



# Emerging Role of Novel Biomarkers of Ly6 Gene Family in Pan Cancer

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## Abstract

Stem cell antigen-1 (Sca-1) is the first identified member of mouse Ly6 gene family. We discovered that Sca-1 disrupts TGF $\beta$  signaling and enhances mammary tumorigenesis in a DMBA-induced mammary tumor model. Sca-1 gene is lost during evolution in humans. Human Ly6 genes Ly6D, LyE, LyH, and LyK on human chromosome 8q24.3 genes are syntenic to the mouse chromosome 15 where Sca-1 is located. We found that Ly6D, E, H, and K are upregulated in human cancer compared to normal tissue and that the increased expression of these genes are associated with poor prognosis of multiple types of human cancer. Several other groups have indicated increased expression of Ly6 genes in human cancer. Here we described the relevance of expression of human Ly6D, LyE, LyH, and LyK in functioning of normal tissues and tumor progression.

## Keywords

Biomarkers · Ly6 · TGF-beta · Survival outcome

## Introduction

Stem cell antigen-1 (Sca-1) was the first identified member of mouse Ly6 gene family [1]. Sca-1 has been described as marker of tissue-resident stem cells and also been recognized as cancer initiating cell population in multiple mouse model of mammary, prostate, and lung cancer among other cancer types [2–4]. We described that Sca-1 binds with TGF $\beta$  receptor 1 (T $\beta$ R1) and disrupts the TGF $\beta$  receptor complex, leading to tumorigenic progression in mouse model of mammary tumorigenesis [5]. A direct homologue of Sca-1 is missing in humans; however, multiple members of mouse Ly6 genes and syntenic human Ly6 genes have been described. Human Ly6 gene family usually contain LU domain. These molecules are scattered throughout the human chromosome 1, 2, 6, 8, 11, and 19 [6]. We will concern our description to human Ly6D, LyE, LyH, and Ly6K, which are present on human chromosome 8q24.3.

## Expression of Ly6D, E, H, and K Genes in Normal Tissues

### Ly6D

Ly6D RNA is expressed in highest quantities in esophageal tissue and in skin as shown in HPA dataset, GTEx dataset, and Fantome5 datasets as

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visualized in Human Protein Atlas available from [www.proteinatlas.org](http://www.proteinatlas.org) [7–9]. The RNA expression was undetectable or expressed at a very low level in normal ovary, lung, testis, colon, breast, and prostate (Fig. 1a–c). The protein expression corroborated with RNA expression, showing increased expression of Ly6D in esophageal tissue and in skin (Fig. 2).

### Ly6E

Ly6E RNA expression was identified in liver tissue, placenta, lung, and spleen by three different databases (Fig. 3a–c) as visualized in Human Protein Atlas available from [www.proteinatlas.org](http://www.proteinatlas.org) [7–9]. The corroborative protein data was not yet available at the human protein atlas. Lowest expression of Ly6E RNA in normal tissues was found in pancreas and skeleton tissues (Fig. 3a–c). The Ly6E expression is restricted to syncytiotrophoblast cells of the mouse placenta [10].

### Ly6H

Ly6H RNA expression was identified highest in Brain tissue in HPA dataset, GTEx dataset, and Fantome5 (Fig. 4a–c) as visualized in Human Protein Atlas available from [www.proteinatlas.org](http://www.proteinatlas.org) [7–9]. Ly6H plays an important role in glutamatergic signaling in brain [11].

### Ly6K

Ly6K RNA is expressed highest in testis in HPA dataset, GTEx dataset, and Fantome5 datasets (Fig. 5a–c) as visualized in Human Protein Atlas available from [www.proteinatlas.org](http://www.proteinatlas.org) [7–9]. The RNA expression was undetectable or expressed at a very low level in normal ovary, lung, testis, colon, breast, and prostate. The protein expression data showed that Ly6K is exclusively expressed in testis (Fig. 6). Male Ly6K homozygous knockout mice showed normal mating hab-

its; however, they were infertile. Female Ly6K homozygous knockout mice were fertile. The male infertility was found to be associated with sperm migration [12].

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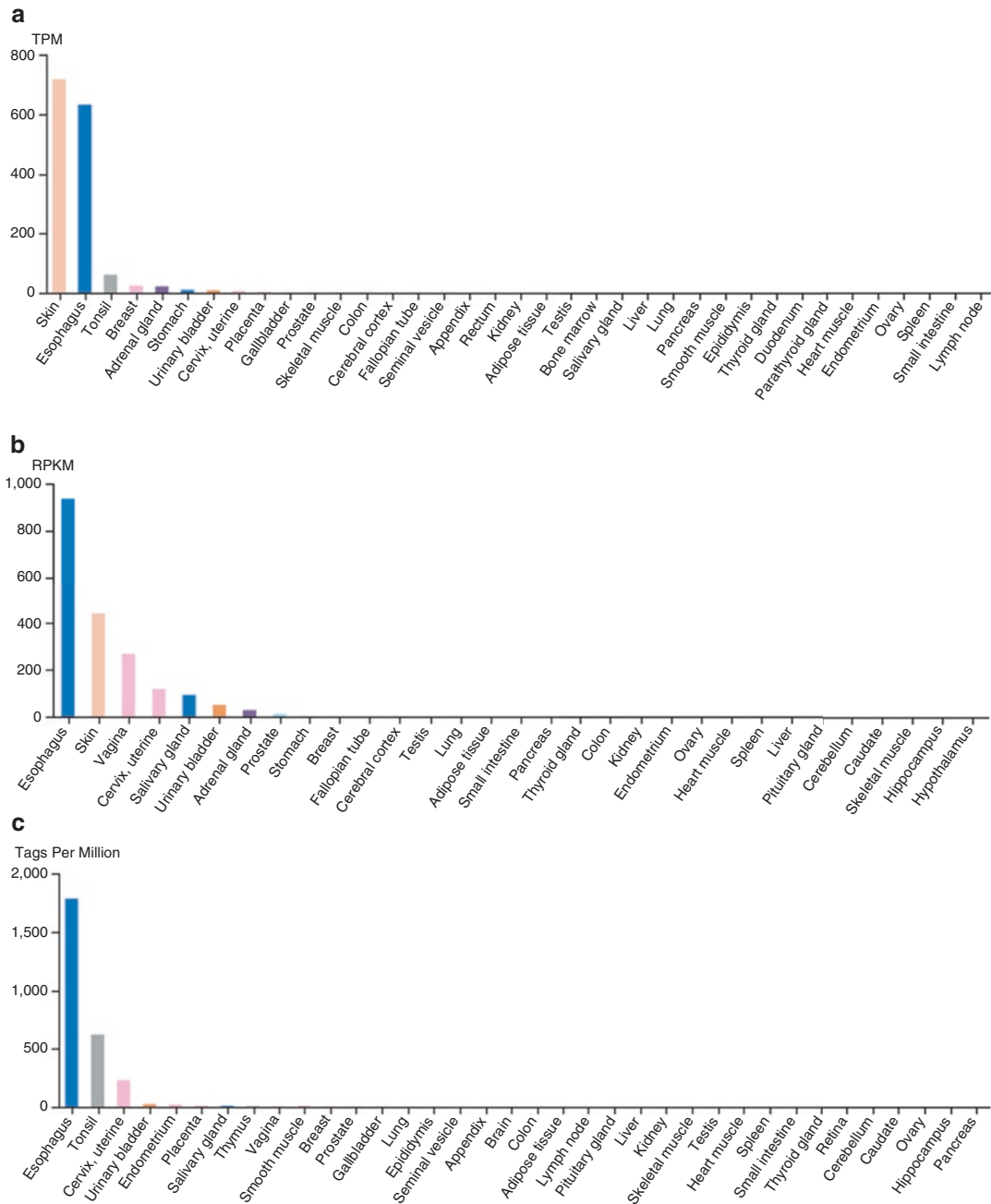
## Expression of Ly6D, E, H, and K Genes in Tumor Tissues

