target". To summarize score interpretations, higher PubMed scores represent higher availability of publications and lower log Novelty scores (more negative) represent lower novelty for the kinase of interest based on the number of PubMed articles. MAPK1 (ERK1/2) is provided as an exemplar of a well-characterized kinase. Additionally, MAP3K members (MAP3K10, MAP3K14, MAP3K15, MAP3K16, MAP3K17, and MAP3K21) described as "2021 NIH designated understudied kinase(s)" are based on the funding announcement RFA- RM-21-012, titled *Pilot Projects Investigating Understudied G Protein-Coupled Receptors, Ion Channels, and Protein Kinases*.

3. Result

3.1 MAP3K1A

MAP3K1 is one of the most-studied MAP3K family members with a PubMed Score of 217.17 and a Novelty Score of –5.49 (Table 1). Unique among MAP3Ks, only MAP3K1 contains both a kinase domain and a plant homeodomain (PHD) motif, allowing it to regulate downstream protein phosphorylation as well as exhibit E3 ubiquitin ligase activity [11,12]. MAP3K1 also has a cleavage site that generates a kinase-domain fragment when cleaved by caspase 3, increasing apoptotic response [13]. Therefore, MAP3K1 promotes cell survival or induces apoptosis via an ERK/NF-κB or caspase 3 mechanism, respectively [14,15]. Consequently, mutations in both pro- survival and pro-apoptotic pathways of MAP3K1 have been identified in cancer [12].

Table 1. PubMed and Novelty scores of MAP3K isoforms.

MAP3K isoforms	PubMed score	Novelty score (log)
MAPK1	1463.91	–7.4
MAP3K1	217.17	–5.49
MAP3K2	83.41	–4.42
MAP3K3	74.03	–4.13
MAP3K4	43.58	–3.82
MAP3K5	812.85	–6.54
MAP3K6	27.05	–3.29
MAP3K7	209.21	–5.22
MAP3K8	220.14	–5.15
MAP3K9	43.94	–3.72
MAP3K10	25.78	–3.34
MAP3K11	117.01	–4.5
MAP3K12	157.61	–5.07
MAP3K13	200.04	–5.38
MAP3K14	29.23	–3.35
MAP3K15	10.11	–2.11
MAP3K16	57.97	–4.07
MAP3K17	46.59	–3.76
MAP3K18	50.8	–3.88
MAP3K19	4.83	–1.31
MAP3K20	16.1	–2.79
MAP3K21	11.8	–1.96

MAP3K isoforms that are IDG-eligible kinases are in bold italic. MAPK1 is included as an example of a well-characterized kinase.

Mutations in MAP3K1 have been implicated in cancers of breast, prostate, stomach, and diffuse large B cell lymphoma [14]. Among these cancer types, MAP3K1 mutations in breast cancers are most well-studied. Genomic studies revealed MAP3K1 as the second most frequently mutated gene with inactivating mutations in MAP3K1 and MAP2K4 as well in upstream kinases of c-Jun N-terminal kinase (JNK) in the apoptotic pathway identified in luminal A subtype tumors [15,16]. Moreover, MAP3K1 has been suggested to have a tumor suppressor role in the crosstalk between PI3Kα and MAP3K1 pathways in

PIK3CA-mutated luminal/ER+ breast cancers [15]. In glioblastoma, an increase in MAP3K1 was associated with survival of glioma, therapeutic resistance to temozolomide chemotherapy, and radiotherapy [17]. Suppression of MAP3K1- mediated androgen receptor (AR)-dependent apoptosis could lead to chemotherapy resistance in AR+ prostate cancer [18].

The mRNA expression of MAP3K1 was associated with increased survival in cervical squamous cell carcinoma, esophageal squamous cell carcinoma, head-neck squamous cell carcinoma, kidney renal clear cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, and thyroid carcinoma. MAP3K1 expression was negatively associated with patient survival in kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, and pancreatic ductal adenocarcinoma (Table 2). MAP3K1 mRNA expression in other cancer types did not make the statistical cutoff.

3.2 MAP3K2

MAP3K2 is a moderately studied kinase with a PubMed score of 83.41 and a Novelty Score of –4.42 (Table 1). Overexpression of MAP3K2 has been identified in non-small cell lung cancer, hepatocellular carcinoma, prostate cancer, gastric cancer, and triple-negative breast cancer (TNBC) [19–23]. Previous studies demonstrated Forkhead box F1 (FOXF1), the transcriptional regulator of epithelial-mesenchymal transition (EMT), promoted tumor growth and invasion by upregulating MAP3K2 [24,25]. Additionally, the knockdown of MAP3K2 inhibited cell migration and metastasis in several cancer types, suggesting the involvement of MAP3K2 in regulating tumor invasion and metastasis via MAP3K2-ERK5 signaling pathways [20–22]. MAP3K2 was also identified as a non-histone substrate of SET and MYND domain-containing protein 3 (SMYD3), a chromatin modifier. SMYD3-mediated lysine methylation of MAP3K2 increased the activation of MAP kinase signaling pathways and promoted Ras-driven carcinomas [26,27]. The mRNA expression of MAP3K2 was positively associated with survival in kidney renal clear cell carcinoma and sarcoma. MAP3K2 expression was correlated with decreased survival in breast cancer and kidney renal papillary cell carcinoma (Table 2). MAP3K2 mRNA expression in other cancer types did not make the statistical cutoff.

3.3 MAP3K3

Similar to MAP3K2, MAP3K3 is a moderately studied member of the MAP3K family, with a PubMed score of 74.03 and a Novelty score of –4.13 (Table 1). MAP3K3 is involved in the development of early embryonic cardiovascular systems, endothelial cell proliferation, apoptosis, as well as inflammatory and immune responses [28,29]. Dysregulated expression of MAP3K3 has been implicated in several cancer types, including ovarian cancer, breast cancer, kidney cancer, NSCC, and esophageal cancer [29–34]. MAP3K3 overexpression increased activation of NF-κB signaling pathway and promoted EMT and tumor cell proliferation in ovarian cancer and breast cancer [29,34]. Santoro *et al*. [31] identified MAP3K3 as a contributor to EMT and stemness in pancreatic cancer by positively regulating the oncogenic activity of yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ). This mechanism is independent of NF-κB pathway. Interestingly, He *et al*. [35] reported that MAP3K3 overexpression correlated with an active immune response in primary lung adenocarcinomas associated with improved patient survival [35]. In cerebral cavernous malformations, increased activity of MAP3K3 and its target genes KLF2/4 in endothelial cells were identified as causal events [28,36]. Expression of MAP3K3 mRNA was associated with increased survival of esophageal adenocarcinoma, esophageal squamous cell carcinoma, head-neck squamous cell carcinoma, lung adenocarcinoma, pancreatic ductal adenocarcinoma, and thymoma. MAP3K3 expression was negatively associated with survival in bladder carcinoma, breast cancer, liver hepatocellular carcinoma, lung squamous cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumor, and uterine corpus endometrial carcinoma (Table 2). MAP3K3 mRNA expression in other cancer types did not make the statistical cutoff.

