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Technical report

Molecular characterization of duck interleukin-17

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ABSTRACT

Interleukin-17 (IL17), belonging to the Th17 family, is a proinflammatory cytokine produced by activated T cells. A 1034 bp cDNA encoding duck *IL17* (*duIL17*) was cloned from Con A-activated splenic lymphocytes of ducks. The encoded protein, which is predicted to consist of 169 amino acids, has a molecular weight of 18.8 kDa and includes a 29 residue NH_2-terminal signal peptide, a single potential N-linked glycosylation site, and six cysteine residues that are conserved in mammalian IL17. The duIL17 shared 84% amino acid sequence identity with the previously described chicken IL17 (chIL17), 36–47% to mammalian homologues, and open reading frame 13 of *Herpesvirus saimiri* (HVS13). The genomic structure of *duIL17* was quite similar to its chicken and mammalian counterparts. The *duIL17* mRNA expression was detected only in Con A-activated splenic lymphocytes by RT-PCR, although its expression was undetectable in a variety of normal tissues. Two mAbs against chIL17 showed cross-reactivity with duIL17 as detected by indirect ELISA and Western blot analysis. These findings indicate that the structure of IL17 is highly conserved among poultry, and two mAbs detecting common epitopes of IL17 are available for molecular and immunological studies of IL17 in birds.

Interleukin-17 (IL17 or IL17A) originally called cytotoxic T lymphocyte-associated antigen-8 (CTLA-8) was initially cloned from a rat T-cell hybridoma (Rouvier et al., 1993; Yao et al., 1995a; Kennedy et al., 1996) and exhibited similarity to the open reading frame (ORF) 13 of *Herpesvirus saimiri* (HVS) (Rouvier et al., 1993; Yao et al., 1995b). IL17 and its related proteins have been cloned, grouped and designated as the IL17 cytokine family (IL17A-F) (Moseley et al., 2003; Weaver et al., 2007). Furthermore, an IL17-producing T-cell subpopulation has been categorized into the Th17 lineage, which is distinct from the Th1 and Th2 lineages (Stockinger and Veldhoen, 2007; Weaver et al., 2007).

IL17 is a proinflammatory cytokine produced mainly by activated $CD4^+$ T cells. In contrast, the IL17 receptor (IL17R) is expressed widely in a variety of tissues and cell types (Yao et al., 1995b, 1997). IL17 plays a role in protective immunity against a variety of infectious agents (Min and Lillehoj, 2002; Kelly et al., 2005; Maek-A-Nantawat et al., 2007; Wu et al., 2007; Matsuzaki and Umemura, 2007), and has been implicated in the pathogenesis of autoimmune and inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, gastritis, bronchial asthma, and allograft rejection (Andoh et al., 2007; Weaver et al., 2007). Furthermore, *IL17*, which is the prototype member of the *IL17* cytokine family, has been

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cloned from human, mouse, chicken, pig, and cow (Yao et al., 1995a; Kennedy et al., 1996; Min and Lillehoj, 2002; Katoh et al., 2004; Riollet et al., 2006).

In chickens, *chIL17* gene initially was characterized from an expressed sequence tag (EST) cDNA library prepared from intestinal intraepithelial lymphocytes (IELs) of chickens infected with *Eimeria* (Min and Lillehoj, 2002). The role of chIL17 in host protective immunity against *Eimeria* infection has been investigated and intestinal IELs in *Eimeria*-infected chickens showed highly up-regulated levels of the *chIL17* transcript (Hong et al., 2006a, 2006b). In addition, *in ovo* vaccination with 3-1E protein, an immunogenic 20 kDa native protein expressed by *E. acervulina* sporozoites and *E. tenella* sporozoites and merozoites (Lillehoj et al., 2000), was enhanced by coadministration of the *chIL17* gene as an adjuvant. Chicks hatched from these eggs manifested reduced fecal-oocyst shedding and increased serum IgG antibody titers compared with *in ovo* vaccination of only 3-1E protein followed by *Eimeria* infection (Ding et al., 2004). To investigate the biological and immunological properties of avian IL17, mouse monoclonal antibodies (mAbs) to recombinant chIL17 protein were recently produced and characterized (Yoo et al., 2008). To extend our knowledge of avian cytokines belonging to the IL17 family, the present study details the cloning of *duIL17* cDNA and genomic DNA, expression of *duIL17* transcripts and cross-reactivity of chIL17 mAbs with recombinant duIL17 protein.