### Ly6D

We looked for RNA expression of Ly6D in various publically available dataset and visualized using Oncomine [13] and TCGA [14] as described by Luo et al. [15]. Ly6D was found to be increased in tumors of ovarian, colorectal, gastric, breast, lung, bladder, brain and CNS, cervical, esophageal, head and neck and pancreatic cancer compared to normal tissue in multiple studies. The increased expression of Ly6D was associated with poor survival in ovarian, colorectal, gastric, breast and lung cancer [15] (Table 1). Since our publication new clinical data were available and added to KM plotter tool [16] (<http://kmplot.com/>), which showed that increased Ly6D expression is associated with poor prognosis in renal clear cell carcinoma and pancreatic ductal adenocarcinoma (Fig. 7). Recently Ly6D expression in addition to OLFM4, S100A7 was found to be associated with distant metastasis of estrogen receptor-positive breast cancer [17]. Ly6D was shown to be increased in aggressive forms of head and neck cancer [18].

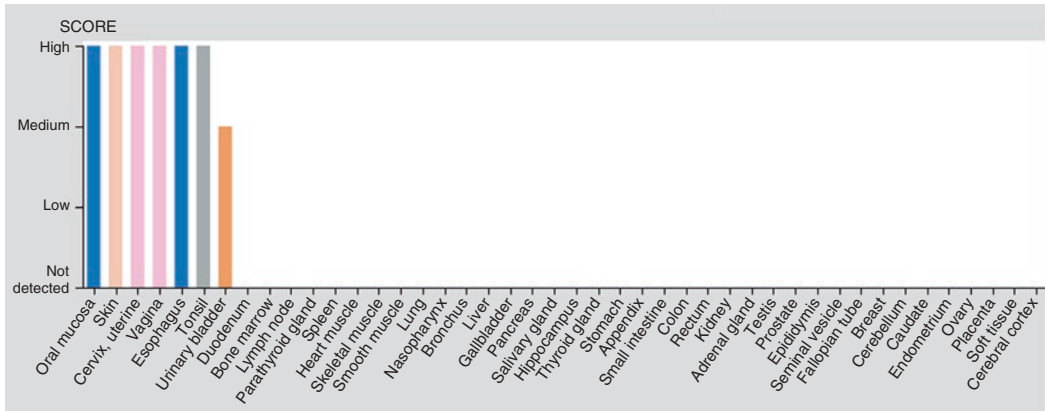
### Ly6E

We looked for RNA expression of Ly6E in various publically available dataset and visualized using Oncomine [13] and TCGA [14] as described by Luo et al. [15]. Ly6E was found to be increased in tumors of ovarian, colorectal, gastric, breast, lung, bladder, brain and CNS, cervical, esophageal, head and neck and pancreatic cancer compared to normal tissue in multiple studies. The increased expression of Ly6E was



**Fig. 1** RNA expression of Ly6D in normal human tissues. (a) HPA data set, (b) GTEx data set, and (c) FANTOM dataset. The data was visualized on the human proteome webtool with expression filter on. X-axis shows the name of tissue type used. Y-axis shows the units of RNA expression as described below. HPA dataset: RNA-seq tissue data is reported as mean TPM (transcripts per

million), corresponding to mean values of the different individual samples from each tissue. Color coding is based on tissue groups, each consisting of tissues with functional features in common. GTEx dataset: RNA-seq data is reported as median RPKM (reads per kilobase per million mapped reads), generated by the Genotype-Tissue Expression (GTEx) project



**Fig. 2** Ly6D protein expression in normal tissues. Immunohistochemistry was performed using anti-Ly6D antibody-rabbit polyclonal affinity purified antibody

HPA024755, HPA064317 from Sigma-Aldrich as described in the human protein atlas webtool: <https://www.proteinatlas.org/ENSG00000167656-LY6D/tissue>

associated with poor survival in ovarian, colorectal, gastric, breast, lung, bladder, and brain and CNS cancer patients [15] (Table 1). Recent data added to KM plotter [16] (<http://kmplot.com/>) show that increased expression of Ly6E is associated with poor overall survival of renal papillary cell carcinoma and good prognostic marker for renal clear cell carcinoma (Fig. 8a, b). These new data indicated that increased expression of Ly6E is associated with poor overall survival of pancreatic ductal adenocarcinoma (Fig. 8c). The use of genome wide data analysis has prompted several new reports showing increased expression of Ly6E in bladder cancer and gastric cancer [19, 20]. The Ly6E gene has been also associated with more aggressive stem-like cells in hepatocellular carcinoma, pancreatic carcinoma, colon, and kidney [21–23].