3.4 MAP3K4

MAP3K4 has a PubMed score of 43.58 and Novelty score of –3.82 (Table 1). Despite its relative novelty being comparable to similarly scored MAP3K16 and MAP3K17, MAP3K4 is not an IDG- eligible kinase. Previous studies reported the involvement of MAP3K4 in EMT and lactate secretion of breast cancer cells via HER2/HER3 signaling pathways [37,38]. The role of MAP3K4 in EMT regulation via histone acetylation in trophoblast stem cells has also been demonstrated [39,40]. MAP3K4 functions as a mediator of the stress-activated p38 MAPK pathway, whose mutation has relevance for endometrial cancer and EBV+ gastric cancer [41,42]. MAP3K4 also contributed to proliferation and invasion of cervical cancer cells by interacting with Erb-b2 receptor tyrosine kinase 3 (ERBB3) [43]. Zhang *et al*. [44] identified MAP3K4 (MEKK4) to be tumor-suppressive via the MEKK4-MKK4-p38-p21signaling pathway in pancreatic cancer. While MAP3K4 was downregulated in parathyroid adenoma, it was constitutively active in urothelial carcinoma cells [45,46]. MAP3K4 also played an important role in neuroepithelial development and loss of MAP3K4 could result in neural tube defects [47].

The mRNA expression of MAP3K4 was positively associated with survival in kidney renal clear cell carcinoma, lung squamous cell carcinoma, pancreatic ductal adenocarcinoma, and rectum adenocarcinoma. MAP3K4 expres-

Table 2. Hazard Ratios (HR) correlating patient survival and mRNA expression of MAP3K isoforms using Kaplan-Meier plotter.

MAP3K isoforms	Cancer type	HR	*p* value
MAP3K1	Cervical squamous cell carcinoma	**0.57 (0.36–0.91)**	**0.017**
	Esophageal Squamous Cell Carcinoma	**0.34 (0.15–0.78)**	**0.008**
	Head-neck squamous cell carcinoma	**0.62 (0.44–0.87)**	**0.0055**
	Kidney renal clear cell carcinoma	**0.54 (0.4–0.73)**	**0.000042**
	Lung adenocarcinoma	**0.55 (0.38–0.81)**	**0.0019**
	Stomach adenocarcinoma	**0.68 (0.48–0.97)**	**0.03**
	Thyroid carcinoma	**0.18 (0.04–0.78)**	**0.01**
	Kidney renal papillary cell carcinoma	*2.23 (0.99–5.02)*	*0.045*
	Liver hepatocellular carcinoma	*1.7 (1.17–2.48)*	*0.0052*
	Pancreatic ductal adenocarcinoma	*1.9 (1.13–3.19)*	*0.014*
MAP3K2	Kidney renal clear cell carcinoma	**0.66 (0.49–0.89)**	**0.0059**
	Sarcoma	**0.62 (0.41–0.93)**	**0.021**
	Breast cancer	*1.44 (1.02–2.03)*	*0.037*
	Kidney renal papillary cell carcinoma	*2.16 (1.18–3.95)*	*0.011*
MAP3K3	Esophageal Adenocarcinoma	**0.34 (0.16–0.73)**	**0.0036**
	Esophageal Squamous Cell Carcinoma	**0.42 (0.18–0.97)**	**0.035**
	Head-neck squamous cell carcinoma	**0.75 (0.57–0.99)**	**0.041**
	Lung adenocarcinoma	**0.67 (0.5–0.91)**	**0.011**
	Pancreatic ductal adenocarcinoma	**0.52 (0.34–0.78)**	**0.0015**
	Thymoma	**0.29 (0.08–1.06)**	**0.046**
	Bladder carcinoma	*1.39 (1.04–1.87)*	*0.027*
	Breast cancer	*1.59 (1.1–2.3)*	*0.013*
	Liver hepatocellular carcinoma	*1.65 (1.12–2.44)*	*0.01*
	Lung squamous cell carcinoma	*1.38 (1.04–1.83)*	*0.024*
	Pheochromocytoma and Paraganglioma	*5.43 (0.98–29.97)*	*0.03*
	Sarcoma	*1.51 (1.01–2.26)*	*0.041*
	Testicular Germ Cell tumor	*7.17 (0.74–69.24)*	*0.047*
	Uterine corpus endometrial carcinoma	*2.09 (1.38–3.18)*	*0.00041*
MAP3K4	Kidney renal clear cell carcinoma	**0.64 (0.44–0.93)**	**0.017**
	Lung squamous cell carcinoma	**0.69 (0.5–0.96)**	**0.026**
	Pancreatic ductal adenocarcinoma	**0.61 (0.4–0.92)**	**0.018**
	Rectum adenocarcinoma	**0.28 (0.1–0.84)**	**0.015**
	Breast cancer	*1.64 (1.18–2.26)*	*0.0025*
	Cervical squamous cell carcinoma	*1.69 (1.06 -2.71)*	*0.026*
	Esophageal Adenocarcinoma	*2.11 (1.11–4)*	*0.02*
	Kidney renal papillary cell carcinoma	*2.07 (1.12–3.81)*	*0.018*
	Liver hepatocellular carcinoma	*1.83 (1.25–2.68)*	*0.0015*
	Ovarian cancer	*1.49 (1.13–1.96)*	*0.0041*
	Stomach adenocarcinoma	*1.39 (1 –1.94)*	*0.049*
MAP3K5	Bladder carcinoma	**0.66 (0.49–0.9)**	**0.0073**
	Head-neck squamous cell carcinoma	**0.61 (0.46–0.82)**	**0.00074**
	Kidney renal clear cell carcinoma	**0.57 (0.42–0.77)**	**0.00023**
	Lung squamous cell carcinoma	**0.67 (0.47–0.94)**	**0.02**
	Rectum adenocarcinoma	**0.25 (0.09–0.72)**	**0.0055**
	Sarcoma	**0.59 (0.39–0.91)**	**0.015**
	Thyroid carcinoma	**0.3 (0.1–0.93)**	**0.027**
	Cervical squamous cell carcinoma	*1.7 (1.04–2.78)*	*0.032*
	Ovarian cancer	*1.34 (1.02–1.76)*	*0.034*
	Pancreatic ductal adenocarcinoma	*2.51 (1.48–4.25)*	*0.0004*

Table 2. Continued.

