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Review

Expression of Novel Kinase MAP3K19 in Various Cancers and Survival Correlations

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Abstract

Mitogen Activated Protein (MAP) kinases are a category of serine/threonine kinases that have been demonstrated to regulate intracellular events including stress responses, developmental processes, and cancer progression Although many MAP kinases have been extensively studied in various disease processes, MAP3K19 is an understudied kinase whose activities have been linked to lung disease and fibroblast development. In this manuscript, we use bioinformatics databases starBase, GEPIA, and KMPlotter, to establish baseline expressions of MAP3K19 in different tissue types and its correlation with patient survival in different cancers.

Keywords: MAP3K19; YSK4; RCK; understudied kinase; dark kinome; MAPK signaling; cancer

1. Introduction

Kinase inhibitors have transformed the landscape for disease management. A classic example of the impact of kinase targeting is Chronic Myelogenous Leukemia, which had an 8-year survival rate of less than 20% that more than quadrupled to 87% with the advent of the revolutionary kinase inhibitor imatinib [1]. Despite the enormous successes of kinase inhibition and dedicated kinase research efforts, over 75% of the kinome remains understudied [2,3]. Discovery of novel kinase targets that have potentially crucial regulatory roles in various disease states may lie within this subset of under-characterized kinases in the human kinome.

The Mitogen Activated Protein Kinase (MAPK) signaling pathways have been well characterized to regulate a variety of cellular processes including stress response, proliferation, and cellular differentiation [4]. The MAPK pathway is an evolutionarily conserved mechanism of signal transduction that functions through a core module of MAP3K $\rightarrow$ MAP2K $\rightarrow$ MAPK, commonly referred to as a "Three Tier Cascade". Two additional tiers, an upstream MAP4K and downstream MAPKAPK, have also been identified in certain cell lines and under certain conditions [5,6]. In addition to its role in physiological processes, MAPK signaling pathways have been identified to play a major role in cancer development with activating BRAF (MAP3K) and RAS (MAPK signaling regulator) mutations found in 40% of all human cancers [7]. Because of its ubiquitous nature in cancer, inhibition of MAPK signaling has been a crucial development in the clinical setting with sorafenib and vemurafenib as examples of FDA approved compounds [8,9].

Our group is focused on identifying and characterizing understudied kinases. Through our research, we identified MAP3K19 as a potential target to inhibit cancer function and progression. Despite the efforts dedicated to MAPK and overall kinase research, MAP3K19 is currently an understudied kinase with a pubmed score of 1.81 (<5 signifies poor data availability) and novelty score of 1.29. For comparison, NEK5, a 2021 NIH designated understudied kinase, has a pubmed score of 3.72 and novelty score of 0.06, and BRAF, a well characterized MAP3-kinase, has a pubmed score of 261.43 and a novelty score of 0 (https://pharos.nih.gov/). The few reports that do exist for MAP3K19 implicate a role in lung disease and pulmonary fibrosis [10–13]. This report aims to spark the interest for MAP3K19 investigations by consolidating mRNA data from bioinformatics databases starBase, GEPIA, and KM-

Table 1. MAP3K19 Tissue Expression.

Cancer types	Cancer expression	Normal expression	Fold change	*p*-value	Cancer (n)	Normal (n)	FDR
Breast invasive carcinoma	0.1	0.03	**3.31**	0.00067	1104	113	0.0018
Prostate adenocarcinoma	0.09	0.03	**2.77**	0.00059	499	52	0.0025
Kidney renal clear cell carcinoma	0.02	0.02	**1.38**	0.0027	535	72	0.0056
Lung squamous cell carcinoma	0.15	0.93	*0.16*	7.30×10^{-24}	501	49	8.80×10^{-23}
Lung adenocarcinoma	0.4	1.09	*0.37*	2.80×10^{-9}	526	59	1.80×10^{-8}
Thyroid carcinoma	0.02	0.03	*0.85*	0.0033	510	58	0.0089
Colon adenocarcinoma	0.03	0.03	*0.92*	0.00012	471	41	0.00053
Pancreatic adenocarcinoma	0.07	0.03	2.46	0.91	178	4	0.96
Kidney renal papillary cell carcinoma	0.04	0.02	1.91	0.46	289	32	0.67
Stomach adenocarcinoma	0.05	0.03	1.6	0.1	375	32	0.16
Bladder urothelial carcinoma	0.03	0.02	1.49	0.058	411	19	0.18
Liver hepatocellular carcinoma	0.02	0.02	1.26	0.2	374	50	0.33
Cholangiocarcinoma	0.03	0.02	1.17	0.34	36	9	0.56
Kidney chromophobe	0.02	0.02	0.86	0.13	65	24	0.24
Uterine corpus endometrial carcinoma	0.92	1.46	0.64	0.88	548	35	0.92
Esophageal carcinoma	0.05	0.1	0.54	0.31	162	11	0.63
Head & neck squamous cell carcinoma	0.04	0.4	0.1	0.25	502	44	0.41