Splenic lymphocytes from 3-week-old female Cherry Valley Pekin ducklings were isolated with Histopaque-1077 (Sigma–Aldrich, USA), resuspended at 1×10^7/ml in Iscove's modified Dulbecco's medium (IMDM) supplemented with 10% FCS and stimulated with 2 μg/ml concanavalin A (Con A) (Sigma–Aldrich) by incubation during 48 h at 41 °C in 5% CO_2. Total RNA was extracted from Con A-activated lymphocytes using RiboEx reagent (Geneall, Korea). Single-stranded cDNA was synthesized from 5 μg total RNA with an oligo (dT) primer and ImProm-II reverse transcriptase (Promega, USA). Primers (P1, 5′-ATCAGCTG-CAGCAAGAAAAGG and P2, 5′-GTCACTTTGGTATCCTG-GTTC) were designed from the *chIL17* sequence (Min and Lillehoj, 2002) and used for amplifying a 5′-flanking region of *duIL17*.

Based on the sequence information of the 5′-flanking region of *duIL17*, the full-length cDNA was generated using high-fidelity DNA polymerase (Bioneer, Korea) with *duIL17* gene-specific primer (P3, 5′-AAGATGTCTCCAACCCTTCGT) for the 5′-flanking region and an oligo (dT)-anchor primer of the 5′/3′ RACE Kit (Roche Applied Science, Germany). The PCR product was cloned into the TA vector (RBC, Taiwan) and sequenced (Macrogen, Korea). PCR was performed on a DNAEngine thermocycler (Bio-Rad, USA) as follows: one cycle of 5 min at 95 °C, followed by 30 cycles of 1 min denaturation at 95 °C, 1 min annealing at 55 °C, 1 min extension at 72 °C, and a final 5 min extension at 72 °C.

For expression and purification of recombinant duIL17, the *duIL17* cDNA without the signal peptide was obtained by PCR from the *duIL17* gene using the following primers: forward primer, 5′-GATCGGATCCAAGGTGATACGGCCCGG-GCTC that contains a BamHI site (underlined), and the reverse primer, 5′-CATTAAGCTTCAAGGAAGTCCTCCTG-CTGTG that contains a HindIII site (underlined). The PCR product was digested with BamHI and HindIII restriction enzymes and inserted into the corresponding sites of the pMAL-c2X expression vector (New England Biolabs, USA) to produce a maltose binding protein (MBP) fused to the duIL17 protein. The recombinant plasmid was transformed into competent *E. coli* DH5α and transformants were selected on ampicillin plates. A single *E. coli* colony was grown at 37 °C to OD_{600} = 0.5, and induced with 1.0 mM isopropyl-β-D-thiogalactopyranoside for 3 h at 37 °C. Bacteria were disrupted by sonication on ice (Misonix, USA). The recombinant protein (MBP-duIL17) was purified on an amylose affinity column (New England Biolabs) according to the manufacturer's instructions.

Cross-reactivity was identified by ELISA as described (Yoo et al., 2008). Briefly, flat-bottom 96-well microtiter plates (Costar, USA) were coated with 100 μl of bacterially expressed, affinity purified MBP-chIL17 (5 μg/ml) or MBP-duIL17 (5 μg/ml) in 0.1 M carbonate buffer, pH 9.6 at 4 °C overnight and washed three times with PBS containing 0.05% Tween 20 (PBS-T). Non-specific binding was blocked with 200 μl of PBS containing 1% bovine serum albumin (PBS–BSA) for 1 h at room temperature; the plates were washed twice with PBS-T, and incubated with 100 μl of hybridoma supernatant for 1 h at room temperature. The bound antibody was detected at OD_{450} after reacting with horseradish peroxidase-conjugated goat anti-mouse IgG antibody (Sigma–Aldrich) and tetramethylbenzidine (USB, USA)