MAP3K isoforms	Cancer type	HR	*p* value
MAP3K6	Breast cancer	**0.64 (0.46–0.89)**	**0.0076**
	Cervical squamous cell carcinoma	**0.49 (0.31–0.79)**	**0.0028**
	Esophageal Adenocarcinoma	**0.45 (0.22–0.9)**	**0.02**
	Head-neck squamous cell carcinoma	**0.63 (0.48–0.83)**	**0.00073**
	Lung adenocarcinoma	**0.67 (0.48–0.93)**	**0.016**
	Stomach adenocarcinoma	**0.7 (0.49 -1)**	**0.047**
	Thyroid carcinoma	**0.28 (0.11–0.76)**	**0.0076**
	Uterine corpus endometrial carcinoma	**0.61 (0.41–0.93)**	**0.02**
	Liver hepatocellular carcinoma	*1.65 (1.14–2.39)*	*0.0077*
	Rectum adenocarcinoma	*2.96 (1.29–6.79)*	*0.0076*
	Thymoma	*5.54 (1.41–21.7)*	*0.0064*
MAP3K7	Esophageal Squamous Cell Carcinoma	**0.23 (0.07–0.81)**	**0.014**
	Ovarian cancer	**0.76 (0.58–0.98)**	**0.034**
	Rectum adenocarcinoma	**0.43 (0.19–1.01)**	**0.047**
	Thymoma	**0.18 (0.05–0.85)**	**0.005**
	Cervical squamous cell carcinoma	*1.81 (1.04–3.15)*	*0.035*
	Esophageal Adenocarcinoma	*2.66 (1.2–5.92)*	*0.013*
	Kidney renal clear cell carcinoma	*1.44 (1.07–1.94)*	*0.017*
	Kidney renal papillary cell carcinoma	*1.81 (1–3.29)*	*0.047*
	Liver hepatocellular carcinoma	*1.91 (1.33–2.75)*	*0.00035*
	Sarcoma	*2.23 (1.47–3.38)*	*0.00011*
MAP3K8	Bladder carcinoma	**0.69 (0.51–0.93)**	**0.013**
	Breast cancer	**0.68 (0.49–0.94)**	**0.018**
	Esophageal Adenocarcinoma	**0.33 (0.13–0.84)**	**0.015**
	Head-neck squamous cell carcinoma	**0.71 (0.54–0.92)**	**0.01**
	Lung adenocarcinoma	**0.63 (0.46–0.84)**	**0.0019**
	Ovarian cancer	**0.7 (0.53–0.91)**	**0.0075**
	Sarcoma	**0.47 (0.31–0.7)**	**0.00012**
	Esophageal Squamous Cell Carcinoma	*3.02 (1.35–6.76)*	*0.0049*
	Kidney renal clear cell carcinoma	*2.15 (1.58–2.91)*	*0.00000048*
	Thymoma	*6.09 (1.44–25.85)*	*0.0054*
	Thyroid carcinoma	*2.73 (1.01–7.36)*	*0.039*
MAP3K9	Kidney renal papillary cell carcinoma	**0.46 (0.24–0.89)**	**0.019**
	Pancreatic ductal adenocarcinoma	**0.61 (0.4–0.93)**	**0.021**
	Stomach adenocarcinoma	**0.57 (0.38–0.86)**	**0.0068**
	Kidney renal clear cell carcinoma	*1.41 (1.02–1.96)*	*0.037*
	Liver hepatocellular carcinoma	*2.16 (1.49–3.13)*	*0.000032*
	Ovarian cancer	*1.31 (1.01–1.7)*	*0.044*
	Pheochromocytoma and Paraganglioma	*12.16 (1.36–108.85)*	*0.0043*
	Thymoma	*4.39 (0.91–21.19)*	*0.044*
	Uterine corpus endometrial carcinoma	*1.68 (1.1–2.56)*	*0.014*
MAP3K10	Bladder carcinoma	**0.56 (0.41–0.76)**	**0.0002**
	Head-neck squamous cell carcinoma	**0.64 (0.49–0.84)**	**0.0011**
	Pancreatic ductal adenocarcinoma	**0.51 (0.34–0.78)**	**0.0013**
	Cervical squamous cell carcinoma	*1.69 (1.01–2.81)*	*0.043*
	Kidney renal clear cell carcinoma	*2.07 (1.53–2.8)*	*0.0000017*
	Liver hepatocellular carcinoma	*1.53 (1.03–2.26)*	*0.032*
	Thyroid carcinoma	*3.77 (1.37–10.39)*	*0.006*
	Uterine corpus endometrial carcinoma	*1.63 (1.07–2.46)*	*0.02*

Table 2. Continued.

MAP3K isoforms	Cancer type	HR	*p* value
MAP3K11	Bladder carcinoma	**0.71 (0.53–0.95)**	**0.02**
	Cervical squamous cell carcinoma	**0.55 (0.35–0.88)**	**0.012**
	Kidney renal clear cell carcinoma	**0.71 (0.52–0.96)**	**0.027**
	Sarcoma	**0.59 (0.37–0.93)**	**0.022**
	Stomach adenocarcinoma	**0.65 (0.46–0.93)**	**0.018**
	Liver hepatocellular carcinoma	*1.85 (1.17–2.93)*	*0.0076*
	Lung squamous cell carcinoma	*1.38 (1–1.9)*	*0.05*
MAP3K12	Lung adenocarcinoma	**0.64 (0.48–0.85)**	**0.0023**
	Pancreatic ductal adenocarcinoma	**0.44 (0.29–0.68)**	**0.00015**
	Sarcoma	**0.46 (0.3–0.69)**	**0.00014**
	Thymoma	**0.21 (0.04–1.02)**	**0.034**
	Kidney renal clear cell carcinoma	*2.33 (1.7–3.19)*	*0.000000062*
	Kidney renal papillary cell carcinoma	*1.83 (1–3.34)*	*0.046*
	Pheochromocytoma and Paraganglioma	*9.65 (1.12–82.77)*	*0.011*
	Stomach adenocarcinoma	*1.5 (1.09–2.08)*	*0.013*
	Uterine corpus endometrial carcinoma	*1.7 (1.12–2.59)*	*0.011*
MAP3K13	Bladder carcinoma	**0.69 (0.5–0.95)**	**0.024**
	Cervical squamous cell carcinoma	**0.53 (0.33–0.86)**	**0.0084**
	Esophageal Adenocarcinoma	**0.46 (0.23–0.92)**	**0.024**
	Kidney renal clear cell carcinoma	**0.54 (0.4–0.72)**	**0.000032**
	Lung squamous cell carcinoma	**0.63 (0.48–0.83)**	**0.00093**
	Ovarian cancer	**0.54 (0.39–0.75)**	**0.00017**
	Rectum adenocarcinoma	**0.38 (0.15–0.95)**	**0.031**
	Stomach adenocarcinoma	**0.69 (0.5–0.96)**	**0.026**
	Pancreatic ductal adenocarcinoma	*2.24 (1.48–3.42)*	*0.00011*
	Pheochromocytoma and Paraganglioma	*5.15 (0.93–28.25)*	*0.036*
	Sarcoma	*1.79 (1.12–2.86)*	*0.014*
	Thymoma	*18.89 (2.33–153.14)*	*0.00016*
	Uterine corpus endometrial carcinoma	*2.38 (1.56–3.62)*	*0.0000320*
MAP3K14	Breast cancer	**0.64 (0.45–0.91)**	**0.011**
	Cervical squamous cell carcinoma	**0.39 (0.25–0.63)**	**0.000053**
	Head-neck squamous cell carcinoma	**0.62 (0.46–0.85)**	**0.0026**
	Pancreatic ductal adenocarcinoma	**0.57 (0.37–0.88)**	**0.011**
	Rectum adenocarcinoma	**0.41 (0.19–0.89)**	**0.02**
	Sarcoma	**0.63 (0.42–0.93)**	**0.019**
	Thyroid carcinoma	**0.27 (0.09–0.79)**	**0.01**
	Kidney renal papillary cell carcinoma	*2.08 (1.15–3.79)*	*0.014*
	Liver hepatocellular carcinoma	*1.44 (1.02–2.03)*	*0.038*
	Thymoma	*17.42 (2.17–139.68)*	*0.00022*
MAP3K15	Pancreatic ductal adenocarcinoma	**0.58 (0.39–0.89)**	**0.011**
	Esophageal Adenocarcinoma	*2.95 (1.56–5.6)*	*0.0005*
	Head-neck squamous cell carcinoma	*1.44 (1.08–1.92)*	*0.013*
	Kidney renal clear cell carcinoma	*1.92 (1.38–2.67)*	*0.000088*
	Kidney renal papillary cell carcinoma	*4.28 (2.11–8.68)*	*0.000011*
	Liver hepatocellular carcinoma	*1.59 (1.12–2.27)*	*0.0088*
	Sarcoma	*2.05 (1.38–3.05)*	*0.00031*
	Thyroid carcinoma	*2.92 (1.02–8.43)*	*0.037*
	Uterine corpus endometrial carcinoma	*3.74 (2.33–6)*	*0.0000000044*

