IL22RA1/JAK/STAT Signaling Acts As a Cancer Target Through Pan-Cancer Analysis

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Cytokines and cytokine receptors are important mediators in immunity and cancer development. Interleukin 22 (IL22) is one of the most important cytokines which has protumor effect. Given that common and specific roles of cytokines/receptors in multiple cancers, we conducted a pan-cancer study to investigate the role of IL22RA1 in cancer using The Cancer Genome Atlas (TCGA) database. Notably, we found IL22RA1 transcript was upregulated in 11 cancer types compared with their corresponding control. The mRNA expression level of IL22RA1 was highest in the pancreas among tumor tissues. The higher expression of IL22RA1 was associated with worse overall survival rate in patients. A total of 30 IL22RA1-correlated genes (e.g. IL17D, IL22RA2, IL20RB, IL10RA, IL10RB, TSLP and TYK2) are involved in the JAK/STAT pathway which promotes tumor progression. The upregulation of IL22RA1 in tumors was correlated with immune cell infiltration level. Higher expression of IL22RA2, IL20RB, IL10RA, IL10RB, TSLP, TYK2, STAT1 and STAT3 was associated with decreased overall survival rate in patients. IL22RA1 mutation was observed more in uterine cancer and melanoma compared with the other cancer types. Deactivation of IL22RA1 induced a lot of changes in gene expression. IL22RA1 mutants had upregulated DNA damage/repair genes in uterine cancer, whereas downregulated genes in the FoxO signaling pathway. In melanoma, mutation of IL22RA1 can upregulate the HIF signaling pathway but downregulate metabolic pathways. Our study suggests that IL22RA1/JAK/STAT signaling can be an important target for cancer treatment.

Keywords: IL22RA1, immune response, jak-stat, overall survival, pan-cancer analysis

INTRODUCTION

Cancer has been a leading cause of death in the world since 2020 (World Health Organization). Among types of cancer treatment, immunotherapy is becoming one of the most effective strategies against cancer, as it can strengthen the power of the immune system (1). Nevertheless, immune responses play a dual role in cancer progression (2). It causes side effects and resistance which also influence the outcome of treatment. The cytokine-cytokine receptor interaction pathway is associated with cancer and other diseases (Comparative Toxicogenomics Database). However, the interaction mechanism is not fully understood. Although different cancers are molecularly distinct, many share common driver mutation and molecular signatures. It is vital to conduct a pan-cancer analysis of specific genes of interest and assess its correlation with clinical prognosis and potential molecular mechanisms.
IL22RA1 is an important heterodimeric receptor for interleukin 22 (IL22) which is involved in chronic inflammation and tumor development. IL22RA1 is expressed on cell membrane of nonimmune cells including epithelial cells from different organs or hepatocytes (3). Through binding to IL22RA1, IL22 activates the STAT3 pathway, thus regulating genes involved in cell proliferation and survival. As a mediator of immune cell-epithelial cell crosstalk, the association of IL22RA1 and immune cell infiltration in cancer is not clear.

IL22 promotes tumorigenicity in pancreatic ductal adenocarcinoma through IL22RA1/STAT3 signaling (4). IL22 signaling interacts with mutant KRAS to promote poor prognosis in colorectal cancer (5). In muscle invasive bladder cancer, the poor outcome is also associated with high expression of IL22RA1 (6). The expression of IL22 was low in glioblastoma tissues (7). These studies indicate that IL22RA1 may be a target in cancer treatment.

Our study used the TCGA databases to conduct a pan-cancer analysis of IL22RA1 for the first time. Here the expression and mutation status of IL22RA1 as well as the associated genes and immune cells were covered.

METHODS

TIMER database analysis

RNA seq data from TCGA database were performed using TIMER 2.0 (http://timer.comp-genomics.org/) (8) including IL22RA1 expression, gene-gene correlation, as well as association between IL22RA1 expression and infiltration levels of immune cells across 31 tumor types.

Kaplan-Meier survival analysis

The overall survival rate of patients with high or low expression of target genes was performed using the TCGA/TARGET/GTEx RNA-Seq dataset based on UCSC Xena (https://xenabrowser.net).

Protein interactions and pathway analysis

A total of 30 genes and proteins have been found related with IL22RA1 by NCI/Nature (http://www.ndxbio.org/). Pathway analysis of these 31 genes was performed by The Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.8. The transcripts level for IL22RA1-related genes were analyzed using the TCGA/TARGET/GTEx RNA-Seq dataset through UCSC Xena.