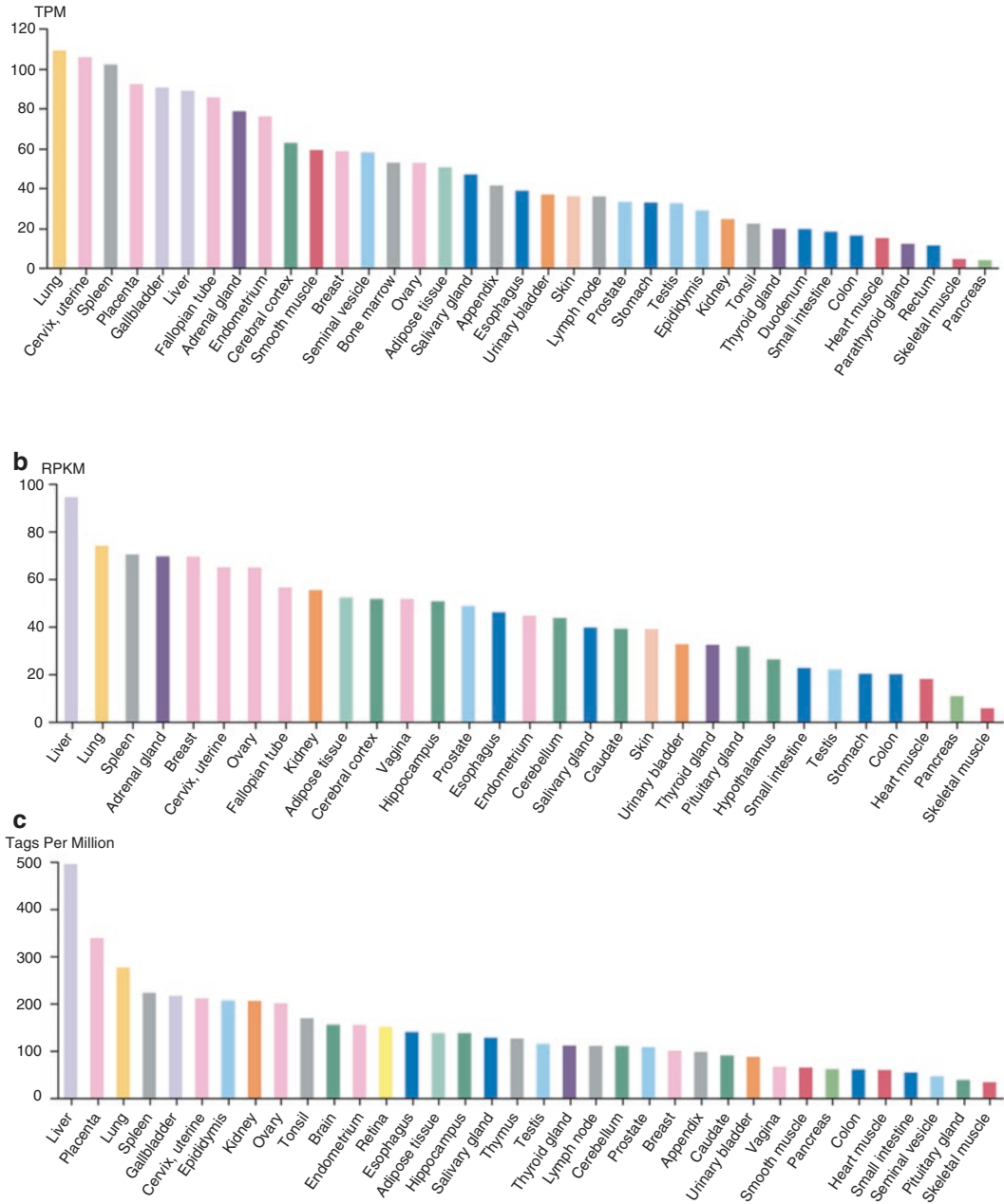
## Ly6H

We looked for RNA expression of Ly6H in various publically available dataset and visualized using Oncomine [13] and TCGA [14] as described by Luo et al. [15]. Ly6H was found be increased in tumors of ovarian, colorectal, gastric, breast, lung, bladder, brain and CNS, cervical, esophageal, head and neck and pancreatic cancer compared to normal tissue in multiple studies. The increased expression of Ly6H was

associated with poor survival in ovarian, colorectal, gastric, and breast cancer patients [15] (Table 1). Recent data added to KM plotter [16] (<http://kmplot.com/>) show that increased expression of Ly6H is associated with poor overall survival of renal clear cell carcinoma and pancreatic ductal adenocarcinoma (Fig. 9a, b).