For Western blotting, the expressed proteins were mixed with equal volumes of sample buffer (0.125 M Tris–HCl, pH 6.8, 4% SDS, 20% glycerol, 10% 2-mercaptoethanol and 0.004% bromophenol blue), heated for 4 min at 94 °C, resolved on 10–12% SDS-polyacrylamide gels and electroblotted to Hybond-P membranes (Amersham Biosciences, USA). The membranes were blocked with PBS containing 1% nonfat dry milk for 16 h at 4 °C, incubated with monoclonal antibodies against chIL17 (Yoo et al., 2008) followed by three washes with PBS-T. Bound antibody was allowed to react with peroxidase-conjugated rabbit anti-mouse IgG antibody (Sigma–Aldrich) in PBS-BSA for 40 min at room temperature. The membrane then was washed five times with PBS-T followed by five times with distilled water and developed using 3, 3′-diaminobenzidine substrate according to the manufacturer's instructions (Sigma–Aldrich).

To obtain the full-length *duIL17* cDNA, a 212 bp cDNA fragment that showed high sequence similarity to *chIL17* was obtained by reverse transcriptase (RT)-PCR using chicken-specific primers P1 and P2. Based on this sequence information, the full-length cDNA of *duIL17* was obtained (GenBank accession number: EU366165). The cDNA contained a 3 bp 5′-UTR, a 510 bp open reading frame (ORF) and a 521 bp 3′-UTR. The 3′-UTR contained three AU-rich (ATTTA) sequences, which previously were shown to be involved in regulating mRNA stability (Shaw and Kamen, 1986).

Analysis of the predicted amino acid sequence (www.expasy.org) of duIL17 revealed the ORF to encode a putative protein of 169 amino acids with an NH_2-

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human    MTPG----KTS--LVSLLLLLSLEAIVKAGITIP----------RNPGCPNSEDKNFPRT  44
HVS13    MTFR----MTS--LV-LLLLLSIDCIVKSEITSA----------QTPRCLAANN-SFPRS  42
swine    MTPV----RSS--SLSLLLLLSLVALVKAGIMIP----------QSPGCPKTEDKNFPQH  44
bovine   MASM----RTS--SMSLLLLLSLVALVKAGVIIP----------QSPGCPPTEDKNFPQH  44
rat      ----------MCLMLLLLLNLEATVKAAVLIP----------QSSVCPNAEANNFLQN  38
mouse    MSPG----RASSVSLMLLLLLSLAATVKAAAIIP----------QSSACPNTEAKDFLQN  46
chicken  MSPIPYSPLFRPLLLVLLAMLSASISAHGKVIRPGLEPESLFKKADAGCLTQKDGKFPQT  60
duck     MSPTLRASLSSSLLLVLLAMLSASSSAYGKVIRPGLKPESLFKQADAGCLTQKDAKFPQT  60
                    **  *                          *       *

human    VMVNLNIHN---RNTNTNPKRSSDYYNRSTSPWNLHRNEDPERYPSVIWEAKCRHLGCIN 101
HVS13    VMVTLSIRN---WNTSS--KRASDYYNRSTSPWTLHRNEDQDRYPSVIWEAKCRYLGCVN  97
swine    VRVNLNILN---RSTPA--RRPSDYSKRFTSPWTLQRNEDPERYSSVIWEAKCSHSGCIN  99
bovine   VRVNLNIVN---RSTNS--RRPTDYHKRSTSPWTLHRNEDPERYPSVIWEAKCSHSGCIN  99
rat      VKVNLKVINSLSSKASS--RRPSDYLNRSTSPWTLSRNEDPDRYPSVIWEAQCRHQRCVN  96
mouse    VKVNLKVFNSLGAKVSS--RRPSDYLNRSTSPWTLHRNEDPDRYPSVIWEAQCRHQRCVN 104
chicken  VRVNISISN---MNQDT--KVTLDISKRSLAPWDYRIDEDHNRFPRLVADAQCRHSRCVN 115
duck     VRVNISISN---MNQDN--KVTLDISKRSLSPWDYRIDEDHNRFPQVIADAECRYSRCVN 115
         * *     *             *   *   **     **  *       * *    * *