Mutation analysis

The effect of mutation status of IL22RA1 on gene expression in cancer was explored using TCGA database by muTarget (https://www.mutarget.com) (9) and UCSC Xena.

Western blotting

Proteins were extracted from uterine cancer tissues and adjacent normal control tissues from dogs at Animal Hospital of Northeast Agricultural University. This study was approved by the Ethical Committee of Northeast Agricultural University. Primary antibodies used were 1:1000 anti-IL22RA1 (Sigma-Aldrich, USA) and 1:7500 anti-β-actin (Bioss antibodies, China). Then membranes were incubated with secondary horseradish peroxidase-HRP conjugated antibodies (ZSGB-BIO, China). The protein bands were visualized using Champ Gel 6000 image system (Sage Creation, Beijing, China). Image-Pro Plus 6.0 software (Media Cybernetics, Washington, USA) was used to analyze the density for each band. Results are presented as the ratio of the intensity of the IL22RA1 band to the intensity of the β-actin band.

Statistics

Data are expressed as means ± standard deviation (SD). Differences were considered statistically significant at p < 0.05. Differentially expressed genes were based on |log2 fold change| > 0.5 and adjusted p < 0.05. GraphPad Prism Version 8.0 (San Diego, CA, USA) was used for graph generation. All data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey’s post hoc test.

RESULTS

Expression of IL22RA1 based on pan-cancer analysis of TCGA data

Compared with normal tissues, the transcript level of IL22RA1 in tumor tissues was upregulated in a total of 11 cancers including bladder urothelial carcinoma (BLCA), cervical and endocervical cancer (CESC), cholangiocarcinoma (CHOL), esophageal carcinoma (ESCA), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), stomach adenocarcinoma (STAD), and uterine corpus endometrial carcinoma (UCEC) (Figure 1A).

In humans, IL22RA1 was highly expressed in the pancreas, rectum, and small intestine (Figure 1B). Notably, higher expression of IL22RA1 was associated with poor survival in patients (Figure 1C).

IL22RA1-related genes involve in the JAK/STAT signaling pathway and cancers

A total of 30 genes (STAT5B, STAT5A, IL13, CSF2, IL10RA, IL20RB, TYK2, IL9, IL23A, IL10RB, IL22RA1, IFN12, IL22, IFN11, IL24, IL19, IFN13, IL17D, IL20, IFNA13, IL22RA2, IL6, IL4, PTPN11, IL2, IL10, JAK1, STAT1, STAT3, IL5, and TSLP) were related with IL22RA1 based on https://www.ndxbio.org/iquery/. Protein interaction network also showed a relationship between these 31 proteins (Figure 2A). We further explored the correlation of IL22RA1 and the related 30 genes in each cancer (from TIMER2). IL22RA1 was positively correlated with STAT1, STAT3, JAK1, PTPN11, IFNA13, IL24, but negatively correlated with IL10 in specific cancers (Figure 2B) (Table S1).

To understand the function of the 31 genes, we performed KEGG pathway analysis using DAVID and found that all genes were involved in the JAK/STAT signaling pathway (Figure 2C).
IL22RA1-Related Genes Were Associated With Overall Survival Rate in Patients

Consistent with IL22RA1, among IL22RA1-related genes, low expression of IL10RA, IL10RB, TSLP, IL20RB, IL17D, TYK2, STAT1, STAT3, and IL22RA2 were associated with better survival in patients by pan-cancer analysis (Figure 3).

IL22RA1 Expression Was Associated With immune Cell Infiltration by TIMER2.0 Estimation

IL22 is derived from immune cells, and IL22 level can influence the expression of IL22RA1 (10). We then used TIMER2.0 to evaluate the correlation between IL22RA1 expression and infiltration level of immune cells estimated by all six algorithms across TCGA cancer types (11). As expected, the upregulated expression of IL22RA1 in 11 cancers was correlated with different immune cell infiltrates. Association with significant difference is shown in Table 1. The correlation between IL22RA1 expression and immune cell infiltration depends on cancer type. For example, IL22RA1 was positively correlated with CD8+ T cells (rho = 0.38) in BLCA which was opposite in STAD.

In CHOL, CD8+ effector memory T cells were also positively correlated with IL22RA1 (rho = 0.44). It was positively correlated with CD4+ Th2 cells in BLCA (rho = 0.24), as well as CD4+ T cells and regulatory T cells (Tregs) in CESC (rho = 0.25), CD4+ effector memory T cells in KIRC (rho = 0.30), CD4+ T cells in LUAD (rho = 0.26). In addition to T cells, IL22RA1 was positively correlated with myeloid dendritic cells (rho = 0.23) and macrophage M0 in BLCA (rho = 0.20) as well as...
macrophage/monocyte in KIRP (rho = 0.43) and KIRC (rho = 0.39) (Table 1).

