МЕДИЧНІ НАУКИ В ЦІЛОМУ

EXPRESSION OF GENES IN THE INFLAMMASOME PATHWAY EFFECTS SURVIVAL IN KIDNEY RENAL CLEAR CELL CARCINOMA

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Inflammation plays a role at all stages of cancer. Inflammasomes are an integral part of inflammation response. Inflammasomes are large multiprotein complexes that are a part of innate immune system. They are potent inducers of maturation and secretion of pro-inflammatory interleukin (IL)-1β and IL-18 during inflammation [1]. Activation of inflammasomes causes a pro-inflammatory form of programmed cell death called pyroptosis accompanied by cytokine secretion [2]. Inflammasome is an important first line of immune defense, and its components tend to be expressed in epithelial tissues, where they respond to signals called danger-associated molecular patterns (DAMPs) produced by the host cell [3].

Proteins that are components of inflammasomes include pyrin, IFI16 (IFN-inducible protein 16), AIM2 (absent in melanoma 2), and NLRs (nucleotide-binding oligomerization domain and leucine-rich repeat-containing receptors) [1]. Through the pyrin domain, the inflammasome interacts with the adaptor protein ASC which activates a caspase. In turn, caspase cleaves precursors of (IL)-1β and IL-18 which may activate the pyroptosis mode of the cell death. Cancer is often accompanied by dysregulation of inflammasome activation [4].

We studied effect of differential gene expression in the inflammasome pathway [5]. on survival of patients with kidney renal clear cell carcinoma. We performed the Kaplan-Meier survival analysis using an online Kaplan-Meier plotter at https://kmplot.com/ that is capable to assess the effect of 54k genes on survival in 21

cancer types. The tool is used for discovery and validation of gene biomarkers of survival in cancer based on meta-analysis of massive cancer databases [6]. Sources for the databases include GEO, EGA, and TCGA. We performed the analysis of 530 patients with kidney renal clear cell carcinoma for whom clinical data was available for analysis in the databases.

We found a significant dysregulation of the inflammasome pathway, in which high expression of a number of genes of the pathway promotes survival of the patients, while high expression of another set of the inflammasome pathway genes decreases survival (Table 1).

Table 1

Gene name	Logrank p	Adjusted p value when significant	Hazard ratio	Hazard ratio confidence interval	FDR, %	Low expression cohort (months)	High expression cohort (months)
High expression of these genes significantly increases survival							
APP	3.2e-9	0.0000007	0.41	0.30 – 0.55	1	23.6	56.5
BCL2	1.5e-8	0.000003	0.43	0.32 – 0.58	1	22.6	54.2
HSP90AB1	6.9e-5	0.01445	0.54	0.39 – 0.73	2	29.3	47.7
NFKB1	2.9e-8	0.000006	0.44	0.55 – 0.59	1	24.2	54.2
SUGT1	3.7e-6	0.00078	0.50	0.37 – 0.67	1	57.5	120.5
High expression of these genes significantly decreases survival							
AIM2	2.2e-5	0.00462	1.92	1.41 – 2.60	1	54.2	29.4
NFKB2	1.1e-6	0.00023	2.09	1.54 – 2.84	1	52.2	23.4
PSTPIP1	9.8e-5	0.02058	2.15	1.45 – 3.19	3	71.5	31.8
PYCARD	4.1e-8	0.000009	2.66	1.85 – 3.82	1	71.5	27.3
High or low expression of these genes does not have significant effect on survival							
BCL2L1	0.0512		0.72	0.51 – 1.00	100	74.7	120.5
CASP1	0.0379		1.40	1.02 – 1.92	over 50	118.5	74.2
HMOX1	0.0015		0.62	0.46 – 0.83	50	70.2	120.5
MEFV	0.0158		1.44	1.07 – 1.95	over 50	118.5	70.2
NLRC4	0.1903		0.81	0.58 – 1.11	100	80.6	94.3
NLRP1	0.0006		1.74	1.26 – 2.41	20	120.5	57.1
NLRP3	0.0905		0.76	0.55 – 1.05	100	74.7	120.5
P2RX7	0.2512		0.83	0.60 – 1.14	100	81.8	118.5
PANX1	0.0009		1.69	1.24 – 2.31	20	118.5	63.7
RELA	0.0883		1.31	0.96 – 1.80	100	118.5	74.7
TXN	0.1028		1.29	0.95 – 1.76	100	45.7	33.4
TXNIP	0.0001		0.46	0.31 – 0.69	3	33.1	74.7

APP, BCL2, HSP90AB1, NFKB1, and SUGT1 are the genes that increase survival of the patients with when highly expressed. BCL2 is a regulator of apoptosis with a complex action [7]. In the case of kidney renal clear cell carcinoma, its high expression increases survival (Fig. 1).