Table 2. Continued.

MAP3K isoforms	Cancer type	HR	*p* value
MAP3K16	Kidney renal clear cell carcinoma	**0.62 (0.46–0.83)**	**0.0013**
	Rectum adenocarcinoma	**0.39 (0.16–0.98)**	**0.038**
	Cervical squamous cell carcinoma	*2.24 (1.22–4.09)*	*0.0072*
	Liver hepatocellular carcinoma	*1.57 (1.11–2.22)*	*0.011*
	Stomach adenocarcinoma	*1.59 (1.14–2.2)*	*0.0051*
MAP3K17	Head-neck squamous cell carcinoma	**0.66 (0.51–0.87)**	**0.0025**
	Kidney renal clear cell carcinoma	**0.73 (0.54–0.98)**	**0.038**
	Kidney renal papillary cell carcinoma	**0.44 (0.24–0.8)**	**0.006**
	Lung adenocarcinoma	**0.63 (0.47–0.85)**	**0.0025**
	Pancreatic ductal adenocarcinoma	**0.42 (0.25–0.7)**	**0.00057**
	Stomach adenocarcinoma	**0.65 (0.45–0.94)**	**0.02**
	Uterine corpus endometrial carcinoma	**0.46 (0.3–0.7)**	**0.00019**
MAP3K18	Kidney renal clear cell carcinoma	**0.45 (0.33–0.61)**	**0.00000021**
	Rectum adenocarcinoma	**0.27 (0.08–0.89)**	**0.02**
	Sarcoma	**0.61 (0.38–0.99)**	**0.044**
	Stomach adenocarcinoma	**0.69 (0.49–0.96)**	**0.026**
	Thymoma	**0.1 (0.01–0.85)**	**0.011**
	Kidney renal papillary cell carcinoma	*2.24 (1.12–4.46)*	*0.019*
	Lung squamous cell carcinoma	*1.43 (1.09–1.88)*	*0.0094*
	Pheochromocytoma and Paraganglioma	*4.89 (0.89–26.99)*	*0.044*
MAP3K19	Bladder carcinoma	**0.58 (0.43–0.79)**	**0.00039**
	Breast cancer	**0.67 (0.47–0.96)**	**0.027**
	Cervical squamous cell carcinoma	**0.47 (0.25–0.9)**	**0.019**
	Liver hepatocellular carcinoma	**0.64 (0.45–0.9)**	**0.011**
	Lung adenocarcinoma	**0.68 (0.48–0.95)**	**0.025**
	Pancreatic ductal adenocarcinoma	**0.6 (0.37–0.97)**	**0.037**
	Rectum adenocarcinoma	**0.28 (0.08–0.95)**	**0.029**
	Uterine corpus endometrial carcinoma	**0.44 (0.24–0.79)**	**0.0048**
	Kidney renal clear cell carcinoma	*1.83 (1.35–2.47)*	*0.000064*
	Kidney renal papillary cell carcinoma	*2.38 (1.01–5.64)*	*0.042*
	Lung squamous cell carcinoma	*1.47 (1.1–1.95)*	*0.008*
MAP3K20	Esophageal Squamous Cell Carcinoma	**0.38 (0.16–0.87)**	**0.018**
	Sarcoma	**0.57 (0.35–0.93)**	**0.022**
	Cervical squamous cell carcinoma	*1.76 (1.08–2.87)*	*0.021*
	Kidney renal papillary cell carcinoma	*2.95 (1.56–5.58)*	*0.00047*
	Lung adenocarcinoma	*1.41 (1.03–1.93)*	*0.029*
	Lung squamous cell carcinoma	*1.38 (1.01–1.88)*	*0.042*
	Pancreatic ductal adenocarcinoma	*1.53 (1.01–2.31)*	*0.041*
MAP3K21	Esophageal Squamous Cell Carcinoma	**0.32 (0.13–0.78)**	**0.0086**
	Rectum adenocarcinoma	**0.42 (0.18–0.96)**	**0.032**
	Breast cancer	*1.54 (1.03–2.31)*	*0.034*
	Kidney renal papillary cell carcinoma	*2.72 (1.3–5.68)*	*0.0056*
	Liver hepatocellular carcinoma	*1.53 (1.07–2.17)*	*0.018*
	Uterine corpus endometrial carcinoma	*1.94 (1.25–3.01)*	*0.0025*

Significant p (<0.05) and HR values that are positively correlated with patient survival are in **bold**, while those *italicized* indicates a negative correlation. Some cancer types are not shown due to non-significant data for that gene and can be found in **Supplementary Table 3**.

sion was correlated with decreased survival in breast cancer, cervical squamous cell carcinoma, esophageal adenocarcinoma, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, ovarian cancer, stomach adenocarcinoma (Table 2). MAP3K4 mRNA expression in other cancer types did not make the statistical cutoff.

