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REVIEW

FELINE IMMUNE SYSTEM

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Abstract—Immunological features of feline lymphocytes, immunoglobulins, monocytes/macrophages, cytokines, major histocompatibility complex and delayed-type hypersensitivity are reviewed. Attention is given to the comparison of the feline immune system with the immune systems of humans and other animals. Also presented is information on the modification of feline immunity by pathogens.

Key words: lymphocytes, CD4, CD8, immunoglobulins, interleukins, major histocompatibility complex, macrophages, interferons, delayed-type hypersensitivity, tumor necrosis factor (TNF).

Résumé—Les caractéristiques immunologiques des lymphocytes, des immunoglobulines, des monocytes et macrophages, des cytokines, du complexe majeur d'histocompatibilité et de l'hypersensibilité de type retardé ont été revues chez le chat. Une attention toute particulière a été apportée à la comparaison du système immunitaire félin avec les systèmes immunitaires chez d'autres animaux et chez l'homme. Nous rapportons aussi les modifications de la réponse immunitaire du chat face à certains pathogènes.

Mots-clés: lymphocytes CD4+, lymphocytes CD8+, immunoglobulines, interleukines, complexe majeur d'histocompatibilité, macrophages, interférons, hypersensibilité de type retardé, facteur de la nécrose tumorale (TNF).

I. INTRODUCTION

Several reviews on the feline immune system were published by 1987 [1–3]. However, the recent discovery of feline immunodeficiency virus [4] and the many similarities between feline immunodeficiency virus and human immunodeficiency virus type 1 had made the feline virus an important model of acquired immunodeficiency syndrome (AIDS) [5–14]. Thus, there has been a dramatic increase in interest in the feline immune system. This review intends to serve as an update on the current state of knowledge on the feline immune system, and hopefully, it will also serve to stimulate further studies on this feline model of AIDS.

II. LYMPHOCYTES

(A) Overview

Feline T and B cells, like human and murine lymphocytes, can be enriched by passage through a nylon wool column [15–18]. Feline B cells have surface immunoglobulins [19, 20]
The pattern of feline B cell development has been found to be similar to that of other mammals [22]. Feline T cells have thymocyte antigen on their surface [19] and can bind to gerbil, guinea pig and rat erythrocytes [21, 23–25]. Based on the ability of rosetted T cells to help B cells in the production of immunoglobulins, it has been suggested that gerbil erythrocytes bind to feline T suppressor cells and guinea pig erythrocytes bind to feline T helper cells [25]. Further studies using monoclonal antibodies to CD4 and CD8 (see below) will be required to confirm this statement. Feline T cells, however, do not bind to antelope, burro, chicken, cow, dog, hamster, horse, mongoose, monkey, pig, rabbit, sheep, tiger and zebra erythrocytes [19, 23, 25]. Also, there is some controversy as to whether feline lymphocytes can form rosettes with human or mouse erythrocytes [19, 20, 23, 25]. It is believed that the binding of erythrocytes by feline lymphocytes is similar to the rosette formation of human T cells with sheep erythrocytes.

Attempts have been made to identify the tissue distribution of feline T and B cells using the ability of feline T cells to form rosettes with guinea pig erythrocytes and the presence of surface immunoglobulins on B cells as criteria for identification. Cells having T-cell properties make up about 35–40% of thymocytes, 21–32% of peripheral blood mononuclear cells, 33% of bone marrow cells and 29% of lymph node cells [20, 23, 25, 26]; while 2.9% of thymocytes, 23–45% of peripheral mononuclear cells and 54% of lymph node cells have B-cell properties [20, 23, 26–29].

Feline lymphocytes are able to proliferate in response to concanavalin A [6, 11, 29–33], phytohemagglutinin [6, 11, 29, 30, 32, 33] and pokeweed mitogen [6, 11, 29–32]. Among these three lectins, concanavalin A is the most mitogenic and phytohemagglutinin is the least mitogenic [6, 11, 29]. Similar to human and mouse lymphocytes, feline lymphocytes have surface lectin receptors that are involved in the binding and capping of mitogen [34]. In contrast to murine and human lymphocytes, feline lymphocytes have either limited response to lipopolysaccharide [32] or none at all [6, 31]. This unresponsiveness to lipopolysaccharide also has been observed in tiger lymphocytes [35].