MAP3K19 expression was quantified for 17 different cancer types as well as their corresponding normal tissues. Baseline Cancer and Normal expression values were normalized to an internal control and are unitless. In addition to baseline levels, fold change values are also displayed and were calculated by dividing cancer expression over normal expression. Statistically significant fold change values that indicate an increased level in cancer tissues are **bolded** while values that indicate a decreased level in cancer tissues are *italicized*.

Plotter, to establish baseline levels of expression in different tissue types & cancers and by correlating MAP3K19 mRNA levels with survival rates in different cancers.

2. Results

2.1 MAP3K19 Expression in Tissues of Different Cancer and Normal Tissue Types

2.1.1 Expression Level in Normal Tissues of Corresponding Cancers

Out of the 17 corresponding normal tissue types analyzed, MAP3K19 is most highly expressed (cutoff of 0.1 and greater) in Normal-Uterine Corpus Endometrial Carcinoma (1.46), Normal-Lung Adenocarcinoma (1.09), Normal-Lung Squamous Cell Carcinoma (0.93), Normal-Head and Neck Squamous Cell Carcinoma (0.4), and Normal-Esophageal Carcinoma (0.1). The remaining groups have comparably low expression levels (0.02–0.03) with no obvious outlier (Table 1).

2.1.2 Expression Level in Cancer Tissues

Out of the 17 cancer types analyzed, MAP3K19 is most highly expressed (cutoff of 0.1 and greater) in Uterine Corpus Endometrial Carcinoma (0.92), Lung Adenocarcinoma (0.4), Lung Squamous Cell Carcinoma (0.15), and Breast Invasive Carcinoma (0.1). Unlike the corresponding normal tissues, different cancer tissues demonstrate a more continuous degree of expression levels with Kidney Chromophobe, Kidney Renal Clear Cell Carcinoma, Liver Hepatocellular Carcinoma, and Thyroid Carcinoma expressing lowest levels of MAP3K19 (0.2) (Table 1).

2.1.3 Fold Change Between Cancer and Corresponding Normal Tissues

In addition to baseline expression of MAP3K19 in cancer types and their corresponding normal tissues, fold change in expression was also generated. Only samples with significant *p*-values (<0.05) will be discussed. A strong increase (>1.2-fold) in MAP3K19 expression is seen in Breast Invasive Carcinoma (3.31), Prostate Adenocarcinoma (2.77), and Kidney Renal Clear Cell Carcinoma (1.38) compared to their corresponding normal tissues. A strong decrease (<0.8-fold) in MAP3K19 expression is seen in Lung Squamous Cell Carcinoma (0.16) and Lung Adenocarcinoma (0.37). Colon Adenocarcinoma (0.92) and Thyroid Carcinoma (0.85) also show slight differences in cancer compared to normal (Table 1).

2.2 MAP3K19 Correlations to Relapse Free Survival in Different Cancer Types

2.2.1 Cancer Types with Positive Survival Correlations to MAP3K19 mRNA Expression

Cancer types that had a positive survival correlation with MAP3K19 expression are: Rectum Adenocar-

Table 2. MAP3K19 KMPlotter Cancer Survival Correlations.