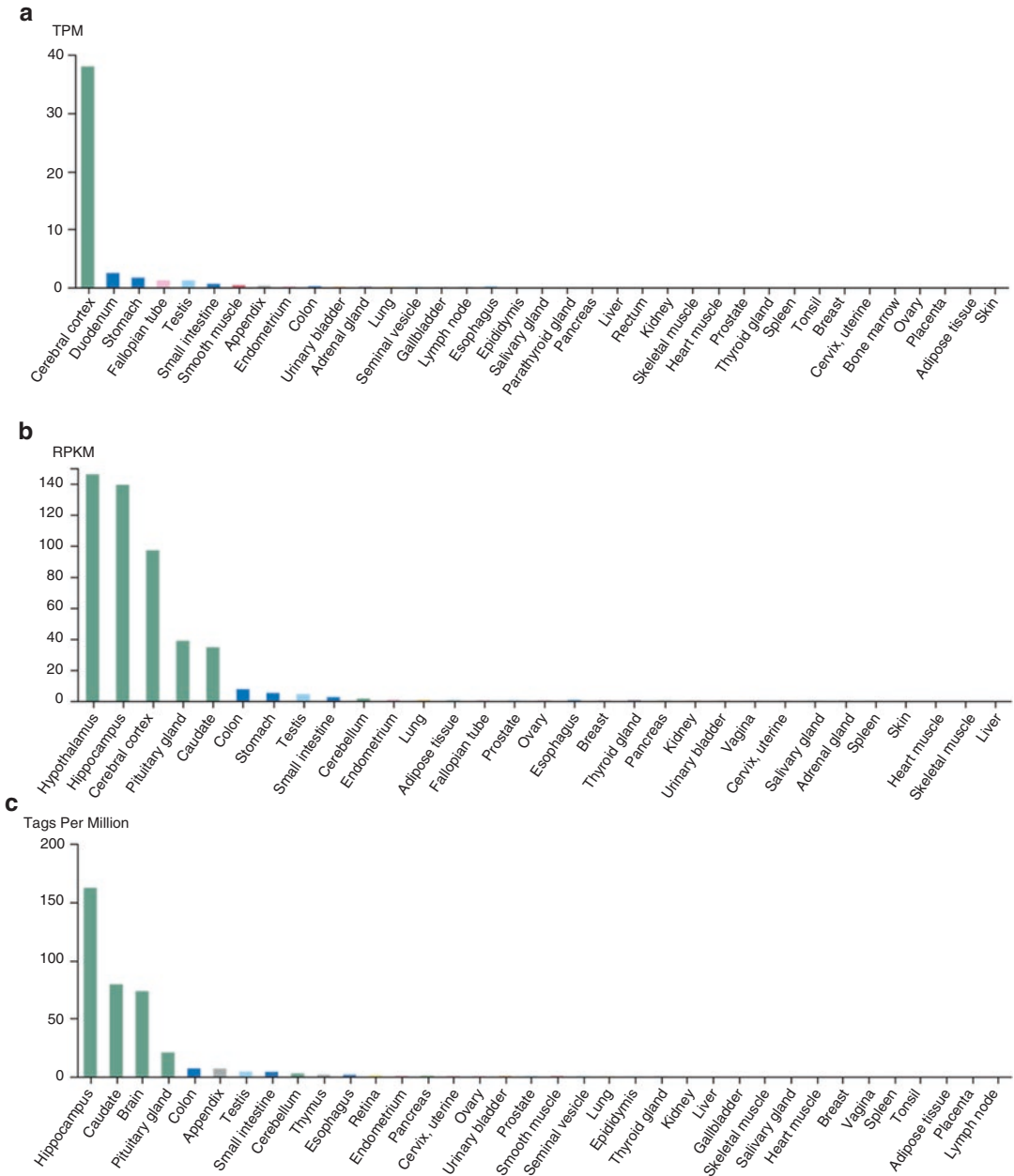
## Ly6K

We looked for RNA expression of Ly6K in various publically available dataset and visualized using Oncomine [13] and TCGA [14] as described by Luo et al. [15]. Ly6K was found be increased in tumors of ovarian, colorectal, gastric, breast, lung, bladder, brain and CNS, cervical, esophageal, head and neck and pancreatic cancer compared to normal tissue in multiple studies. The increased expression of Ly6K was associated with poor survival in ovarian, colorectal, gastric, breast, lung, bladder, and brain and CNS cancer patients [15] (Table 1). Increased expression of Ly6K in metastatic ER-positive breast cancer [24, 25], esophageal squamous cancer [26], gingivobuccal cancers [27], bladder cancer [28], and lung cancer [29] was observed. Recent data added to KM plotter [16] (<http://kmplot.com/>) show that increased expression of Ly6K is associated with poor overall survival of renal clear cell carcinoma, renal papillary cell carcinoma, and uterine corpus endometrial carcinoma (Fig. 10a–c).



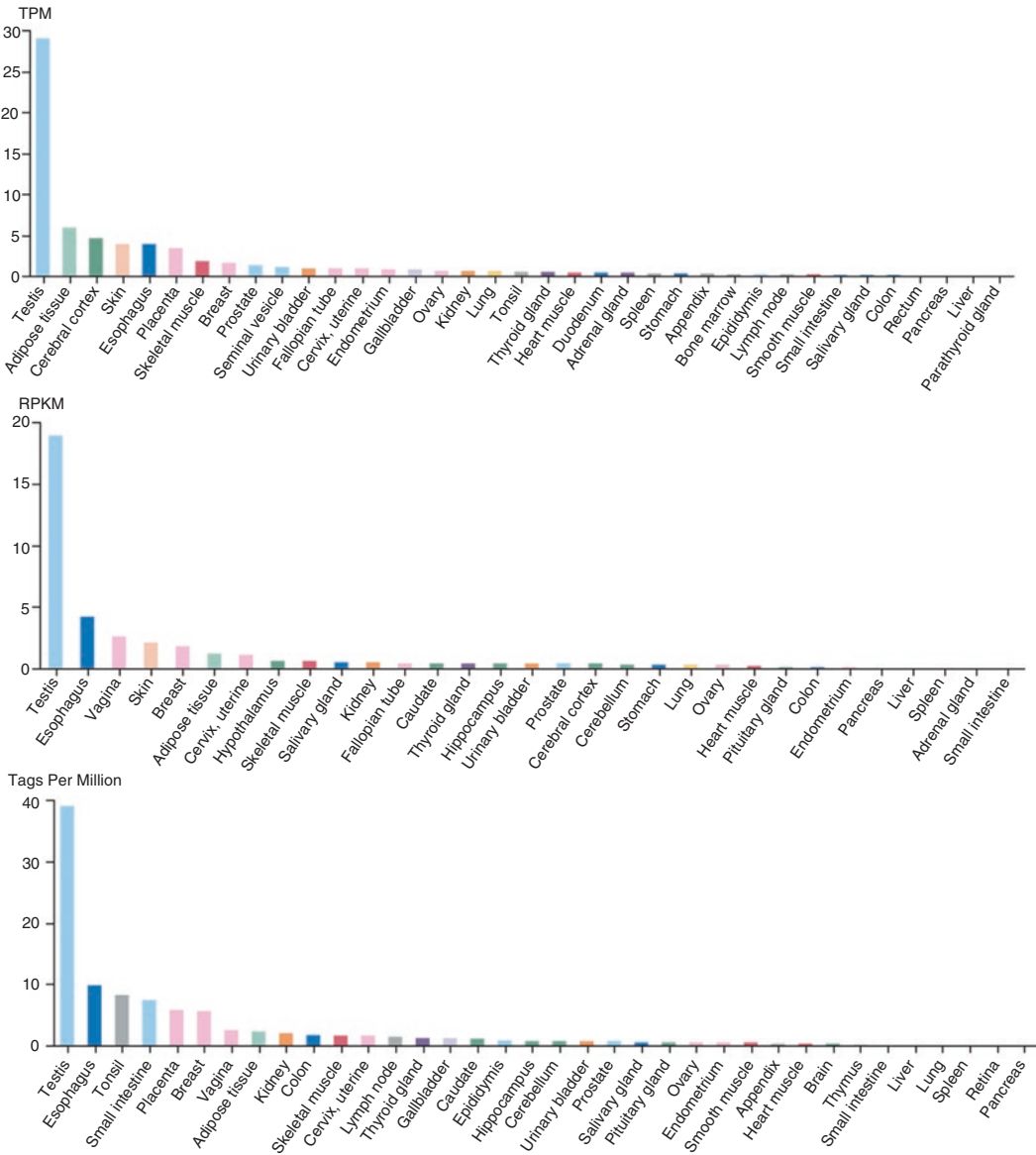
**Fig. 3** RNA expression of Ly6E in normal human tissues. (a) HPA data set, (b) GTEx data set, and (c) FANTOM dataset. The data was visualized on the human proteome webtool with expression filter on. X-axis shows the name of tissue type used. Y-axis shows the units of RNA expression as described below. HPA dataset: RNA-seq tissue data is reported as mean TPM (transcripts per