Mutation Incidence of IL22RA1 in Cancer
As both genomic and transcriptomic changes are important signatures for cancer development, and gene mutation can alter the expression of certain genes. We further wanted to investigate whether mutation of IL22RA1 can change gene expression, and what are the functions of the affected genes. The non-silent mutation among diverse cancer types is mainly distributed in uterine cancer (>25%) and melanoma (>20%) (Figure 4A).

Based on mutant (n = 19) versus wild-type (n = 507) in uterine cancer, IL22RA1 mutation upregulated 156 genes, which involved in DNA repair (fanconi anemia pathway [SLX4, RAD51, EME1, FANCA, BRCA1], homologous recombination [RAD51, EME1, RBBP8, BRCA1]), and one carbon pool by folate [DHFR, MTHFD2L, TYMS], whereas downregulated 59 genes involving alcoholic liver disease (C3, PRKAG2, PPARGC1A) and the FoxO signaling pathway (CDKN2B, BCL6, PRKAG2) (Figure 4B). Gene encoding CCND1 was also upregulated in IL22RA1 mutant compared with wild-type. CCND1 is dysregulated in many cancers, indicating mutation of IL22RA1 contributes to cancer development (Figure 4B).

In melanoma, a total of 14 genes were upregulated, whereas 77 genes were downregulated when comparing IL22RA1 mutated and wild-type patient cohorts. Upregulated SERPINE1 and PFKP by IL22RA1 mutation were involved in the HIF-1
signaling pathway. However, genes in biosynthesis of unsaturated fatty acids (HSD17B12, FADS1), butanoate metabolism (ALDH5A1, OXCT1), and other metabolic pathways (PDHX, ALDH1A3, HSD3B2, PDE3B, MBOAT1, CTPS2, CMBL, B4GALT6), as well as ECM-receptor interaction (SV2B, ITGβ3, CHAD) were downregulated by IL22RA1 mutation (Figure 4C).

Validation of IL22RA1 Expression in Uterine Cancer From Animals and Humans

The protein level of IL22RA1 was increased in uterine cancer compared with normal control tissues from dogs (p < 0.01; Figure 5A). The transcript level of IL22RA1 in UCEC was confirmed using human datasets from GEO database. Compared with the control, IL22RA1 transcript was higher in
UUCEC tissues (GSE115810; p < 0.05) (Figure 5B). Consistently, the transcript level of IL22RA1 in UUCEC case was 3-fold change higher than the control in humans (GSE182132) (Figure 5C).

**DISCUSSION**

Cytokine and cytokine receptor interaction is the pathway related with inflammation and cancer therapy (12). IL22 is multifunctional and involved in various diseases including cancer. We previously investigated the role of IL22 signaling in response to infection, and found that IL22 can be upregulated by probiotics and provide a protective effect against pathogens at barrier surfaces (13–15). IL22 is produced by immune cells (CD4+ helper T, CD8+ cytotoxic T, NKT, γδ T, and innate lymphoid cells) in numerous tissues. However, the expression of IL22 in systemic organs is usually low. IL22 acts by binding its receptor, a heterodimeric receptor complex including IL22RA1 and IL10RB. It has been confirmed that the IL22/IL22RA1 pathway modulates the expression of many genes involved in survival, differentiation, and remodeling (13, 16). In this study, we demonstrated the role of receptor of IL22 (IL22RA1) in cancers by studying the crosstalk between IL22RA1 and immune system.

IL22RA1 expression is abundant in the pancreas, gastrointestinal tissues and liver at transcriptional level. At single cell level, IL22RA1 is mainly expressed on non-immune cells, especially epithelial cells. Pan-cancer analysis shows that IL22RA1 is highly expressed in 11 types of tumors including uterine cancer. Consistently, we identified that the expression of IL22RA1 in uterine cancer was increased significantly at both transcript and protein level. Remarkably, upregulation of...
IL22RA1 is associated with decreased overall survival in patients. Consistent with other studies (4, 17), it has been found that IL22 and its receptor IL22RA1 promote tumorigenicity and contribute to pathogenesis. We further performed correlation analysis between IL22RA1 and tumor infiltrating immune cells in different types of cancer, as IL22 is produced mainly by immune cells. It has been found that IL22-producing CD4+ T cells promote colorectal cancer stemness which enhance tumorigenesis (18). IL22RA1 was negatively associated with monocytes but positively correlated with macrophages M1 in lung adenocarcinoma (19). IL22 can increase the mRNA expression of IL22RA1 by promoting binding of STAT3 directly to the promoter region of IL22RA1 (4, 10). Our study shows that correlation between IL22RA1 expression and different immune cells infiltration depends on the type of cancer. In consistency, the principal cellular source of IL22 is various between tissues (10). It suggests that regulation of IL22RA1 and IL22 in different tumors is involved in targeting different immune cell populations. However, the relationship between IL22RA1 and various types of IL22-producing cells in specific tumor tissues still needs to be confirmed in the future.