human    ADGNVDYHMNSVPIQQEILVLRREPPHCPNSFRLEKILVSVGCTCVTPIVHHVA 155
HVS13    ADGNVDYHMNSVPIQQEILVVRKGHQPCPNSFRLEKMLVTVGCTCVTPIVHNVD 151
swine    AEGKEDHHMNSVPIQQEILVLRREPRHCPNSFRLEKVMVTVGCTCVTPIVRHIS 153
bovine   AEGKVDHHMNSVTIQQEILVLRRESQHCPHSFRLEKMLVAVGCTCVTPIVRHLA 153
rat      AEGKLDHHMNSVLIQQEILVLKREPEKCPFTFRVEKMLVGVGCTCVSSIVRHAS 150
mouse    AEGKLDHHMNSVLIQQEILVLKREPESCPFTFRVEKMLVGVGCTCVASIVRQAA 158
chicken  SAGQLDHSVNSVPIKQEILVLRREPKGCQHSYRLEKKMITVGCTCVTPLIQHQA 169
duck     SAGQLDHSLNSIPINQEILVLRRELKGCHHSYRLEKKIITVGCTCVTPLIQHQA 169
           *  *   **  * *****       *    * **    ******
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Fig. 1. Alignment of deduced amino acid sequences of HVS13 and mammalian and avian IL17. Sequences were aligned using the ClustalW program. Asterisks (*) indicate identical residues among sequences. The predicted signal region is underlined. The six conserved cysteine residues are highlighted by black boxes. HVS13 indicates the open reading frame 13 of *Herpesvirus saimiri*. The GenBank accession numbers used in the comparison are U32659 (human), X64346 (HVS13), AB102693 (swine), AF412040 (bovine), L13839 (rat), U43088 (mouse), AJ493595 (chicken), and EU366165 (duck).