million), corresponding to mean values of the different individual samples from each tissue. Color-coding is based on tissue groups, each consisting of tissues with functional features in common. GTEx dataset: RNA-seq data is reported as median RPKM (reads per kilobase per million mapped reads), generated by the Genotype-Tissue Expression (GTEx) project



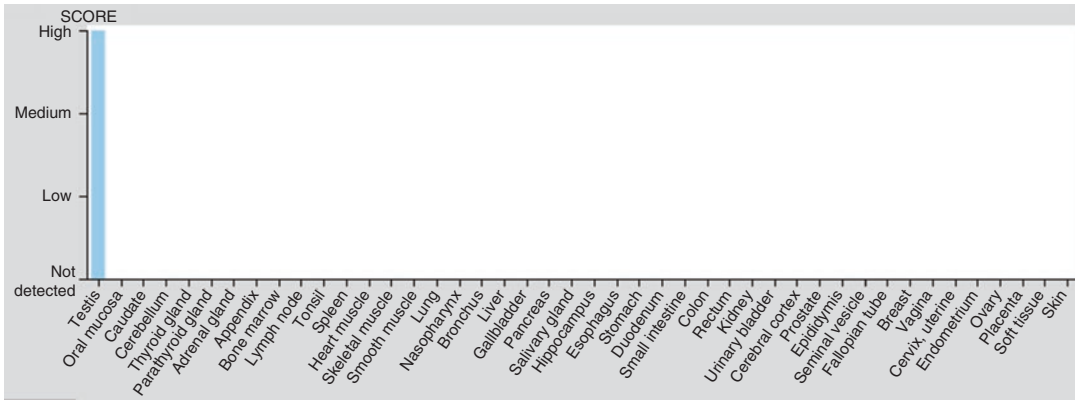
**Fig. 4** RNA expression of Ly6H in normal human tissues. **(a)** HPA data set, **(b)** GTEx data set, and **(c)** FANTOM dataset. The data was visualized on the human proteome webtool with expression filter on. X-axis shows the name of tissue type used. Y-axis shows the units of RNA expression as described below. HPA dataset: RNA-seq tissue data is reported as mean TPM (transcripts per

million), corresponding to mean values of the different individual samples from each tissue. Color coding is based on tissue groups, each consisting of tissues with functional features in common. GTEx dataset: RNA-seq data is reported as median RPKM (reads per kilobase per million mapped reads), generated by the Genotype-Tissue Expression (GTEx) project



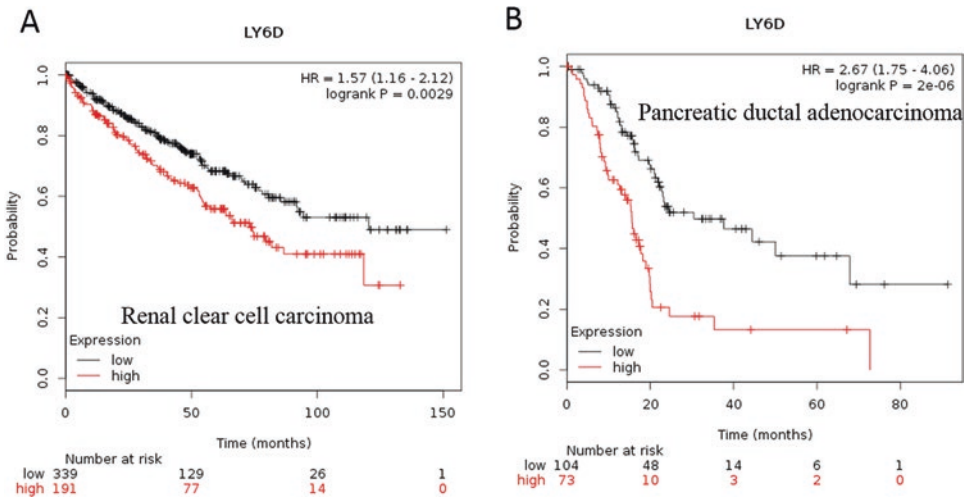
**Fig. 5** RNA expression of Ly6K in normal human tissues. (a) HPA data set, (b) GTEx data set, and (c) FANTOM dataset were visualized on the human proteome webtool with expression filter on. X-axis shows the name of tissue type used. Y-axis shows the units of RNA expression as described below. HPA dataset: RNA-seq tissue data is reported as mean TPM (transcripts per million),

corresponding to mean values of the different individual samples from each tissue. Color coding is based on tissue groups, each consisting of tissues with functional features in common. GTEx dataset: RNA-seq data is reported as median RPKM (reads per kilobase per million mapped reads), generated by the Genotype-Tissue Expression (GTEx) project



**Fig. 6** Ly6K protein expression data in normal tissues. Ly6K protein is exclusively expressed on human testis. Immunohistochemistry was performed using anti-Ly6K antibody-rabbit polyclonal affinity-purified antibody

HPA017770 and protein A/G purified mouse monoclonal antibody AMAb90986, AMAb90987 from Sigma-Aldrich as described in the human protein atlas webtool: <https://www.proteinatlas.org/ENSG00000160886-LY6K/tissue>

