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Review Article

Interleukin-17 in veterinary animal species and its role in various diseases: A review

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ABSTRACT

Interleukin 17 (IL-17) as one of the pro-inflammatory cytokines is a very important player in the immune response to many pathogens and seems to play a role also in certain chronic and autoimmune diseases. Many studies showing the importance of this cytokine were conducted on murine models and human patients. In recent years, some experiments with other animals in which interleukin-17 was measured were carried out. This review is focused on the findings that have been observed and described in important veterinary species of animals.

1. Introduction

Interleukin 17, originally identified as cytotoxic T lymphocyte associated antigen 8 (CTLA-8), was first described in 1993 in mice, rats and humans and this protein showed 57% homology to the putative protein encoded by the open reading frame 13 gene of T lymphotropic *Herpesvirus saimiri*. The mRNA of CTLA-8 had AU-rich repeats in the 3′-untranslated region previously found in mRNA of many cytokines, growth factors and oncogenes [1]. Two years later, this protein was described as a novel cytokine and it was proposed that it should be called interleukin 17 [2]. The discovery of five related molecules formed a new family of cytokines. The first member of this family, IL-17, is now also called IL-17A and the other members are IL-17B to IL-17F [3]. IL-17A is the pro-inflammatory cytokine which abolished the Th1/Th2 paradigm and gave rise to a new effector Th subset named Th17 [4,5]. IL-17E, also known as IL-25, is Th2 cytokine [6]. IL-17B, IL-17C and IL-17D are products of many cell types but not of activated T-cells [7,8]. IL-17F is produced by the same cell subsets such as IL-17A and has similar functions [3]. This review is focused on IL-17A (hereinafter IL-17) which has been characterized not only in mammals such as pigs [9], horses [10] and cows [11] but also in birds such as chicken [12] or ducks [13]. Some characteristics of IL-17 in these species are summarized in Table 1.

The main sources of IL-17 include $CD4^+\alpha\beta$ T-cells (Th17) and $\gamma\delta$ T-cells [14–16]. Moreover, $CD8^+$ T-cells, NK-cells and NKT-cells also seem to be able to produce IL-17 [17]. There are some studies which show the production of IL-17 mRNA by non-lymphocytes like Paneth cells [18], neutrophils, eosinophils and monocytes [19] but the production of IL-17 protein by these cells remains unclear. Receptor of IL-17 was found in almost all tissues [3]. IL-17, binding to its receptor, can activate the Jak/STAT pathway and also three groups of MAPK: p38, Erk and Jnk [20]. In somatic cells, IL-17 induces the production of G-CSF [21,22], chemoatractant molecules such as IL-8 [22], CXCL1, CXCL5, CXCL6 [23] and MCP-1, antimicrobial peptides [24], IL-6, prostaglandin E2 [22], matrix metalloproteinase 3 [20] and ICAM-1 [25]. All these effects lead to increased inflammatory response not only during the infections but also in autoimmune diseases and graft rejection [26].

The information concerning the role of IL-17 in farm animals and pets is very fragmented. That is why this review is divided into four sections dealing with fields in which it is possible to compare some studies (IL-17 in GIT, airways, mammary gland and joints) and in the end, other known findings which, however, also bring too fragmented information are mentioned. The information about the animal species and diseases mentioned in these sections is in the Table 2. The information about primers for qRT-PCR, available kits and antibodies which have been used for detection of IL-17 and which can be useful for further studies in this species is summarized in Tables 3 and 4.

2. IL-17 in the gastrointestinal tract

In recent years, the importance of IL-17 is often mentioned in the context of gut inflammation, both acute and chronic. In human patients, increased expression of IL-17 is usually highlighted in connection with inflammatory bowel disease (IBD) [50–52].

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Table 1
Known sequences of IL-17 in veterinary animal species.

Animal	Base pairs in ORF	Amino acid residues	Molecular weight	Similarity to human IL-17 (%)	Similarity to mouse IL-17 (%)	Refs.
Pig	462	153	17.3 kDa	72.9	64.7	[9]
Horse	462	Not published	17.26 kDa (deduced)	76	70	[10]
Cow	462	153	17.2 kDa	73.5	67	[11]
Chicken	507	169	18.9 kDa	46	37	[12]
Duck	510	169	18.8 kDa	46	36–38	[13]

Table 2
Animal species and diseases mentioned in this review.

