Integrative genomic analyses on IL28RA, the common receptor of interferon-λ1, -λ2 and -λ3

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Abstract. Interferon (IFN)-λs, including INF-λ1, -λ2, and -λ3, are a newly described group of cytokines distantly related to the type I IFNs and IL-10 family members. IFN-λ1, -λ2, and -λ3 bind to the same receptor (known as IL28RA) to exert their antiviral, antitumor and immunomodulatory effects. Here, we identified IL28RA genes from the genome of human, chimpanzee, macaque, orangutan, mouse, horse, rat, dog, chicken, and found that only one IL28RA existed in each genome. All the identified IL28RAs are single-pass type I membrane proteins except chicken IL28RA. They belong to the type II cytokine receptor family and contain one fibronectin type-III domain. We found human IL28RA was expressed in lymphs, testes, lymphoma, teratocarcinoma, pediatric pre-B cell acute lymphoblastic leukemia, germinal center B cells, embryonic stem cells, fetal lung, and also expressed in bladder, blood and breast cancers, glioma, head and neck cancer and lung cancer tissues. Three tumor-related transcriptional factor binding sites (AP-2, c-Jun and P53) were identified within the 1.0-kb regions upstream of the transcriptional start site of human IL28RA. Meta-analysis of the prognostic value of IL28RA genes in various cancers found that the expression of IL28RA was indeed related to the cancer prognosis in certain cancers. The STAT1 binding sites in the promoter region of IL28RA implied a specific mechanism for the amplifying effects of IFN-λs. The LyF-1 binding sites in the promoter region of IL28RA imply that IFN-λs were involved in the differentiation of early B and T cells.

Introduction

Interferon (IFN)-λs, including IFN-λ1, -λ2, and -λ3, also known as IL-29, IL-28A, or IL-28B, are a newly described group of cytokines distantly related to the type I IFNs and IL-10 family members (1). IFN-λ1, -λ2, and -λ3 bind to the same receptor (known as IL28RA) and induces a conformational change that enables another receptor (known as IL10R2) to interact with the newly formed ligand-receptor complexes. This in turn activates a signal-transduction cascade (2). Sheppard *et al* (2) mapped the IL28RA genes to chromosome 1p36.11, located ~10 kb centromeric to the IL22RA gene, and both genes were transcribed in the telomeric direction. They were also identified as putative splice variants encoding IL28RA by genomic sequence analysis. Two of the predicted IL28RA proteins contain 520 and 491 amino acids, including an extracellular region with cytokine-binding and fibronectin III domains, followed by transmembrane and variable intracellular regions. The third protein contains 211 amino acids, lacks intracellular and transmembrane regions, and appears to be a soluble protein. The three IL28RA proteins are mostly identical to IL22RA2 (2).

It is well known that IFN-λs have antiviral activity against a broad spectrum of viruses including human immunodeficiency virus type 1 (HIV-1) (3), influenza A (4,5), Apeu (6), hepatitis C (HCV) (7-8), hepatitis B (HBV) (9), respiratory syncytial (RSV) (10), encephalomyocarditis (EMCV) (11) and West Nile (12) viruses. Another important property of IFN-λs is their potential anti-proliferative activities inhibiting the growth of the human glioblastoma LN319 cell line (13), human neuroendocrine BON1 tumor cells (14), human keratinocyte cell line HaCaT (15), human fibrosarcoma 2fTGH cell line (16) and murine BW5147 thymoma cell line (16). These effects of IFN-λs were fulfilled by the IFN-λ receptor complex that leads to the activation of signal transducers and activators of transcription (STAT)1 and STAT2, which, together with IFN regulatory factor-9, form a transcriptional complex called IFN-stimulated gene factor-3.1,7,9 (16-18). This factor then induces the so-called IFN-stimulated genes (ISGs) (17). Moreover, as a main feature of signal transduction induced by IL-10 related cytokines, STAT3 and STAT5 were also activated by engagement to the IFN-λ receptor.