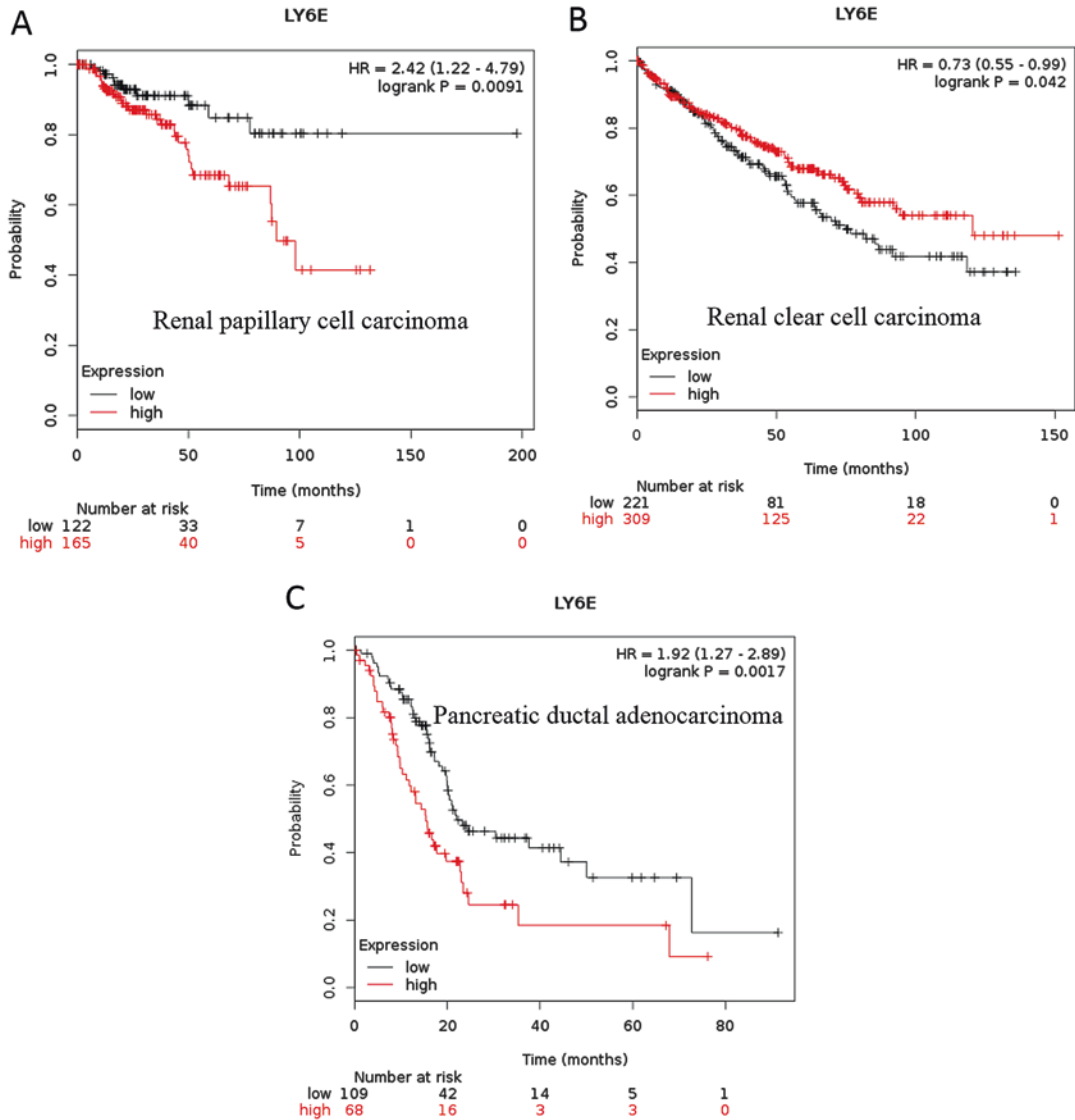


**Fig. 7** Increased Ly6D mRNA expression in cancer and patient survival. High Ly6D RNA expression leads to poor survival in (a) renal clear cell carcinoma and (b) pancreatic ductal adenocarcinoma



**Table 1** Correlation of high mRNA expression and patient survival outcome in multiple cancer types

Cancer type	Genes	Expression in tumors ( $p < 0.05$ )	Survival analysis ( $p < 0.05$ )
Ovarian	LY6D	Up	Poor prognosis
	LY6E	Up	Poor prognosis
	LY6H	Up	Poor prognosis
	LY6K	Up	Poor prognosis
Colorectal	LY6D	Up	Poor prognosis
	LY6E	Up	Poor prognosis
	LY6H	Up	Poor prognosis
	LY6K	Up	Poor prognosis
Gastric	LY6D	Up	Poor prognosis
	LY6E	Up	Poor prognosis
	LY6H	Up	Poor prognosis
	LY6K	Up	Poor prognosis
Breast	LY6D	Up	Poor prognosis
	LY6E	Up	Poor prognosis
	LY6H	Up	Poor prognosis
	LY6K	Up	Poor prognosis
Lung	LY6D	Up	Poor prognosis
	LY6E	Up	Poor prognosis
	LY6H	Up	OS (NS), others (NA)
	LY6K	Up	Poor prognosis
Bladder	LY6D	Up	OS (NS), others (NA)
	LY6E	Up	Poor prognosis
	LY6H	NS	OS (NS), others (NA)
	LY6K	Up	Poor prognosis
Brain and CNS	LY6D	Up	OS (NS), others (NA)
	LY6E	Up	Poor prognosis
	LY6H	Up	OS (NS), others (NA)
	LY6K	Up	Poor prognosis
Cervical	LY6D	Up	OS (NA), RFS (NS)
	LY6E	Up	OS (NA), RFS (NS)
	LY6H	Up	OS (NA), RFS (NS)
Esophageal	LY6K	Up	OS (NA), RFS (NS)
	LY6D	Up	OS (NS), others (NA)
	LY6E	Up	OS (NS), others (NA)
	LY6H	Up	OS (NS), others (NA)
Head and neck	LY6K	Up	OS (NS), others (NA)
	LY6D	Up	OS (NS), others (NA)
	LY6E	Up	OS (NS), others (NA)
	LY6H	Up	OS (NS), others (NA)
Pancreatic	LY6K	Up	OS (NS), others (NA)
	LY6D	Up	OS (NS), others (NA)
	LY6E	Up	OS (NS), others (NA)
	LY6H	Up	OS (NS), others (NA)
	LY6K	Up	OS (NS), others (NA)
	LY6D	Up	OS (NS), others (NA)
	LY6E	Up	OS (NS), others (NA)
	LY6H	Up	OS (NS), others (NA)



**Fig. 8** Increased Ly6E mRNA expression in cancer and patient survival. High Ly6E RNA expression leads to poor survival in (a) renal papillary cell carcinoma, good prognosis for (b) renal clear cell carcinoma, poor survival in (c) pancreatic ductal adenocarcinoma