Cancer types	Hazard ratio	*p*-value	Low expression (n)	High expression (n)
Kidney renal papillary cell carcinoma	**2.38 (1.01–5.64)**	0.042	76	211
Kidney renal clear cell carcinoma	**1.83 (1.35–2.47)**	6.4×10^{-5}	322	208
Lung squamous cell carcinoma	**1.47 (1.1–1.95)**	0.008	201	294
Rectum adenocarcinoma	*0.28 (0.08–0.95)*	0.029	118	47
Uterine corpus endometrial carcinoma	*0.44 (0.24–0.79)*	0.0048	399	143
Cervical squamous cell carcinoma	*0.47 (0.25–0.9)*	0.019	224	80
Bladder carcinoma	*0.58 (0.43–0.79)*	0.00039	124	280
Pancreatic ductal adenocarcinoma	*0.6 (0.37–0.97)*	0.037	130	47
Liver hepatocellular carcinoma	*0.64 (0.45–0.9)*	0.011	127	243
Breast cancer	*0.67 (0.47–0.96)*	0.027	691	398
Lung adenocarcinoma	*0.68 (0.48–0.95)*	0.025	367	137
Thymoma	3.91 (0.73–20.97)	0.088	87	31
Ovarian cancer	1.14 (0.86–1.51)	0.36	117	256
Head and neck squamous cell carcinoma	0.81 (0.61–1.07)	0.14	148	351
Sarcoma	0.8 (0.53–1.22)	0.3	157	102
Stomach adenocarcinoma	0.77 (0.56–1.07)	0.12	156	215
Esophageal adenocarcinoma	0.69 (0.31–1.52)	0.35	57	23
Thyroid carcinoma	0.61 (0.23–1.64)	0.32	178	324
Esophageal squamous cell carcinoma	0.59 (0.26–1.31)	0.19	19	62
Pheochromocytoma and paraganglioma	0.25 (0.03–2.16)	0.17	93	85
Testicular germ cell tumor	0 (0–inf)	0.033	59	75

The KMPlotter database was used to correlate MAP3K19 expression to relapse free survival for 21 different cancer types. Hazard ratios that are statistically significant ($p < 0.05$) are *italicized* to indicate positive survival correlation and **bolded** to indicate negative survival correlation.

cinoma, Uterine Corpus Endometrial Carcinoma, Cervical Squamous Cell Carcinoma, Bladder Carcinoma, Pancreatic Ductal Adenocarcinoma, Liver Hepatocellular Carcinoma, Breast Cancer, and Lung Adenocarcinoma. Positive survival correlation is defined as hazard ratio <1 and p-value < 0.05 (Table 2).

2.2.2 Cancer Types with Negative Survival Correlations to MAP3K19 mRNA Expression

Cancer types that had a negative survival correlation with MAP3K19 expression are: Kidney Renal Papillary Cell Carcinoma, Kidney Renal Clear Cell Carcinoma, and Lung Squamous Cell Carcinoma. Negative survival correlation is defined as hazard ratio >1 and p-value < 0.05 (Table 2).

The remaining cancer types, Esophageal Adenocarcinoma, Esophageal Squamous Cell Carcinoma, Head and Neck Squamous Cell Carcinoma, Ovarian Cancer, Pheochromocytoma & Paraganglioma, Sarcoma, Stomach Adenocarcinoma, Testicular Germ Cell Tumor, Thymoma, and Thyroid Carcinoma, had no significant correlations with MAP3K19 expression.

3. Discussion

Two publicly available datasets, starBase (http://starbase.sysu.edu.cn) and GEPIA (Gene Expression Profiling Interactive Analysis) (http://gepia.cancer-pku.cn/), were analyzed to generate (Table 1). The data reveals tissue dependent variation of MAP3K19 expression levels. Interestingly, Uterine Corpus Endometrial Carcinoma, Lung Adenocarcinoma, and Lung Squamous Cell Carcinoma had the highest levels of expression in both cancer and corresponding control samples. In general, corresponding normal samples had a more binary distribution with low expression levels consistently ranging between 0.02 and 0.03. This pattern is lost with cancer samples as low expression levels demonstrate a continuous distribution between 0.02 and 0.09. This suggests that MAP3K19 is normally only highly expressed in lung and endometrial tissue, and that basal levels may increase in a cancer setting. Furthermore, this analysis reveals that MAP3K19 is a very lowly expressed gene. For example, GAPDH, a commonly used housekeeping gene, has an expression score that ranges from 12.67 at the lowest to 12.67 at the highest. This is several-fold greater than the highest 1.46 seen in endometrial tissue. Because MAP3K19 is not a highly expressed kinase, arguments