In a previous study, we identified IFN-λ genes from the genome sequences of human, chimpanzee, macaque, orangutan, mouse, rat and dog, and found that the locations and copy of specific IFN-λs varied in different genomes and not just the copies of IFN-λs (19). Moreover, we found that IFN-λs were expressed in bladder, blood and breast cancers, giloma, head and neck cancer and lung cancer tissues, and the expression of IFN-λs are related to the cancer prognosis in some cancers

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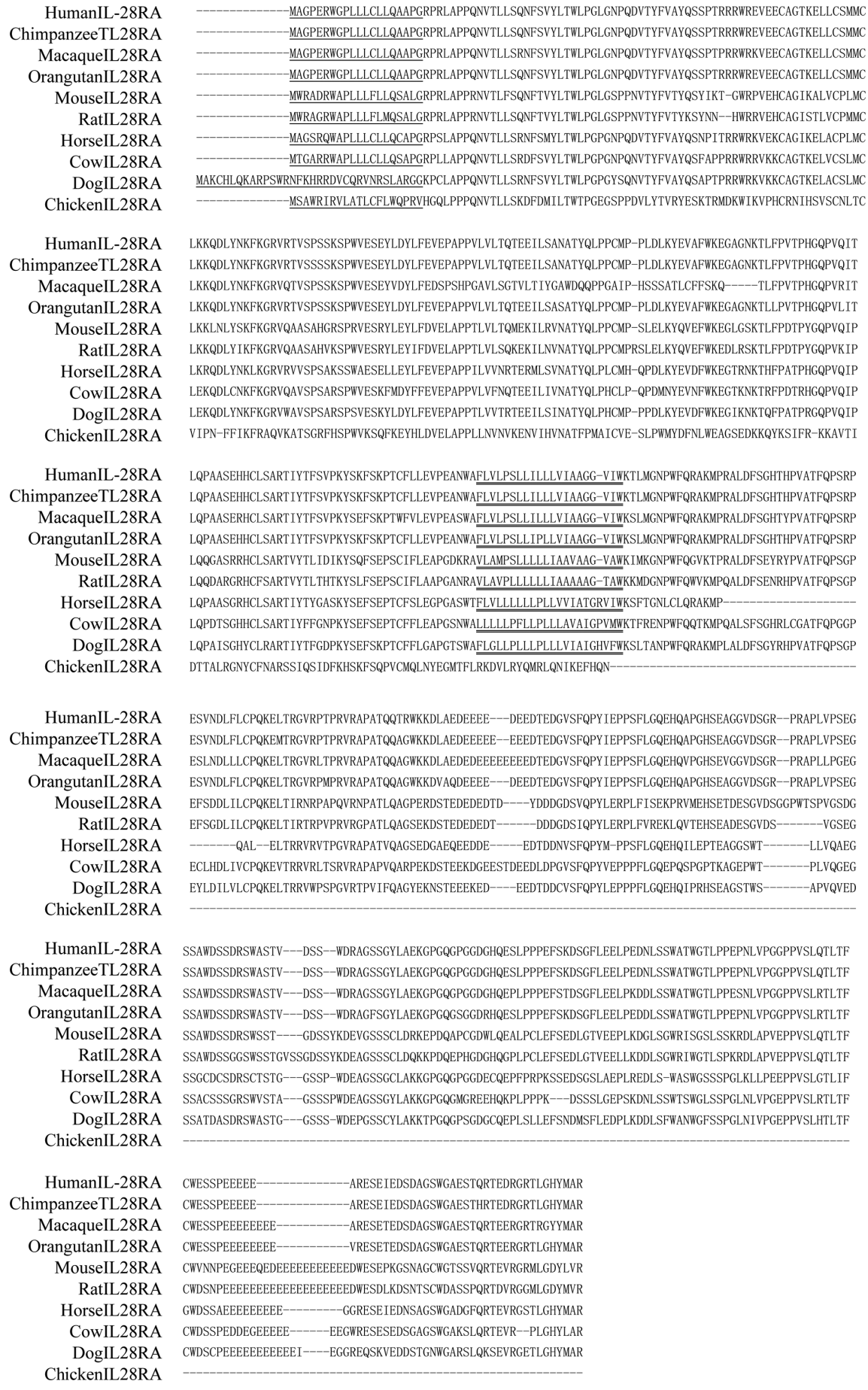

Figure 1. Alignments of amino acid sequences of identified IL28RAs. IL28RA genes were identified in the genome sequences of the human, chimpanzee, macaque, orangutan, mouse, horse, rat, dog and chicken. Except chicken IL28RA, all signal peptide (underline), transmembrane region (double underline) and fibronectin type-III domain (bold) are shown in the amino acid sequences of identified IL28RAs.