### Mechanisms Associated Ly6D, E, H, and K Gene Family

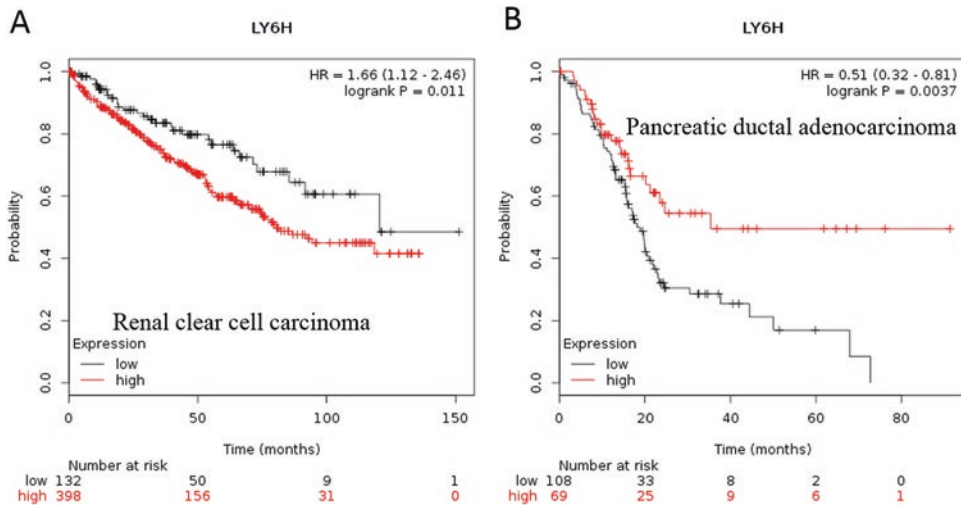
#### Ly6D

The functional role of Ly6D in human or mouse is not very well described. Ly6D was found to be important in selection of CD4+CD8+ subset of T cells in thymus [30]. Ly6D was shown to be involved in cell adhesion using NIH3T3 fibro-

blast cells [31]. The molecular pathways which may lead to regulation of Ly6D remain to be understood.

#### Ly6E

We discovered that Ly6E is required for increased TGFβ signaling, IFNγ/PDL1 signaling in breast cancer [32]. Ly6E was also shown to modulate



**Fig. 9** Increased Ly6H mRNA expression in cancer and patient survival. High Ly6H RNA expression leads to poor survival in (a) renal clear cell carcinoma and (b) pancreatic ductal adenocarcinoma

the PTEN/PI3K/Akt/HIF-1 axis in breast cancer cell lines [33]. Ly6E was found to be important in enhancing the infectivity of multiple, enveloped RNA viruses in late steps using influenza A virus model [34]. Ly6E has been shown to be an interferon-inducible gene in lymphoid cells and plays an important role in HIV infection [35, 36]. Mouse Ly6E is a receptor syncytin A and plays important role in syncytiotrophoblast fusion and placental morphogenesis [37, 38].

## Ly6H

Ly6H is required for nicotine-induced glutamatergic signaling via synaptic signaling of alpha7 nicotinic acetylcholine receptors [11].