could be made that perturbances in expression levels may have no effect or may lead to major biological effects. For either scenario, further investigation is warranted.

In addition to baseline MAP3K19 expression in different tissue types, a comparison was made between cancer types and their corresponding normal tissues. Breast Invasive Carcinoma, Prostate Adenocarcinoma, and Kidney Renal Clear Cell Carcinoma showed statistically significant fold-change increases in diseased versus normal tissues at 3.31, 2.77, and 1.38 times, respectively. Interestingly, all corresponding normal tissues had low basal expressions (0.02–0.03) but only diseased Breast Invasive Carcinoma had MAP3K19 expression level that met the cutoff of 0.1 or greater. This suggests an important role for MAP3K19 in breast cancer compared to other cancer types, warranting investigation.

Conversely, tissue types with statistically significant decreased MAP3K19 expression in cancer versus corresponding normal tissues are Lung Squamous Cell Carcinoma, Lung Adenocarcinoma, Thyroid Carcinoma, and Colon Adenocarcinoma at 0.16, 0.37, 0.85, and 0.92, respectively. Among these four sets of cancer and corresponding normal tissue, only Lung Squamous Cell Carcinoma and Lung Adenocarcinoma had levels that met the cutoff of 0.1 or greater. The high levels of MAP3K19 expression in normal tissues and the strong decrease, but still high overall, in the corresponding cancers strongly suggests a possible physiological role for MAP3K19 in the pulmonary setting, warranting additional investigation.

The remaining groups had non-significant fold change results ($p > 0.05$). Despite the lack of statistical significance, we will discuss some honorable mentions that may provide useful information if a sufficiently powered repeat of this screen is performed. Head and Neck Squamous Cell Carcinoma, Esophageal Carcinoma, and Uterine Corpus Endometrial Carcinoma are cancers that had MAP3K19 expression levels that met the cutoff value of 0.1 or greater in corresponding normal tissues. Interestingly, all 3 groups had a reduction in MAP3K19 expression levels in diseased tissue with fold changes of 0.1, 0.54, and 0.64, respectively. Additionally, Uterine Corpus Endometrial Carcinoma had the highest levels of MAP3K19 expression in both diseased and corresponding normal tissues at 0.92 and 1.46, respectively. This suggests a possible important role for MAP3K19 in the female reproductive organ, warranting further investigation.

KMPlotter survival analysis shows varying correlations depending on cancer types. In no particular order, Bladder Carcinoma, Breast Cancer, Cervical Squamous Cell Carcinoma, Liver Hepatocellular Carcinoma, Lung Adenocarcinoma, Pancreatic Ductal Adenocarcinoma, Rectum Adenocarcinoma, and Uterine Corpus Endometrial Carcinoma patients with higher MAP3K19 mRNA expression had improved survival rates compared to low expression. On the opposite end, Kidney Renal Clear Cell Carcinoma, Kidney Renal Papillary Cell Carcinoma, and Lung Squamous Cell Carcinoma patients with higher MAP3K19 levels had worse survival outcomes compared to lower levels. MAP3K19's complex relationship with cancer survival is further highlighted by the conflicting hazard ratios seen in Lung Adenocarcinoma (0.68) and Lung Squamous Cell Carcinoma (1.47). This is especially interesting because although both are neoplasias of the lung, they have differing qualities such as how Lung Adenocarcinoma tends to be located peripherally while Lung Squamous Cell Carcinoma tends to be located centrally and arise from the bronchus [14,15]. Overall, MAP3K19 expression and correlation to patient survival is complex and dependent upon cancer type. Additional investigations are warranted.