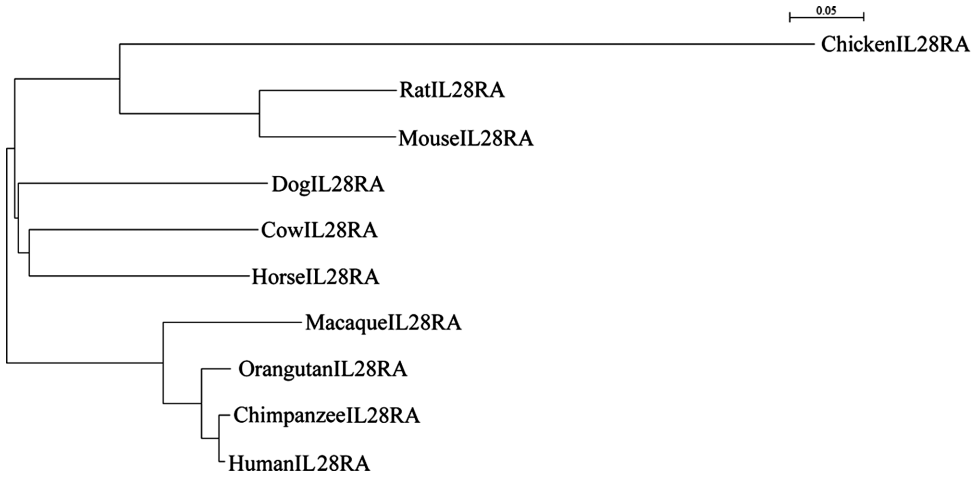

Figure 2. Phylogenetic analysis of IL28RAs. The phylogenetic tree of IL28RAs gene was obtained by using ML and NJ methods. Primate IL28RAs clustered into one group, different from other IL28RAs.

(19). However, there are few studies on the integrative genomic analyses of their receptor (IL28RA). In the present study, we identified IL28RA genes from the genome sequences of human, chimpanzee, macaque, orangutan, mouse, rat and dog by comparative genomic analyses. Then conserved transcription factor-binding sites within promoter regions of human IL28RA genes were searched for. Furthermore, meta-analysis of the prognostic value of IL28RA genes in various cancers was also performed.

Materials and methods

Identification of novel IL28RA in mammals and chicken and comparative genomic analyses. IL28RA genes were searched in the genome sequences of human (*Homo sapiens*), chimpanzee (*Pan troglodytes*), macaque (*Macaca mulatta*), orangutan (*Pongo pygmaeus*), mouse (*Mus musculus*), horse (*Equus caballus*), rat (*Rattus norvegicus*), dog (*Canis familiaris*) and chicken (*Gallus gallus*) by the method described before using human IL28RA (NM_170743) as queries. The assemblies used were human NCBI 36, chimpanzee CHIMP2.1, macaque MMUL 1.0, orangutan PPYG2, mouse NCBI m37, horse Equ Cab 2, rat RGSC 3.4, dog Canfam 2.0 and chicken WASHUC2. The identified putative IL28RA genes were BLASTed against the GenBank database to confirm that the best hits were IL28RA genes. Conserved transcription factor-binding sites within promoter regions of human IL28RA genes were then searched for based on the Patch program (http://www.gene-regulation.com) as well as manual inspection as previously described (20-31).

Comparative proteomic analyses of IL28RAs. Amino acid sequences of IL28RA were deduced from the identified IL28RA genes and aligned using Clustal X 1.8 software (32). The signal peptide sequences of identified IL28RAs were predicted by SignalP software (33). The transmembrane regions of identified IL28RAs were predicted by TMpred software (34). The phylogenetic tree of IL28RAs was obtained by using maximum likelihood (ML) (PHYML v2.4.4) (35) and neighbor-joining (NJ) (MEGA 3.0) (36) methods, and the reliability of the trees was evaluated by the bootstrap method with 1,000 replications.

In silico expression analyses. Expressed sequence tags (ESTs) derived from human IL28RA were searched for using the BLAST programs as previously described (21-31). Human IL28RA (NM_170743) was used as query sequences for the BLAST programs.