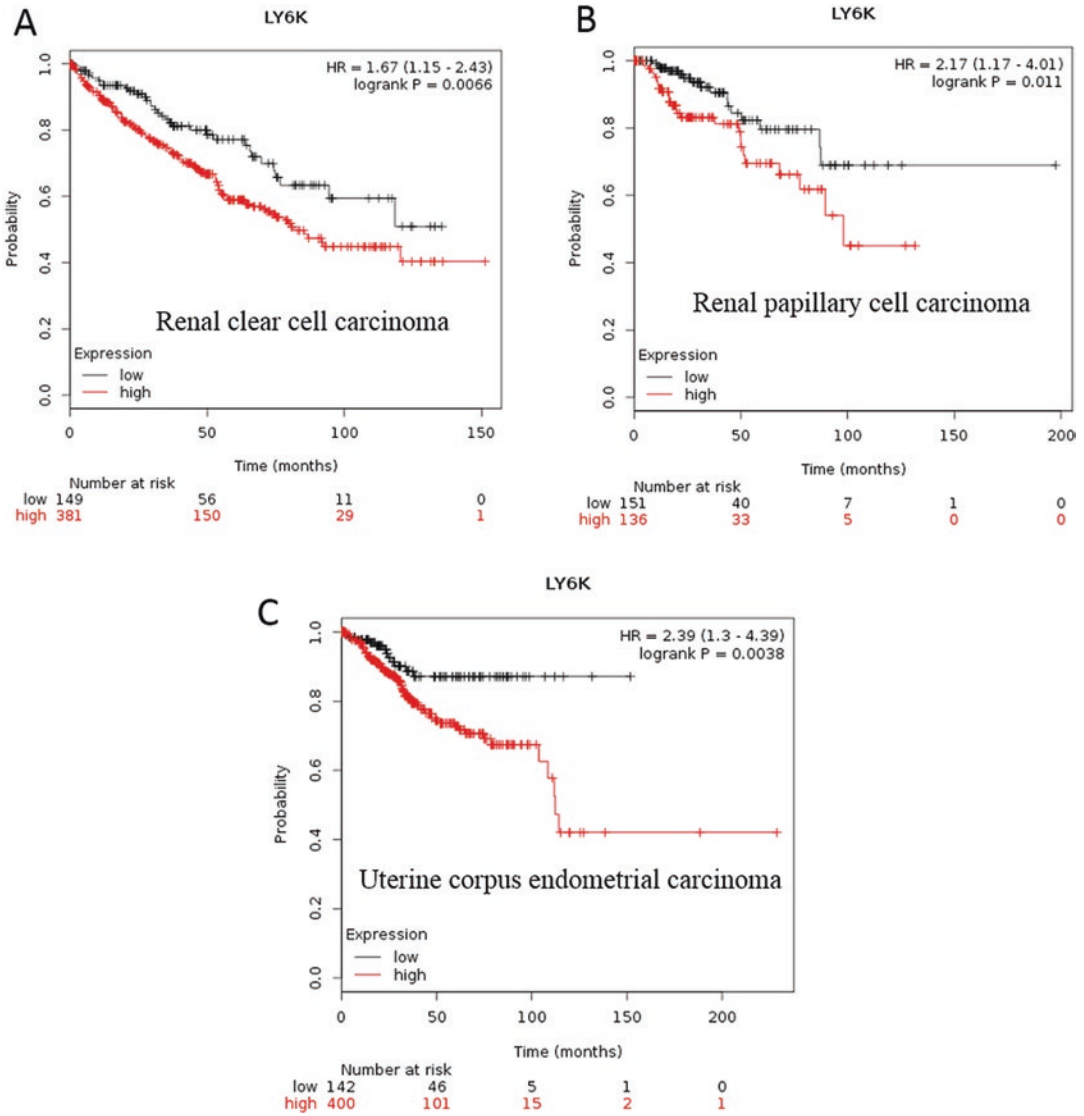
## Ly6K

We discovered that Ly6E is required for increased TGF $\beta$  signaling, IFN $\gamma$ /PDL1 signaling in breast cancer [32]. High Ly6K expression is shown to have been linked with low expression of tumor suppression microRNA 500a-3p in non-small cell lung carcinoma [39]. AP1 activa-

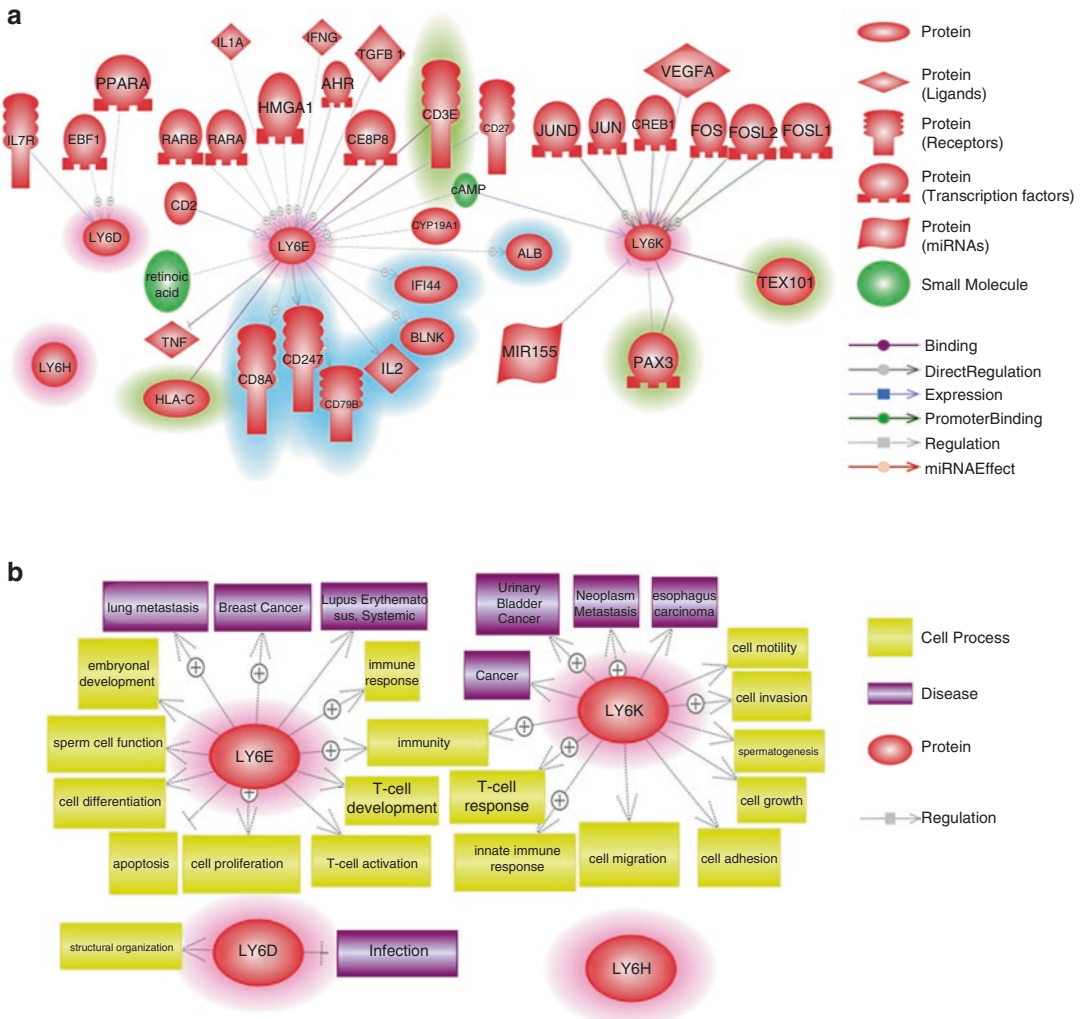
tion is shown to be important in increased expression of Ly6K in breast cancer cell lines [40]. Ly6K protein expression in testis was shown to be stabilized by TEX101, a glycoprotein important in fertility [41].

## Summary

The important role of Ly6 gene family in physiology and disease is emerging. The Ly6 gene family members can emerge as valid therapeutic target in correcting conditions of infection, nicotine addiction, cancer, immunotherapy, and fertility. Our laboratory is focused on understanding the molecular mechanism of Ly6 protein in cancer and validating Ly6 molecules as therapeutic targets in targeted cancer therapy. The network analysis of Ly6 gene family members showed that Ly6 signaling is involved in a broad range of molecules including growth factor, nuclear receptor, and micro RNAs (Fig. 11a). Pathway studio network analysis showed that Ly6 gene family affect multitude of cellular fate and cell-cell interaction with microenvironment ranging from growth, apoptosis, autophagy, and immune response (Fig. 11b).



**Fig. 10** Increased Ly6K mRNA expression in cancer and patient survival. High Ly6K RNA expression leads to poor survival in (a) renal clear cell carcinoma, (b) renal papillary cell carcinoma, and (c) pancreatic ductal adenocarcinoma



**Fig. 11** Network analysis of Ly6 gene family members. **(a)** Pathway studio network analysis showed that Ly6 signaling is involved in broad range of molecules including growth factor, nuclear receptor, and micro RNAs. The upstream regulators are not highlighted, the downstream effectors are

highlighted with blue, and the potential binding partners are highlighted with green. **(b)** Pathway studio network analysis showed that Ly6 gene family affect multitude of cellular fate and cell-cell interaction with microenvironment ranging from growth, apoptosis, autophagy, and immune response

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