(B) CD4 and CD8 Cells

It has been reported that feline T suppressor cells can be induced by ConA stimulation in an in vitro functional assay [29, 36]. Also, feline cytotoxic lymphocytes can be induced in cats infected with feline sarcoma virus [37, 38]. The molecular characteristics of these feline lymphocyte markers were virtually unknown until recently. A monoclonal antibody, FT2, has been produced that recognizes a feline homologue of the CD8 antigen (mol. wt 1000) in a group of feline T cells which responded to concanavalin A and phytohemagglutinin and had a cytotoxic function [39]. Subsequently, another monoclonal antibody, Fe17, has been identified that recognizes a feline homologue of the CD4 antigen (mol. wt 65,000) [40]. Expression of this feline CD4 antigen is down-regulated and the molecule is phosphorylated when T cells are stimulated with phorbol ester. The addition of Fe17 antibody also blocks the concanavalin A-induced proliferation of T cells. These two feline T cell markers are expressed by mutually exclusive sub-populations of peripheral T cells [40]. Using Fe17 antibody, the distribution of CD4-positive lymphoid cells in the thymus is 52%, lymph nodes 39%, spleen 14%, blood 20–25% and bone marrow 2% [11, 40]. Using FT2 antibody, the distribution of CD8-positive lymphoid cells in the thymus is 63–76%, lymph node 15–20%, spleen 9–14%, blood 6–18% and bone marrow 1–3% [11, 39, 40].
Feline immune system

III. IMMUNOGLOBULINS

Immunoglobulins G, M, A and E have been described in cats [11, 29, 41–46] with lambda as the predominant light chain [22, 47]. The normal immunoglobulin concentration in cat serum varies considerably depending on the environment where cats have been reared. For instance, cats reared in catteries have higher immunoglobulin levels than specific-pathogen-free and household cats [48]. In response to infections, cats are able to produce intraocular and intrathecal IgG against pathogens [13, 49]. Structurally, feline IgG is similar to human IgG [47]. Some antisera to human or mammalian immunoglobulins also recognize the corresponding classes of feline immunoglobulins [42, 50, 51].

IV. MONOCYTES AND MACROPHAGES

Feline macrophages are similar to other mammalian macrophages. They are plastic-adherent, have eccentric and kidney-shaped nuclei and large perinuclear vacuoles, possess α-naphthyl acetate esterase and acid phosphatase activity, are without any apparent peroxidase activity and display Fc-mediated rosetting and phagocytosis of IgG-coated sheep red blood cells [52, 53]. Also, macrophages from pathogen-infected (Toxoplasma gondii, feline immunodeficiency virus) cats are more active in their microbicidal activity than those from uninfected cats [12, 29]. This microbicidal activity is enhanced by incubation of feline macrophages with mitogen-stimulated lymphocyte culture medium [29]. When compared to feline alveolar macrophages, feline peritoneal macrophages have higher microbicidal activity and release more interleukin 1 (IL-1) in response to lipopolysaccharide stimulation [29]. In contrast to humans, mice and dogs, removal of blood-borne pathogens and particulates in cats is effected predominantly by pulmonary intravascular macrophages but not spleen or liver macrophages [54]. Feline monocytes, which make up less than 5% of the white cells in the peripheral blood [3], have high affinity receptors for lectin derived from the seeds of Erythrina cristagalli [55]. It has been reported that feline monocytes are effector cells in antibody-dependent cellular cytotoxicity [56].

V. CYTOKINES

(A) Interleukins

(1) Overview

To date at least twelve interleukins have been described. These molecules play a wide variety of roles in many physiological responses. Although all these molecules are designated as interleukins, there are significant differences as to their cellular sources and functions. In this review, only those interleukins that have been examined in the cat are discussed.

(2) Interleukin 1

IL-1 is secreted mainly by macrophages and monocytes and is important for the induction of lymphokine release by T cells, co-stimulation of B cell differentiation and proliferation and augmentation of natural killer cell activity [57–60]. Feline IL-1 was first described by Goitsuka et al. [61] and has a molecular weight of approximately 12,000–20,000 Da. It can be inactivated by heating at 70°C for 30 min [61], and its activity also can be partially blocked by antibody to human IL-1 [12]. Like murine and human IL-1,
feline IL-1 is present in culture supernatants from lipopolysaccharide-stimulated mono-
cytes or macrophages and can enhance mouse thymocyte proliferation in the presence of
sub-mitogenic concentration of phytohemagglutinin [12, 29, 61]. The similarities of feline
and human IL-1 are further supported by the fact that cats are responsive to human IL-1.
Intravenous inoculation of cats with human IL-1 causes a sustained fever and selective
prostaglandin 2 production [62]. Human IL-1 either inhibits (high dose) or promotes (low
dose) sleep when it is injected into cats intracerebroventricularly [63]. IL-1-like activity has
also been detected in the cerebrospinal fluid of cats [64, 65]. Interestingly, feline infectious
peritonitis virus induces the secretion of IL-1 by macrophages [66, 67].