3.5 MAP3K5

MAP3K5 is the most well-studied MAP3K family member with a PubMed score of 812.85 and a Novelty score of –6.54 (Table 1). MAP3K5, also known as ASK1, is a member of the stress- induced apoptosis signal-regulating kinase (ASK) family [48]. ASK1 activates both p38 and JNK pathways responding to stressors such as cytokines, reactive oxygen species (ROS), and endoplasmic reticulum (ER) stress [49]. Thus, ASK1 plays a critical role in stress response and its dysfunction is involved in various diseases, including cancers, neurodegeneration, and cardiovascular diseases. Existing studies identified ASK1 as an antioncogene by promoting ROS- induced and ER-mediated apoptosis [49,50]. Low expression or downregulated activity of ASK1 has been demonstrated in several cancer types, including HCC, breast cancer, and Ewing sarcoma [51–53]. However, some studies also reported that overexpression of ASK1 and its upregulated activity promotes cancer cell motility and proliferation in oral squamous cell carcinoma and ovarian cancer, and pancreatic cancer [54–56]. Therefore, ASK1 can be a therapeutic target by either activating ASK1-mediated apoptosis or inhibiting its activity based on specific cancer types. Novel triazolothiadiazines were identified as potent anticancer agents by triggering oxidative stress-induced apoptosis through ASK1 activation in HCC [57]. Selonsertib (GS-4997), an ASK1 inhibitor, attenuates multidrug resistance in cancer cells overexpressing ATP-binding cassette transporters ABCB1 and 2 [58,59]. The mRNA expression of MAP3K5 was associated with increased survival in bladder carcinoma, head-neck squamous cell carcinoma, kidney renal clear cell carcinoma, lung squamous cell carcinoma, rectum adenocarcinoma, sarcoma, and thyroid carcinoma. MAP3K5 was expression negatively correlated with survival in cervical squamous cell carcinoma, ovarian cancer, and pancreatic ductal adenocarcinoma (Table 2). MAP3K5 mRNA expression in other cancer types did not make the statistical cutoff.

3.6 MAP3K6

MAP3K6 is one of the less studied members of the MAP3K family with a PubMed score of 27.05 and Novelty score of –5.22 (Table 1). Despite having scores similar to IDG-eligible kinases MAP3K10 and MAP3K14, MAP3K6 did not receive this designation. MAP3K6 is also a member of the ASK family, known as ASK2 [48]. Existing literature demonstrate that MAP3K6 is inhibited by CDK5 to regulate melanin production in mice [60]. Furthermore, MAP3K6 mutations are associated with cerebral small vessel disease (cSVD) causing stroke, cognitive impairment, and tremor, as well as the development of gastric cancer [61,62]. Along with MAP3K5, MAP3K6 also known as ASK2, is a member of ASK family [49]. ASK2 has been reported to regulate tumor angiogenesis [63]. The mRNA expression of MAP3K6 was positively associated with survival in breast cancer, cervical squamous cell carcinoma, esophageal adenocarcinoma, head-neck squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, thyroid carcinoma, and uterine corpus endometrial carcinoma. MAP3K6 expression was negatively associated with survival in liver hepatocellular carcinoma, rectum adenocarcinoma, and thymoma (Table 2). MAP3K6 mRNA expression in other cancer types did not make the statistical cutoff.

3.7 MAP3K7

MAP3K7 is one of the better studied members of MAP3K family with a PubMed score of 209.21 and a Novelty score of –5.22 (Table 1). MAP3K7, also known as TGF-β-activated kinase 1 (TAK1), is a critical mediator of NF-κB and JNK signaling pathways that regulate embryonic development, immune responses, and cell survival [64]. Because MAP3K7 downstream molecules NF-κB and JNK are involved in cancer cell survival and apoptosis, MAP3K7 regulates tumor initiation, proliferation, and metastasis as a cancer promoter or suppressor depending on specific receptors and cell types [65]. While specific deficiency MAP3K7 causes cell death, inflammation, fibrosis, and carcinogenesis of hepatocytes due to inhibition of NF-κB-dependent survival, higher co-expression of MAP3K7 and mTOR was positively correlated with proliferation of HCC [65,66]. Overexpression and hyperactivation of MAP3K7 have been implicated in multiple cancers, including esophageal, thyroid, gastric, and ovarian [67–71]. As a critical mediator between receptors and transcription factors, MAP3K7 was identified as a potential therapeutic target for cancer therapy. Several chemical MAP3K7 inhibitors include the natural compound 5(Z)-7- oxozeaenol, LYTAK1, AZ-TAK1, Takinib, and NG25 [72–76].

The mRNA expression of MAP3K7 was associated with increased survival in esophageal squamous cell carcinoma, ovarian cancer, rectum adenocarcinoma, and thymoma. MAP3K7 expression was negatively associated with survival in cervical squamous cell carcinoma, esophageal adenocarcinoma, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, and sarcoma (Table 2). MAP3K7 mRNA expression in other cancer types did not make the statistical cutoff.

3.8 MAP3K8

MAP3K8 is the second most-studied kinase of the MAP3K family with a PubMed score of 220.14 and a Novelty score of –5.15 (Table 1). MAP3K8, also commonly

known as tumor progression locus 2 (Tpl2), regulates both innate and adaptive immunity, as well as inflammatory responses. Previous studies reported that overexpression of Tpl2 activates the ERK, JNK, and p38 MAPK pathways, as well as the transcription factors NFAT and NF-κB, and ultimately regulates the production of various cytokines [77–80]. MAPK8 has variable effects on tumors and its role as both tumor suppressor and tumor promoter has been reported. For example, MAP3K8 acts as a tumor suppressor gene, and a low expression of MAP3K8 is associated with reduced lung cancer patient survival and an increase in metastasis biomarkers in skin cancer [81,82]. However, MAP3K8 overexpression contributes to tumor proliferation, and metastasis in ovarian cancer, squamous cell carcinoma, colorectal cancer, prostate cancer, and breast cancer [83–87]. The mRNA expression of MAP3K8 was positively correlated with survival in bladder carcinoma, breast cancer, esophageal adenocarcinoma, head-neck squamous cell carcinoma, lung adenocarcinoma, ovarian cancer, and sarcoma. MAP3K8 expression was associated with decreased survival in esophageal squamous cell carcinoma, kidney renal clear cell carcinoma, thymoma, and thyroid carcinoma (Table 2). MAP3K8 mRNA expression in other cancer types did not make the statistical cutoff.

3.9 MAP3K9

MAP3K9 has a PubMed score of 43.94 and a Novelty score of –3.72 (Table 1). Despite its relative novelty being comparable to similarly scored MAP3K16 and MAP3K17, MAP3K9 is not an IDG- eligible kinase. MAP3K9, also known as mixed lineage kinase I (MLK1), belongs to the MLK family, which are upstream activators of MEK/ERK and JNK pathways [88]. While the role of MAP3K9 in cancer is not well-defined, previous studies reported that targeting MAP3K9 using microRNA suppressed tumor progression in pancreatic cancer, pharyngolaryngeal cancer, HCC, and esophagus squamous cell carcinoma, suggesting its involvement in cancer pathogenesis [89–91]. In lung cancer cells, gain-of-function mutation MAP3K9 leads to the increased activation of downstream ERK pathway, which potentially promotes tumor proliferation [92]. Marusiak *et al.* [93] demonstrated MAP3K9 (MLK1) reactivates MEK/ERK pathway independently of RAF, contributing to the resistance of RAF inhibitors in melanoma. Additionally, MAP3K9 has been identified as a gene that is frequently mutated in metastatic melanoma [94]. The mRNA expression of MAP3K9 was positively correlated with survival in kidney renal papillary cell carcinoma, pancreatic ductal adenocarcinoma, and stomach adenocarcinoma. MAP3K9 expression was negatively correlated with survival in kidney renal clear cell carcinoma, liver hepatocellular carcinoma, ovarian cancer, pheochromocytoma and paraganglioma, thymoma, and uterine corpus endometrial carcinoma (Table 2). MAP3K9 mRNA expression in other cancer types did not make the statistical cutoff.