Meta-analysis of the prognostic value of IL28RA gene in cancer. A database named 'PrognoScan' has been developed (37). This is i) a large collection of publicly available cancer microarray datasets with clinical annotation, as well as ii) a tool for assessing the biological relationship between gene expression and prognosis. PrognoScan employs the minimum P-value approach for grouping patients for survival analysis. PrognoScan provides a powerful platform for evaluating potential tumor markers and therapeutic targets and is publicly accessible at http://gibk21.bse.kyutech.ac.jp/PrognoScan/index.html. Human IL28RA genes were inputted as queries and data were collected for analysis.

Results

Comparative proteomics of IL28RAs identified in mammal and chicken genomes. IL28RA genes were searched in the genome sequences of human, chimpanzee, macaque, orangutan, mouse, horse, rat, dog and chicken. Their amino acid sequences are shown in alignment format in Fig. 1. Except chicken IL28RA, all identified IL28RAs contain signal peptide, extracellular, transmembrane and cytoplasmic regions (Fig. 1). All the identified IL28RA contained a fibronectin type-III domain (Fig. 1). Refined phylogenetic tree using the identified IL28RA amino acid sequences by ML and NJ methods was almost the same (Fig. 2). It seemed that primate IL28RAs clustered into one group, different from other IL28RAs.

Expression profile of human IL28RA. Human IL28RA was expressed in lymphs, testes, lymphoma, teratocarcinoma, pediatric pre-B cell acute lymphoblastic leukemia, germinal center B cells, embryonic stem cells, and fetal lung. When searched in PrognoScan database, human IL28RA was also found to be expressed in bladder, blood, breast cancers, giloma, head and neck cancer and lung cancer tissues.

Figure 3. The identification of transcription factor-binding sites within the 5'-region of human IL28RA genes. The transcription factor-binding sites are underlined. The transcriptional start sites (ATG) of human IL28RA is in bold.

Comparative genomics on human IL28RA. Transcription factor-binding sites within the 5'-region of human IL28RA were identified (Fig. 3). Two activator protein 2 (AP-2), one c-Jun, lymphoid transcription factor 1 (LyF-1), signal transducer and activator of transcription 1 (STAT1) and P53 binding sites were identified within the 1.0-kb regions upstream of the transcriptional start site of human IL28RA.

Meta-analysis of the prognostic value of IL28RA genes in cancer. When given the gene, PrognoScan displays a summary in table format of tests for the gene with columns for dataset, cancer type, subtype, endpoint, cohort, contributor, array type, probe ID, number of patients, optimal cutpoint, Pmin and Pcor. Among the databases which detected the expression of IL28RA 2 out of 31 tests showed an association between microarray expression in IL28RA and cancer prognosis (bladder 0/1, blood 0/6, breast 1/12, giloma 0/3, head and neck 0/2, lung 1/7) with a 5% significance level. By clicking the probe ID of the positive breast cancer cases in the list, we found the Rotterdam cohort for distant metastasis-free survival (DMFS) that patients can be dichotomized at the 14 percentile to give the minimum P-value and the group with low IL28RA expression has poorer survival (Pcor=0.0017). In the lung cancer case, Rotterdam cohort for overall survival (OS) that patients can be dichotomized at the 12 percentile to give the minimum P-value and the group with low IL28RA expression has poorer survival (Pcor=0.014).

Discussion

IFN-λs are a newly described group of cytokines distantly related to type I IFNs and IL-10 family members. It was found that there are between one and potentially nine copies of IFN-λ genes co-existing in other mammalian genomes (38) and the locations and copy of specific IFN-λs also varied in different genomes (20). However, only one IL28RA was identified in each genome suggesting that all IFN-λs shared the same receptor though their variation in different genomes. Like IFN-λs, IL28RAs were not detected in fish, frog, or invertebrates. All the identified IL28RAs are single-pass type I membrane protein except chicken IL28RA, which lacks the transmembrane and cytoplasmic regions. They belong to type II cytokine receptor family and contain one fibronectin type-III domain (39). The phylogenetic tree of IL28RAs showed that primate IL28RAs clustered together and chicken IL28RA is separated from mammalian IL28RAs. From the alignment and the phylogenetic tree, mammalian IL28RAs are conversed among mammalian genomes, suggesting that the function of IL28RA is essential for all the mammalians in the long evolution process.