Section	Disease	Animal
GIT	DSS-induced colitis	Pig
	Inflammatory bowel disease	Dog
	Johne's disease	Cow
	Bacterial infection	Cow, pig, chicken, rabbit
	Parasitic infection	Cow, sheep, chicken
	Intestinal inflammation of the offspring induced by maternal obesity	Sheep
Airway	Inflammatory airway disease	Horse
	Recurrent airway obstruction	Horse
	Rhodococcus equi infection	Horse
	Bovine tuberculosis	Cow
Mammary gland	Mastitis	Cow, goat
Joints	Osteoarthritis	Horse, dog
	Cartilage degradation model	Cat, cow, pig
	Pyometra	Dog
	Skin inflammation	Sheep
Other	Middle ear inflammation	Rabbit
	Bacteremia	Rabbit, chicken
	Recurrent uveitis	Horse
	Brucella abortus infection	Cow
	Neospora caninum infection	Cow

Human IBD is a chronic gastrointestinal tract disorder, associated with abnormal immune responses to food antigens and microbes in GALT [53] and it includes a group of diseases, mainly ulcerative colitis and Crohn's disease – CD [54]. There are too few studies trying to find the therapy for IBD using a pig model of dextran sodium sulfate (DSS)-induced colitis. In pigs with DSS-induced colitis, the expression of IL-17 was higher in mesenteric lymph nodes than in negative controls and pigs with induced colitis treated with soy di- and tri-peptides [55], L-tryptofan [30], hen egg lysozyme [56] and hen egg white peptides [57]. A significant decrease in inflammatory response, including IL-17 mRNA level decrease, was found in all of these experiments after the treatment. In contrast to humans or pigs, down-regulation of IL-17 was observed in the duodenum of dogs with IBD, which shows that canine IBD may have different pathophysiology [58].*Mycobacterium avium* subsp. *paratuberculosis* (MAP), the etiologic agent of Johne's disease (JD) in ruminants, is considered as one of the factors involved in development of human CD [59]. That was the reasons why Allen and co-workers made a bovine model for comparative studies to see the differences and similarities between mechanisms of pathogenesis of CD and JD. In their study they used human isolates of MAP for infection of calves and compared the results with those obtained from adult cows affected with JD and healthy cows as the control group. In both experimentally and clinically infected animals, up-regulation of IL-17 m-RNA was detected by qRT-PCR [60]. In another study of MAP, the changes of IL-17 transcription in peripheral blood mononuclear cells (PBMCs) were detected by qRT-PCR. The aim of the study was to compare immune responses to MAP mutant and wild-type (wt) strains for the possibility of further vaccine development. In this study, calves were experimentally infected either with mutant or with wt MAP. PBMC from these calves were isolated before infection and three months post-infection and then they were *in vitro* stimulated with live MAP. In both infected groups, the response of PBMC by production of IL-17 was up-regulated three months post-infection [37].

Changes in IL-17 expression were also found during acute gut inflammation induced by bacterial infection. In a model of Salmonella-infected bovine ligated ileal loops, the increased expression of IL-17 mRNA was detected 2 h post-infection, with a higher response to serotype Typhimurium than serotype Typhi [36]. In contrast, significantly decreased expression of IL-17 mRNA was detected in swine ileal mucosa obtained from pigs 2 days post-infection by serotype Typhimurium [61]. In another study of pigs

Table 3
Primers used for IL-17 detection by qRT-PRC in veterinary animals species.

Animal	Forward	Reverse	Accession number	Refs.
Rabbit	CCAGCAAGAGATCCTGGTCCTA	ATGGATGATGGGGGTTACACAG	XM_002714498	[27]
Sheep	TGCTACTGCTTCTGAGTCTGGTGGC	TGACCCTCACATGCTGTGGGAAGTT		[28]
Pig	CGGAGCACACCTGCCAGACG	AGGAGTTGGGGCAGTGGCGA	NM_001005729.1	[29]
	TCATGATCCCACAAAGTCCA	AGTCCATGGTGAGGTGAAGC	NM_001005729	[30]
	ATCCTCGTCCCTGTCACTGC	ACATGCTGAGGGAAGTTCTTGTC		[15]
	CTCTCGTGAAGGCGGGAATC	GTAATCTGAGGGCCGTCTGG	AB102693	[31]
Dog	CACTCCTTCCGGCTAGAGAA	CACATGGCGAACAATAGGG	XM_538958	[32]
	TGACTCTGGTGACAACTTCATCCATGTTCC	CCACCAGGCTCAGAAGCAGTAGCA		[33]
Cow	GGACTCTCCACCGCAATGAG	GGTCCACCTTCCCTTCAGC		[34]
	GCCCACCGATTATCACAAG	TGGCCTCCCAGATCACAGA		[35]
	TCCATCTCACAGCGAGCACAAG	AGCCACCAGACTCAGAAGCAGTAG		[36]
	GGACTCTCCACCGCAATGAG	TGGCCTCCCAGATCACAGA	NM001008412	[37]
Horse	ACCTAAACGTCCTTAACCG	CTACCTTCCCTTCGGCAT		[38]
	TATCGTGAAGGCGGGAATAG	TCCCAGATCACAGAGGGGTA	EU744563	[39]
	AAGGGCCTCAGATTACCACAAC	TCGCCTCCCAGATCACAGA		[40]
	ACTGTGAAGGCGGGAATAGTAA	TCGTTTTCCGGTTAAGGACG		[41]