3.10 MAP3K10

MAP3K10 is an IDG-eligible kinase with a PubMed score of 25.78 and Novelty score of –3.34 (Table 1). MAP3K is also a member of the MLK family, known as MLK2 [88]. Existing literature identifies MAP3K10 as a mediator of TGFß activation with a role in regulating atherosclerotic inflammatory responses [95,96]. Furthermore, MAP3K10 has been implicated to play a role in pancreatic cancer, esophageal carcinoma, and osteosarcoma [97]. Additionally, targeting MAP3K10 with microRNA MiR-146b-3p and MiR-155-5p has been demonstrated to, respectively, abrogate pancreatic cancer stem-cell proliferation and sensitize esophageal carcinoma cells to radiation and chemotherapy [98,99]. The mRNA expression of MAP3K10 was associated with increased survival in bladder carcinoma, head-neck squamous cell carcinoma, and pancreatic ductal adenocarcinoma. MAP3K10 expression was negatively associated with survival in cervical squamous cell carcinoma, kidney renal clear cell carcinoma, liver hepatocellular carcinoma, thyroid carcinoma, and uterine corpus endometrial carcinoma (Table 2). MAP3K10 mRNA expression in other cancer types did not make the statistical cutoff.

3.11 MAP3K11

MAP3K11 is a moderately studied member of the MAP3K family with a PubMed score of 117.01 and a Novelty score of –4.5 (Table 1). MAP3K1, also known as MLK3, has been shown to activate p38 pathway besides MEK/ERK and JNK pathways [88]. The role of MLK3 (MAP3K11) in cancer cell migration has been demonstrated in several cancer types, including breast and lung cancers [100–102]. Chen *et al.* [102] reported a crucial role of MLK3 (MAP3K11) in cell migration in breast cancer by activating JNK signaling to AP-1, which promotes EMT and an invasive breast cancer phenotype [102]. Another proposed mechanism of MLK3 (MAP3K11) regulating cancer cell migration is through dysregulating mediators critical for cytoskeletal rearrangement and focal adhesion dynamics, including Cdc42, Rac1, and RhoA GTPases [100,101,103]. In prostate cancer MLK3 (MAP3K11) also facilitates the collagen type I-induced EMT switch, leading to JNK- mediated increased expression of N-cadherin, an EMT marker associated with promoting migratory and invasive capacity [103,104]. Ma *et al.* [105] showed that MLK3 expression is upregulated in cervical cancer cells and MLK3 blocking suppresses cancer progression via autophagy- dependent apoptosis. Additionally, targeting MAP3K11 using microRNA inhibited tumor proliferation in NSCLC and esophageal cancer [106,107]. Similar to MAP3K9 (MLK1), MAP3K11 (MLK3) also promotes resistance to RAF inhibitor vemurafenib by reactivating MEK/ERK pathway independently of RAF, contributing to cell survival and progression in melanoma [106]. MLK3 also plays a role in inflammation by regulating

NF-κB/NLRP3 signaling pathway-mediated inflammation and JNK/p53 signaling pathway-mediated oxidative stress, which are associated with myocardial fibrosis [108]. The mRNA expression of MAP3K11 was correlated with increased survival in bladder carcinoma, cervical squamous cell carcinoma, kidney renal clear cell carcinoma, sarcoma, and stomach adenocarcinoma. MAP3K11 expression was associated with decreased survival in liver hepatocellular carcinoma, lung squamous cell carcinoma (Table 2). MAP3K11 mRNA expression in other cancer types did not make the statistical cutoff.

3.12 MAP3K12

MAP3K12 is a moderately studied member of the MAP3K family with a PubMed score of 157.61 and a Novelty score of –5.07 (Table 1). MAP3K12, also known as dual leucine zipper kinase (DLK), is a member of MLK family [88]. It has been investigated in the pathogenesis of neurodegenerative diseases and diabetes mellitus, its role in cancer has not been as well-studied in cancer. Yu *et al*. [109] demonstrated that targeting MAP3K12 using microRNA miR-150-5p suppresses cell proliferation and invasion in prostate cancer cells. MAP3K12 is also upregulated in T-cell acute lymphoblastic leukemia (T-ALL), suggesting that MAP3K12 could be a marker of T-ALL for future studies [110]. DLK (MAP3K12) regulates the stress-induced JNK signaling in neurons and has been identified as a central regulation of various neuronal degradation models [111–116]. In diabetes mellitus, MAP3K12-mediated JNK signaling pathway can underlie endothelial dysfunction, suggesting MAP3K12 as a potential therapeutic target [117]. The mRNA expression of MAP3K12 was positively correlated with lung adenocarcinoma, pancreatic ductal adenocarcinoma, sarcoma, and thymoma. MAP3K12 expression was negatively associated with survival in kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, stomach adenocarcinoma, and uterine corpus endometrial carcinoma (Table 2). MAP3K12 mRNA expression in other cancer types did not make the statistical cutoff.

3.13 MAP3K13

MAP3K13 is one of the better-studied members of the MAP3K family with a PubMed score of 200.04 and a Novelty score of –5.38 (Table 1). MAP3K13, also known as leucine zipper-bearing kinase (LZK), belongs to the MLK family and has a high sequence identity to DLK/MAPK312 [88]. LZK was shown to regulate NF-κB and JNK signaling pathways, which could be cancer promoting [118, 119]. In breast cancer, MAP3K13 overexpression stabilizes and enhances the transcriptional activity of Myc oncogene, contributing to poor patient survival [120]. Amplified MAP3K13 promotes cancer cell viability and proliferation by maintaining expression of gain-of- function mutant p53 [121]. Additionally, Fu *et al*. [122] reported that long non-coding RNAs (lncRNA) LINC01287 activated NF-κB signaling through regulating MAP3K13, potentially regulating migration, invasion, and EMT in colon cancer [122]. More recently, LZK has been identified as a novel positive regulator of axon growth [123]. The mRNA expression of MAP3K13 was positively associated with survival in bladder carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, kidney renal clear cell carcinoma, lung squamous cell carcinoma, ovarian cancer, rectum adenocarcinoma, and stomach adenocarcinoma. MAP3K13 expression was associated with decreased survival in pancreatic ductal adenocarcinoma, pheochromocytoma, and paraganglioma, sarcoma, thymoma, and uterine corpus endometrial carcinoma (Table 2). MAP3K13 mRNA expression in other cancer types did not make the statistical cutoff.