The main data discussed have been generated from two databases for different cancer types. In **Supplementary Table 1**, we took cancers that were common to both databases and aligned their respective fold change (cancer vs corresponding normal) and hazard ratios (high vs low). Among the 13 cancers that were found in both databases, only 4 had significant *p*-values for both fold change and hazard ratios. Some cancers had clear cut relationships with MAP3K19 expression. Kidney Renal Clear Cell Carcinoma tissues have a 1.38-fold increase in MAP3K19 expression compared to corresponding normal tissues while also having a high hazard ratio of 1.83 for patient survival. Lung Adenocarcinoma tissues have a 0.37-fold decrease of MAP3K19 compared to corresponding normal tissues while also having a low hazard ratio of 0.68 for patient survival. This suggests a more straightforward and pathological role for MAP3K19 in these cancer types. The other 2 cancers, however, have a more paradoxical relationship with MAP3K19 expression. Breast Invasive Carcinoma tissues have a 3.31-fold increase in MAP3K19 expression compared to normal, indicating a tumor promoting role in breast neoplasia, but Breast Cancer has a hazard ratio of 0.67, indicating a protective effect for MAP3K19 in breast cancer patients. Lung Squamous Cell Carcinoma tissues have a 0.16-fold decrease in MAP3K19 expression compared to normal, suggesting a protective effect in this cancer type, while also having a hazard ratio of 1.47, suggesting negative effects on patient survival.

In summary, MAP3K19 is highest expressed in lung and endometrial tissue and, in general, weakly expressed in other tissue types. Its role in cancer pathology is complicated and dependent on disease type. For example, lung cancers seem to have decreased expression while breast carcinoma seems to have increased levels. This complexity is recapitulated in the clinical setting with varying hazard ratios for different cancer types. For example, high MAP3K19 expression is correlated with increased survival in breast cancer but with decreased survival in kidney renal clear cell carcinoma. Overall, MAP3K19 is an understudied kinase that plays a diverse role in different cancers. While our report here gives a preliminary view into

its possible roles in cancers, further studies are necessary to validate the mRNA sequencing data with protein expression and activity. Furthermore, the mechanism by which MAP3K19 exerts its effects will also be elucidated. The goal of this brief report is to establish an understanding for the role of MAP3K19 and the results warrant deeper investigations.

4. Methods

4.1 The KM Plotter Online Tool

MAP3K19 mRNA expression levels and survival data correlations were generated by KMPlot pan-cancer RNA-seq analysis [16]. The "Auto select best cutoff" option was used to algorithmically generate groups of high vs low MAP3K19 expression. This allows for data comparison between groups within a disease but is not necessarily valid for comparisons between different cancer types. Analysis was performed for all cancer types without restrictions to subtype, grade, mutation burden, cellular content, or patient background.

4.2 Tissue Expression Databases

The analysis of cancer and normal samples were performed using data from The Cancer Genome Atlas (TCGA) project in The Encyclopedia of RNA Interactomes (ENCORI) database [17]. The TCGA dataset was also evaluated using the Gene Expression Profiling Interactive Analysis (GEPIA) database [18]. The expression data of cancers were downloaded from the TCGA project via the Genomic Data Commons Data Portal. The expression values of genes from RNA-seq data were scaled with log2 (FPKM + 0.01). Fold change values were calculated prior to rounding of expression values.

Abbreviations

MAPK, mitogen activated protein kinase; MAP, Mitogen Activated Protein.

Author Contributions

KN and MEB conceptualized this manuscript. KN and HY worked closely together to generate the bioinformatics and write the manuscript. TC, JM, ABH, MA, KH, CKB, MKW, CEB, AR, SCO, MDM, HW, and SE contributed by analyzing the bioinformatics data, and fine tuning and revising the manuscript drafts. MJM, SBL, BMC, SKA, DHD, and MEB interpreted the bioinformatics data and gave the final approval for the drafts and the way the data is presented in manuscript sections and tables.

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 http://doi.org/10.31083/j.fbl2706196.

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