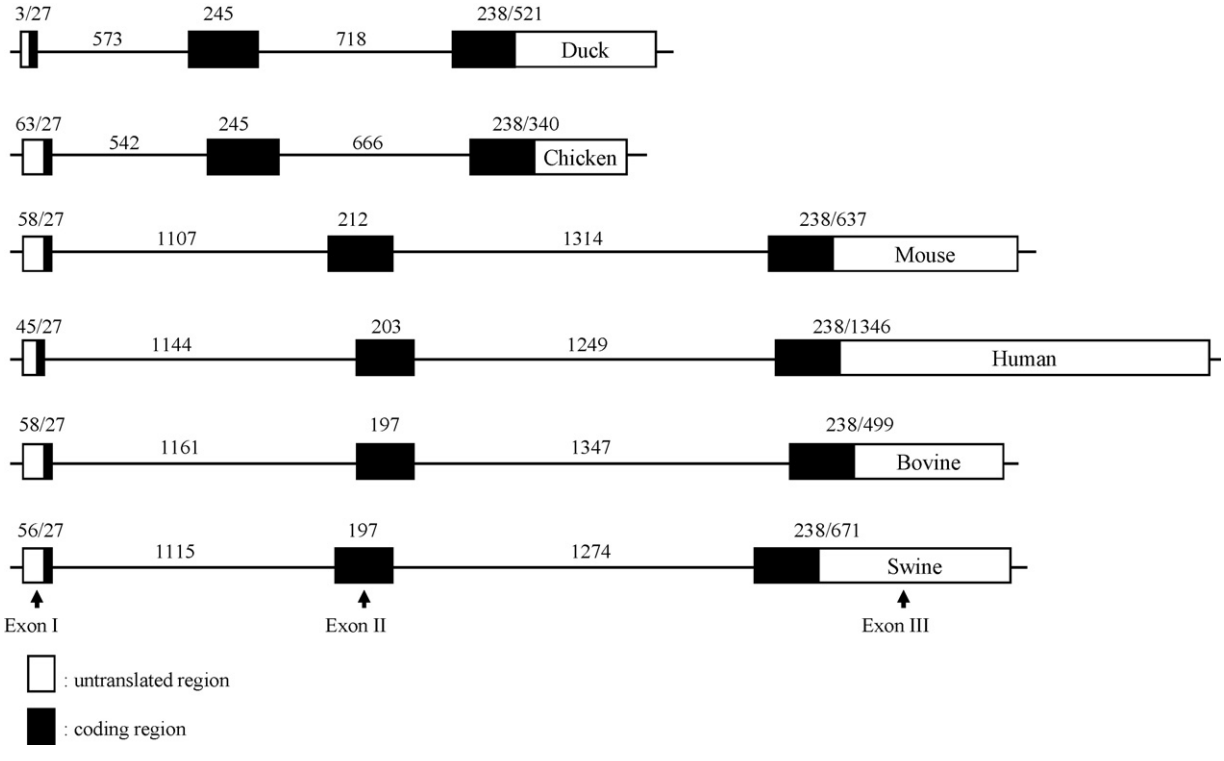

Fig. 2. Schematic diagram of intron–exon structure of avian and mammalian *IL17A* genes. The numbers indicate lengths in base pairs encoded by each exon (box) and intron (thin line). Open boxes, untranslated regions; Black boxes, translated regions. The GenBank accession numbers used in the comparison are NT_007592 (human), NW_001886464 (swine), NW_001494165 (bovine), NT_039169 (mouse), NW_001471673 (chicken), and FJ755182 (duck).

terminal hydrophobic leader sequence of 29 amino acids, a single potential N-linked glycosylation site, a predicted molecular mass of 18.8 kDa (non-glycosylated), and a calculated isoelectric point of 9.11. Comparison of amino acid sequences using ClustalW (www.ebi.ac.uk/Tools/clustalw2) indicated that duIL17 shared 84% identity to chIL17, 47% to swine IL17, and 46% to human IL17A and bovine IL17. Duck IL17 also shared 36–38% identity to HVS13, as well as rat and mouse IL17A. In addition, the six cysteine residues conserved among chicken, HVS13, and mammalian IL17A were observed in duIL17 (Fig. 1). Phylogenetic and molecular evolutionary analysis was carried out on amino acid sequences encoded by duIL17 and its homologs using MEGA version 4 (Tamura et al., 2007). The phylogenetic tree showed the expected clustering, confirming the highest similarity between duck and chicken IL17 (data not shown).

The expression of *IL17* transcripts in various duck tissues and Con A-activated splenic lymphocytes was measured by RT-PCR. Duck *IL17* mRNA was expressed only in Con A-activated splenic lymphocytes while normal tissues such as liver, bursa, brain, kidney, lung, thymus, and spleen had no detectable levels of *duIL17* mRNA (data not shown). These data correlate with detection of *chIL17* mRNA only in Con A-activated splenic lymphocytes by Northern blot analysis, but not in a series of normal tissues examined (Min and Lillehoj, 2002). Furthermore, prior studies showed no detectable *IL17* transcript in normal tissues from other mammals as determined by Northern blot analysis (Kennedy et al., 1996, Yao et al., 1995a). However, expression of porcine *IL17* mRNA was strongly detected in the adult heart, skin, and jejunum but was restricted in neonatal tissues under normal conditions as measured by real-time quantitative PCR analysis (Katoh et al., 2004).