3.14 MAP3K14

MAP3K14 is an IDG-eligible kinase with a PubMed score of 29.23 and Novelty score of –3.35 (Table 1). It has been described, in mantle cell lymphoma (MCL), as a mediator in the non-canonical NfκB pathway. Mutations in the NFκB pathway leads to dependence of MAP3K14, both *in vitro* and *in vivo*, suggesting that MAP3K14 is potentially a therapeutic target in MCL [124]. Additionally, MAP3K14 has been identified to be a regulator of the innate and adaptive immune responses with mutations leading to atypical-combined immunodeficiency [125,126]. The mRNA expression of MAP3K14 was associated with increased survival in breast cancer, cervical squamous cell carcinoma, head-neck squamous cell carcinoma, pancreatic ductal adenocarcinoma, rectum adenocarcinoma, sarcoma, and thyroid carcinoma. MAP3K14 expression was negatively associated with survival in kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, and thymoma (Table 2). MAP3K14 mRNA expression in other cancer types did not make the statistical cutoff.

3.15 MAP3K15

MAP3K15 is an IDG-eligible kinase with a PubMed score of 10.11 and Novelty score of –2.11 (Table 1). MAP3K15 is also known as ASK3, a member of the ASK family [49]. It has been identified to play an important role in immune-related activities against cancer with one study demonstrating a correlation between MAP3K15 expression and immune infiltration in osteosarcoma [127]. Despite this report, other studies found that high levels of MAP3K15 to be correlated with poor prognosis in Osteosarcoma and uterine cancer [127,128]. More broadly, studies on MAP3K15 have shown that it has protective effects against osmotically driven hypertension, and a knockdown phenotype of MAP3K19 results in an inherited form of hypertension [129].

The mRNA expression of MAP3K15 was positively associated with pancreatic ductal adenocarcinoma. MAP3K15 expression was associated with decreased survival in esophageal adenocarcinoma, head-neck squamous cell carcinoma, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, sarcoma, thyroid carcinoma, and uterine corpus endometrial carcinoma (Table 2). MAP3K15 mRNA expression in other cancer types did not make the statistical cutoff.

3.16 MAP3K16 (TAOK1)

Better known as TAOK1, MAP3K16 is the most characterized IDG-eligible MAP3K member with a PubMed score of 57.97 and Novelty score of –4.07 (Table 1). Existing literature identifies TAOK1 involvement in neurodevelopment with dysregulation and de-novo variants leading to neurodevelopmental disorders [130,131]. Furthermore, MAP3K16 is a positive regulator of TLR4-induced inflammatory responses, activating macrophages through promotion of ERK1/2 [132]. The mRNA expression of TAOK1 was associated with increased survival in kidney renal clear cell carcinoma and rectum adenocarcinoma. TAOK1 expression was negatively associated with survival in cervical squamous cell carcinoma, liver hepatocellular carcinoma, and stomach adenocarcinoma (Table 2). TAOK1 mRNA expression in other cancer types did not make the statistical cutoff.

3.17 MAP3K17 (TAOK2)

Better known as TAOK2, MAP3K17 is one of the better characterized IDG-eligible MAP3K members, second to MAP3K16, with a PubMed score of 46.59 and Novelty score of –3.76 (Table 1). Existing literature identifies TAOK2 as an ER-localized kinase that acts to catalyze ER-microtubule interactions [133]. Furthermore, TAOK2 has been demonstrated to play a role in neurodevelopment and cognition with studies showing control over behavioral responses to ethanol, in mice, and the development of autism spectrum disorder through RhoA signaling [134,135]. The mRNA expression of TAOK2 was positively associated with survival in head-neck squamous cell carcinoma, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, lung adenocarcinoma, pancreatic ductal adenocarcinoma, stomach adenocarcinoma, and uterine corpus endometrial carcinoma. TAOK2 expression did not correlate with decreased survival in any studied cancer types (Table 2). TAOK2 mRNA expression in other cancer types did not make the statistical cutoff.

3.18 MAP3K18 (TAOK3)

Better known as TAOK3, MAP3K18 has a PubMed score of 50.8 and a Novelty score of –3.88 (Table 1). Despite its relative novelty being comparable to similarly scored MAP3K16 and MAP3K17, TAOK3 is not an IDG-eligible kinase. Existing literature identifies TAOK3 as a contributing regulator of osteoblast differentiation and skeletal mineralization, lipid partitioning in the liver, and t-cell receptor signaling [136–139]. Furthermore, TAOK3 has also been identified to regulate cancer stem-cells in pancreatic cancer and enhance microtubule-targeted drug resistance in breast cancer through NF-κB signaling [140,141]. The mRNA expression of TAOK3 was positively correlated with survival in kidney renal clear cell carcinoma, rectum adenocarcinoma, sarcoma, stomach adenocarcinoma, and thymoma. TAOK3 was negatively correlated with survival in kidney renal papillary cell carcinoma, lung squamous cell carcinoma, and pheochromocytoma and paraganglioma (Table 2). TAOK3 mRNA expression in other cancer types did not make the statistical cutoff.

3.19 MAP3K19

MAP3K19 is the least studied MAP3K family member with a PubMed Score of 4.83 and Novelty Score of –1.31 (Table 1). Despite having the lowest number of publications available and the highest novelty, MAP3K19 was not among the list of IDG-eligible MAP3K members. Existing literature identifies a role for MAP3K19 in lung pathology. Boehme *et al*. [142,143] identified MAP3K19 as a novel TGFß regulator in pulmonary fibrosis and as a central mediator of cigarette smoke induced pulmonary inflammation. Furthermore, Hoang *et al*. [144] and Jones *et al*. [145] identified MAP3K19 as a mediator for idiopathic pulmonary fibrosis and KRAS-mutant lung cancer. The mRNA expression of MAP3K19 was positively associated with survival in bladder carcinoma, breast cancer, cervical squamous cell carcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, pancreatic ductal adenocarcinoma, rectum adenocarcinoma, and uterine corpus endometrial carcinoma. MAP3K19 expression was associated with decreased survival in kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, and lung squamous cell carcinoma (Table 2). MAP3K19 mRNA expression in other cancer types did not make the statistical cutoff.

3.10 MAP3K20

MAP3K20 is among the least characterized MAP3K family of kinases with a PubMed score of 16.1 and Novelty score of –2.79 (Table 1). Despite its relative novelty being comparable to similarly scored MAP3K10 and MAP3K21, MAP3K20 is not an IDG-eligible kinase. Existing literature identifies MAP3K20 as an ERK and JNK activator with multiple isoforms. Some isoforms of MAP3K20 have been identified to be positively correlated with gastric and colorectal cancer development while others have been demonstrated to have anti-tumor roles by promoting apoptosis in osteosarcoma [146–149]. The mRNA expression of MAP3K20 was associated with increased survival in esophageal squamous cell carcinoma and sarcoma. MAP3K20 expression was negatively associated with survival in cervical squamous cell carcinoma, kidney renal

papillary cell carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, and pancreatic ductal adenocarcinoma (Table 2). MAP3K20 mRNA expression in other cancer types did not make the statistical cutoff.