IL28RA expression was detected in most human tissues, with the highest amounts seen in the pancreas, thyroid, skeletal muscle, heart, prostate and testes (2). It was also variably expressed in hematopoietic (HL-60, K-562, MOLT-4 and Raji) and nonhematopoietic (HeLa S3, SW480, A549 and G-361) cell lines (17). In the present study, we found human IL28RA was also expressed in lymphs, testes, lymphoma, teratocarcinoma, pediatric pre-B cell acute lymphoblastic leukemia, germinal center B cells, embryonic stem cells, fetal lung by ESTs search. Moreover, IL28RA was also found to be expressed in bladder, blood and breast cancers, glioma, head and neck cancer and lung cancer tissues. Recently, Witte *et al* identified the IL28RA expression in the human immune system and the skin. They found that keratinocytes and melanocytes expressed significant levels of IL28RA and clearly responded to IFN-λ stimulation (40). However, human blood immune cells, except B cells, did not respond to type III IFNs though IL28RA expression was detected in these cells. They found there existed a short form of IL28RA which lacks the transmembrane and intracellular domain encoding parts and corresponds to the extracellular domain of IL28RA and represent a secreted, single-chain receptor that should have

IFN-l-binding sites identical to IL28RA. This short form of IL28RA may contribute to the immune cellular insensitivity toward IFN-λs (40). The varied expression of short and full forms of IL28RA in different tissues or cells may control the effect of IFN-λs on different targets.

IFN-stimulated response element, NF-κB, SF-1, WT1 and P53 binding sites were identified in the promoter regions of IFN-λs (19). However, few studies were conducted to identify the transcription factor-binding sites of human IL28RA. We identified two AP-2, one c-Jun, LyF-1, STAT1 and P53 binding sites within the upstream of the transcriptional start site of human IL28RA, but NF-κB, SF-1 and WT1 binding sites were not identified in the transcriptional start site of human IL28RA. This suggests that IFN-λs and their receptor were regulated by different mechanism. The AP-2 transcription factor has been shown to be a critical regulator of gene expression during embryogenesis (41). It regulates the development of facial prominence and limb buds, and are essential for cranial closure and development of the lens. It has also been implicated in tumorigenesis. AP-2 protein expression levels have been found to affect cell transformation, tumor growth and metastasis, and may predict survival in some types of cancer (42). c-Jun was originally identified as the normal cellular counterpart of the viral Jun oncoprotein (v-Jun) encoded by an avian sarcoma virus (ASV17) (43). It is a major component of the transcription factor complex AP-1, which regulates the expression of multiple genes essential for cell proliferation, differentiation and apoptosis (44). AP-1 has a central role in multiple processes involved in tumorigenesis including proliferation, migration, invasion and metastasis (45). The p53 gene is mutated in about half of all human tumors. p53 is a transcription factor whose activity gives rise to a variety of cellular outcomes, most notably cell cycle arrest and apoptosis, eliminating cancer-prone cells from the replicative pool (46). IFN-λs were found to inhibit tumor growth *in vitro* and *in vivo* (13-16). Moreover, the expressions of IFN-λs are indeed related to the cancer prognosis in some cancer (19). IL28RA was also found to be expressed in many cancer tissues and the expression of human IL28RA was indeed related to the cancer prognosis in some cases by meta-analysis. Combined the identifications of transcription factor-binding sites related to tumors in the promoter regions of IL28RA, it can be predicted that IL28RA, as IFN-λs, take part in the cancer development. STAT1 signaling regulates the expression of important genes controlling cell growth, differentiation, apoptosis, and immune functions (47). Activation of IL28RA leads to the activation of STAT1 and STAT2, to form the transcriptional complex IFN-stimulated gene factor-3.1,7,9 (16-18). The identified STAT1 binding sties in the promoter regions of IL28RA, suggests that activation of IL28RA regulates its expression, representing a specific mechanism for the amplifying effects of IFN-λs. LyF-1, are considered master regulators of differentiation in early B and T cells (48). In addition to antiviral and antiproliferative activities, IFN-λs also exert immunomodulatory effects such as increasing NK and T cell cytotoxicity, promoting Th1 responses, up-regulating MHC class I molecule expression (1). The identified LyF-1 binding sites in the promoter regions of IL28RA implied IFN-λs were involved in the differentiation of early B and T cells.

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