IL22RA1 together with the other 30 genes interact with each other and are involved in the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. The JAK/STAT signaling pathway directly regulates the crosstalk between transmembrane receptors to the nucleus (20). Through binding...
to IL22RA1 and IL10R2, IL22 can activate JAK1/TYK2 kinases and downstream phosphorylation of STAT proteins, in particular STAT3 (21). JAK activation usually stimulates cell proliferation, differentiation, cell migration and apoptosis. However, activation of the JAK/STAT signaling pathway contributes to cancer progression (22, 23). IL22 promoted malignant transformation of mesenchymal stem cells in rats through IL22RA1/STAT3 signaling (7). In addition, STAT1 and STAT3 are involved in PD-L1 expression and PD-1 checkpoint pathway in cancer by pathway analysis. We have found that high level of STAT3 and STAT1 transcripts was associated with poor survival in patients through pan-cancer analysis.

Consistent with IL22RA1, higher expression of IL10RB, IL10RA and IL20RB in tumor tissues was associated with worse survival in patients. IL22R1 is expressed only by nonhematopoietic cells, whereas IL10RB (IL10R2) is ubiquitously expressed by all tissues and cells (24). Overexpression of IL10R2 contributes to colorectal carcinogenesis by IL22/STAT3 signaling (24). IL20RB has been proposed as a prognostic and therapeutic biomarker in clear cell renal cell carcinoma (25).

Overexpressed thymic stromal lymphopoietin (TSLP) and tyrosine kinase 2 (TYK2) was also associated with worse survival through pan-cancer analysis. TSLP is an epithelial–cell–derived cytokine that contributing to inflammation driven by Th2 cells (26). TSLP also has an important role in cancer, and the pro- or anti-tumor effect is dependent on the type of tumor (27, 28). TYK2 belongs to subfamily of JAKs involved in cytokine signaling including the IL22/IL22RA1 signaling. TYK2 acts as an oncogene, and its overexpression has been detected in many types of cancer (29–31). Taken together, our analysis indicates that IL22RA1 contributes to tumor progression through activating the JAK/STAT signaling pathway.

Gene alterations lead to cancer initiation and driving progression (32). Silent mutations can affect gene expression which may relate to tumorigenesis and cancer cell fitness (33). It is worth to note that the non-silent mutation rate of IL22RA1 is high in UCEC and SKCM compared with the other types of cancer. IL22RA1 mutation in uterine cancer upregulated genes in the fanconi anemia pathway and homologous recombination which were involved in DNA damage and repair. Upregulation of the fanconi anemia pathway components such as RAD51 and BRCA1/2, leads to homologous recombination restoration and drug resistance (34, 35).

In melanoma, IL22RA1 mutation upregulated the expression of genes involved in the hypoxia-inducible factor-1alpha (HIF-1α) signaling pathway, whereas the metabolic pathways including biosynthesis of unsaturated fatty acids and butanoate metabolism were downregulated. Hypoxia, as a major feature of solid tumors, activates HIF-1α that enhances tumor growth and leads to melanoma progression by regulating the expression of genes involved in angiogenesis, metabolism, cell proliferation, and metastasis (36).

In conclusion, IL22RA1 together with genes involved in the JAK/STAT pathway contribute to cancer development. Immune cell infiltration level in tumor tissues is associated with IL22RA1 expression. IL22RA1 mutation in uterine cancer and melanoma induced overexpression of genes that are favorable in tumor progression. These findings indicate that IL22RA1 may act as a contributor to tumorigenesis with a direct and indirect role in the
process. However, more detailed mechanism in specific cancer still needs to be investigated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Subplementary Material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by Ethical Committee of Northeast Agricultural University. Written informed consent was obtained from the owners for the participation of their animals in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, GY; Data analysis and writing, SZ and GY; The manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.915246/full#supplementary-material

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SUPPLEMENTARY MATERIAL

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