3.21 MAP3K21

MAP3K21 is one of the least studied MAP3K family members, second to MAP3K19, with a PubMed Score of 11.8 and Novelty Score of –1.96 (Table 1). Additionally, MAP3K21 is an NIH designated IDG-eligible kinase. Existing reports identify a correlation between MAP3K21 and pediatric obesity, *E. coli* induced diarrhea, and disease resistance in African chickens [150–152].

Additionally, MAP3K21 has been found to be cancer promoting in breast cancer, hepatocellular carcinoma, colorectal carcinoma, ovarian cancer, and gliomas [153–160]. The mRNA expression of MAP3K21 was positively associated with survival in esophageal squamous cell carcinoma and rectum adenocarcinoma. MAP3K21 expression was negatively associated with survival in breast cancer, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, and uterine corpus endometrial carcinoma (Table 2). MAP3K21 mRNA expression in other cancer types did not make the statistical cutoff.

4. Discussion

While performing a chemical compound based kinase screen, we identified MAP3K19 as a lead target in our cell models and have published a review comparing MAP3K19 expression levels in different normal and cancerous tissue types [161]. We then decided to take a broader look at the MAPK family and the lesser known MAP3K members. Mitogen-activated protein kinase (MAPK) pathways are signaling networks that regulate crucial cellular processes such as growth, proliferation, differentiation, migration, and apoptosis. MAP3Ks are upstream MAPK serine/threonine kinases that directly activate MAP2Ks through protein phosphorylation, leading to the activation of downstream MAPKs and their associated effects. This review evaluates the MAP3K family members (1 through 21) using PubMed and Novelty scores, current literature, and a critical analysis of isoform expression level with patient survival outcomes across multiple cancer types. Furthermore, this review develops a comparative characterization for each MAP3K member and provides the scientific community with a bioinformatic basis for further investigation of MAP3K signaling.

Kinase inhibitors are a major advancement in clinical therapies and have transformed disease management. Despite enormous successes with kinase inhibitors and dedicated research effort into kinase signaling, the majority of the kinome remains understudied [162,163]. To address this gap, the NIH launched the “Illuminating the Druggable Genome” (IDG) Program in 2014. This program’s purpose is to fund pilot projects to generate additional data and tools around understudied proteins. Furthermore, this program led to the development of Pharos, an informatics database that integrates information from various sources to generate PubMed and Novelty scores for each kinase. In this review, we reference RFA-RM-21-012 to identify the list of IDG-eligible MAP3K members. Among the 21 MAP3K members, only 6—MAP3K10, MAP3K14, MAP3K15, MAP3K16, MAP3K17, and MAP3K21—members were IDG-eligible. The PubMed and Novelty scores of the IDG-eligible MAP3K members range from 11.8 to 57.97 and –4.07 to –1.96, respectively. Interestingly, MAP3K4, MAP3K6, MAP3K9, MAP3K18, MAP3K19, and MAP3K20 were not eligible despite having PubMed scores well below the highest scored IDG-eligible MAP3K16 (57.97), indicating less available publications for these 6 kinases contrasted to MAP3K16. An analogous correlation is seen when comparing Novelty scores for the same 6 kinases; higher novelty scores are seen when compared to the lowest scored MAP3K: MAP3K16 (–4.07). This relationship is especially surprising for MAP3K19, a MAP3K member with the lowest PubMed score (4.83) and highest Novelty score (–1.31) (Table 1). Altogether, this leads us to anticipate future funding opportunity announcements including MAP3K4, MAP3K6, MAP3K9, MAP3K18, MAP3K19, and MAP3K20 in the list of IDG-eligible kinases.

The MAPK pathway is a signaling pathway that is a crucial regulator of a diverse multitude of cellular processes. Because of the ubiquitous nature of MAPK signaling in cellular biology, we decided to analyze the correlations between mRNA expression levels of different MAP3K members and patient survival of different cancer types. Using the KMPlotter database, we generated a table of different MAP3K’s and their corresponding hazard ratios for different cancers. Overall, the major conclusion is that MAP3K’s play different roles in different cancers. For example: MAP3K1 expression seems to have a pro-tumor role in pancreatic ductal adenocarcinoma, MAP3K3 demonstrates antitumor effects, and MAP3K2 demonstrates no correlation. This phenomenon provides supporting evidence for the broad biological roles of MAP3K signaling. Another example is that MAP3K1 has a beneficial hazard ratio in squamous cell carcinomas of the cervix, esophagus, and of head-neck origins while having a harmful hazard ratio in kidney renal papillary cell and liver hepatocellular carcinomas. This provides supporting evidence the tissue dependency of MAP3K functions with squamous cell tumors having the most benefit from MAP3K1 expression.

One potential drawback to this bioinformatic analysis approach is that correlations were generated from tissue mRNA levels. Because mRNA expression does not always perfectly reflect protein expression levels or post-translational activity, KMPlotter correlations may not perfectly align with existing literature or pathophysiology. For example, MAP3K8 mRNA overexpression is correlated

with improved ovarian cancer patient survival rates despite existing literature suggesting a pro- tumor role [87]. This quandary can be addressed by analyzing protein expression databases for supporting data. However, that process also has limitations because protein expression does not always directly correlate with protein activity. So regardless of bioinformatics technique used, scientific rigor must be addressed with supplemental validation and functional studies.

5. Conclusions

To summarize, our intent with this manuscript is to highlight the importance of the MAPK signaling pathway with an emphasis on the MAP3K family of kinases. We do this by discussing the most recent literature for each kinase, emphasizing its roles in pathology and associated signaling mechanisms. Additionally, we also use the KMPlotter bioinformatics database to generate correlations between mRNA expression levels and patient survival in different cancer types. Lastly, we discuss the PubMed and Novelty scores for each kinase and compare them to the previous IDG-eligible kinases. This comparison leads us to predict MAP3K4, MAP3K6, MAP3K9, MAP3K18, MAP3K19, and MAP3K20 to receive IDG-eligible designation in the future due to their relatively low PubMed and high Novelty scores. Overall, the MAPK pathway is diverse, complex, and ubiquitous in essential cellular processes. Disruption of this signaling axis can lead to diseases such as cancers. This review is focused on the less studied MAP3K family of the MAPK signaling pathway. Our goal is to establish a foundation for future MAP3K research by providing a summary of existing literature, preliminary bioinformatics data, and discussing potential funding sources through the NIH Illuminating the Druggable Genome program.

Author Contributions

This manuscript idea was originally conceived by KN and MEB and refined with the help of DHD, SBL, and BMC-B. KN and MNT did the majority of the research, database analysis, and writing. AR, TC, GOW, AC, JEC, and PTF contributed to the writing, data analysis and interpretation, and data presentation.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbl2705167.

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