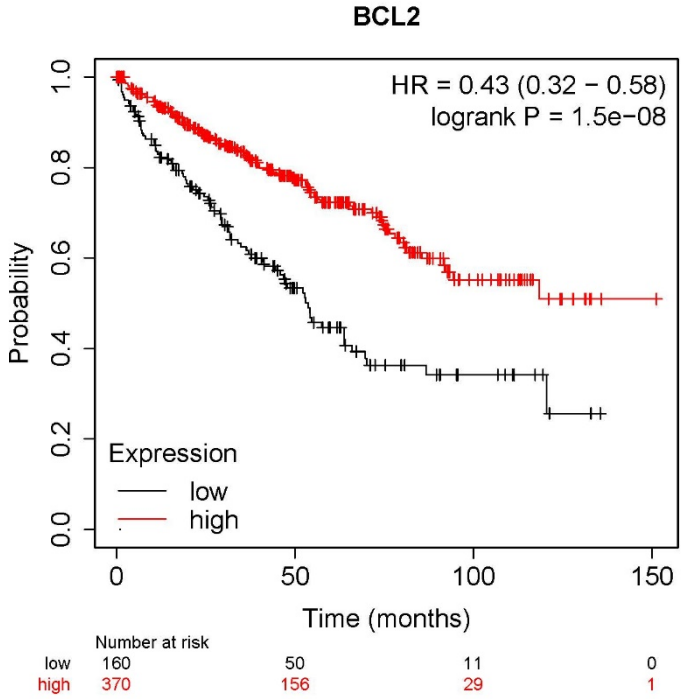

Figure 1. Effect of BCL2 on survival of patients with kidney renal clear cell carcinoma.

NFKB1 is nuclear factor kappa B subunit 1 which in some cases drives cancer progression and in some cases acts as tumor suppressor [8]. We found, that its high expression significantly increases survival in kidney renal clear cell carcinoma (Fig. 2). Interestingly, high expression of nuclear factor kappa B subunit 2 decreases survival in the cancer type.

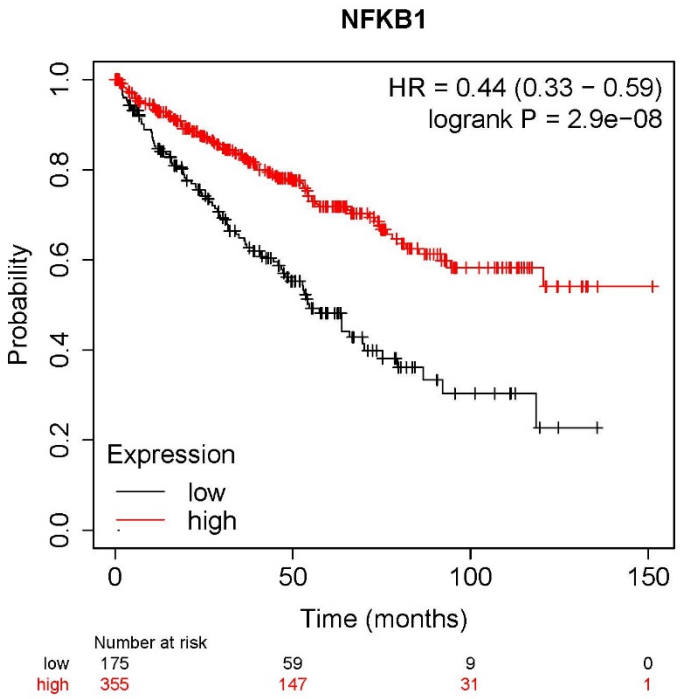

Figure 2. Effect of NFKB1 on survival of patients with kidney renal clear cell carcinoma.

AIM2, NFKB2, PSTPIP1, PYCARD are the genes that decrease survival of the patients with when highly expressed. PYCARD is apoptosis-associated speck-like protein containing a CARD (caspase activation and recruitment domain). It is a central adaptor molecule of the inflammasome complex, which mediates the secretion of inflammatory cytokines (i.e., IL-1β and IL-18) and has been reported to have dual role in carcinogenesis [9]. We found, that its high expression significantly decreases survival in kidney renal clear cell carcinoma (Fig. 3).

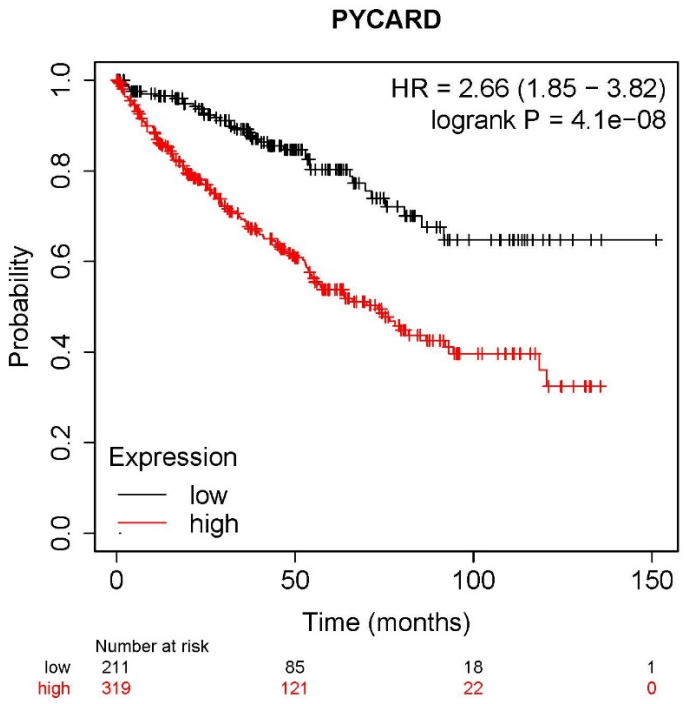

Figure 3. Effect of PYCARD on survival of patients with kidney renal clear cell carcinoma.

In summary, we found that expression of the inflammasome pathway genes is highly dysregulated in kidney renal clear cell carcinoma. In addition, the effects of the genes that show the strongest influence on survival of patients with the disease differ from those that have been reported for some other cancer types.

Literature

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