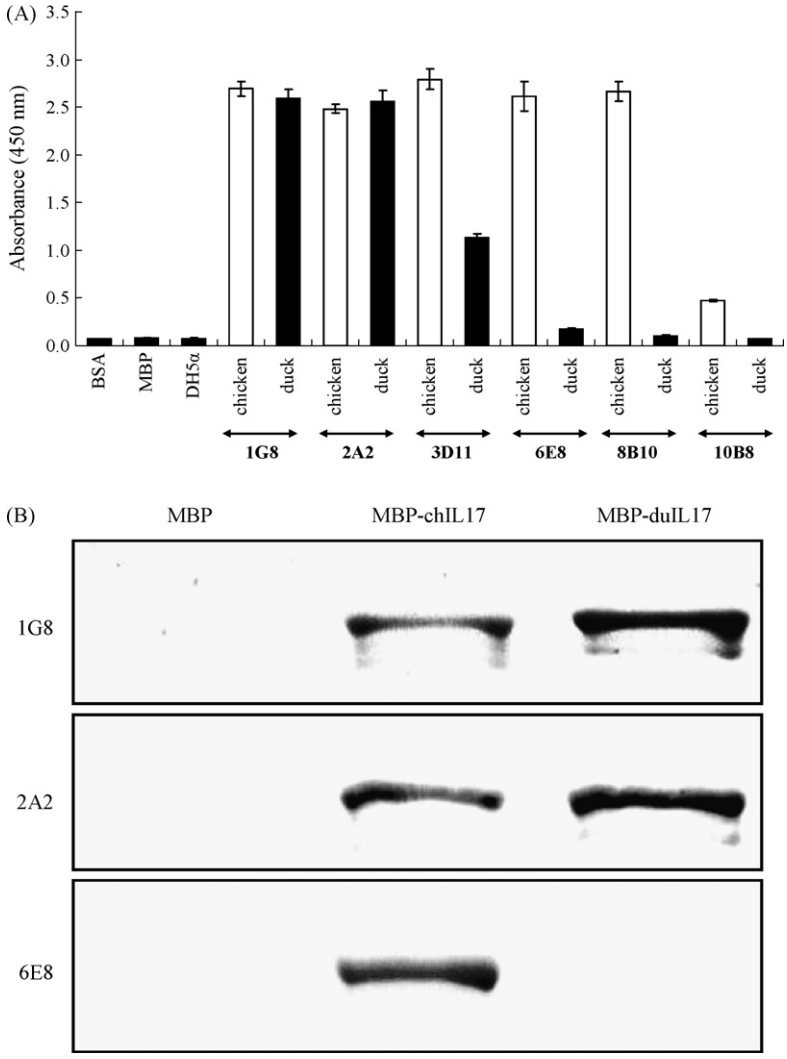

Fig. 3. Cross-reactivity of six mAbs to chIL17 with duIL17 was analyzed by indirect ELISA and Western blot analysis. (A) Flat-bottom 96-well microtiter plates were coated with 0.5 μg of BSA, MBP, DH5α, MBP-chIL17, and MBP-duIL17. The MBP, MBP-chIL17 and MBP-duIL17 proteins expressed in *E. coli* DH5α were purified on an amylose affinity column. *E. coli* DH5α was disrupted by sonication. Each point represents the means ± S.D. of triplicate determinations. (B) Bacterially expressed, affinity purified MBP, MBP-chIL17, and MBP-duIL17 were resolved by SDS-PAGE under reducing conditions. The blots were applied to three chIL17 mAbs: 1G8, 2A2, and 6E8.

To compare genomic organization of *duIL17* with its mammalian counterparts, the genomic *duIL17* gene was amplified with genomic DNA extracted from duck spleen by PCR using the *duIL17*-specific primers (P3 and 5′-GGCTGATTTTTTTTTATTGCA) and sequenced (GenBank accession number: FJ755182). The genomic fragment consisted of three exons spanning approximately 2.3 kb (Fig. 2). The exon/intron organization of the *duIL17* gene was quite similar to the chicken homologue and its mammalian counterparts. Generally, the genomic structure of avian cytokine genes is very similar to that of their mammalian counterparts (Kaiser et al., 1998; Min et al., 2002).

Recently, six monoclonal antibodies (mAbs) (1G8, 2A2, 3D11, 6E8, 8B10, and 10B8) reactive with chIL17 were produced and characterized (Yoo et al., 2008). By comparison of amino acid sequences (Fig. 1), duIL17 showed 84% identity to chIL17. Thus, cross-reactivity of six mAbs to chIL17 with duIL17 was evaluated by indirect ELISA. The binding intensity of antibodies 1G8 and 2A2 to recombinant chIL17 was similar to recombinant duIL17; antibody 3D11 bound moderately to duIL17, while the others (6E8, 8B10, 10B8) were negative (Fig. 3A). Following initial ELISA screening, three mAbs with binding affinity were chosen for further characterization by Western blot analysis. As shown in Fig. 3B, mAbs 1G8 and 2A2 detected the MBP-duIL17 fusion protein but did not recognize MBP used as a negative control. However, the mAbs 6E8 was negative for the MBP-duIL17 fusion protein. Therefore, these two cross-reactive mAbs (1G8, 2A2) can be a useful tool for molecular and immunological studies of IL17 in birds.

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