(3) Interleukin 2

The presence of interleukin 2 (IL-2)-like activity in feline lymphocyte cultures stimulated
with concanavalin A or calcium ionophore A23187 plus phorbol myristate acetate has been
reported [11, 29, 68–71]. Feline IL-2 activity was first characterized by Goitsuka et al. [72]
and was further described by Bauer and Olsen [73]. Feline IL-2 closely resembles rat and
human IL-2 in having a molecular weight of approx. 16,000 Da [72]. Also, the activity of
feline IL-2 can be partially blocked by monoclonal antibody to human IL-2 [29]. The
similarities of feline and human IL-2 are further supported by the findings that feline
lymphocytes are responsive to human IL-2 [74] and large granular feline cytotoxic
lymphocytes are induced by human IL-2 in vitro [71]. Also, infected cats given human IL-2
in combination with 3'-azido-3'-deoxythymidine (AZT) resist challenge with feline
leukemia virus [75]. In contrast to human and murine IL-2, feline IL-2 is labile to trypsin
treatment and is rather sensitive to heating at 70°C for 15 min, incubation at pH 3.2 or
10.5 and treatment with urea.

About 18–22% of feline peripheral lymphocytes are recognized by a monoclonal
antibody to the human IL-2 receptor [76]. It is not clear at this time whether these cells
actually bear a feline IL-2 receptor. It has also been observed that lymphocytes from blood
of a 6-month-old or older cat secrete higher levels of IL-2 than lymphocytes from kittens
younger than 6 months of age [14].

IL-2 is one of the lymphokines produced by T cells stimulated with either antigens or
mitogens and has many biological properties such as the induction of cytotoxic T cells,
activation of natural killer cells and enhancement of interferon-τ (IFN-τ) production by
T cells. These findings suggest that IL-2 plays an important role in the regulation of
cell-mediated immunity [57, 77, 78]. Similar to other systems, feline IL-2-rich supernatants
are able to promote cytotoxic activity by peripheral blood lymphocytes from cats [70].

(4) Interleukin 6

Interleukin 6 (IL-6) is produced by activated monocytes or macrophages, endothelial
cells, fibroblasts and activated T cells. IL-6 acts on a variety of target cells including T
cells, B cells, fibroblasts, myeloid progenitors and hepatocytes [79, 80]. Using an IL-6
specific cell line, feline IL-6-like activity has been identified in the culture supernatants
of concanavalin A-stimulated splenocytes and non-stimulated alveolar macrophages [81].
Feline IL-6 is similar to human and murine IL-6 in its biological activities [81]. These
molecules are slightly different, however, in their physico-chemical properties. Feline IL-6
has a molecular weight of 30,000–40,000 Da and elutes into fractions at salt concentrations
of 0.2–0.3 M NaCl in gel filtration, while murine and human IL-6 has a molecular weight
about 25,000–35,000 and elutes using 0.1–0.2 M NaCl [81].
(B) Interferons

Three main types of interferons (IFNs) are known to be produced in different cell types: IFN-α in B and null lymphocytes and macrophages, IFN-β in epithelial and fibroblast cells and IFN-τ in T lymphocytes [82]. Traditionally, feline IFN is measured using a plaque reduction assay employing vesicular stomatitis virus on monolayers of feline cell lines [83-85]. The Crandell feline kidney cell line secretes IFN after Newcastle disease virus stimulation in vitro [84]. A pyrimidinol compound (U-25, 166), polyriboinosinic:polyribo- cytidylic acid and Newcastle disease virus also can induce IFN production in cats in vivo [83, 85]. Feline IFN-τ-like activity is also induced in feline lymphocytes stimulated with Staphylococcus enterotoxin A [86].

Recently, the three types of feline IFNs have been partially characterized and they are similar to those of other mammals and humans in their biological properties [87]. Feline lymphocytes are responsive to human IFN-α [88, 89]. Human IFN-α plus IFN-β and human IFN-α in combination with 2’,3’-dideoxycytidine have been found to inhibit the proliferation of feline infectious peritonitis virus and feline leukemia virus in feline cell cultures, respectively [75, 90, 91]. In addition, infected cats given human IFN-α in combination with AZT resist challenge with feline leukemia virus [75].

(C) Tumor Necrosis Factors

Tumor necrosis factor (TNF) was described as a serum derived tumor specific cytoidal factor in mice primed with Bacille bili de Calmette-Guerin (BCG) after endotoxin administration [92]. Since then TNF has been intensively studied [93-97]. It is now known that TNF-α is secreted mainly by macrophages and is identical to cachectin. TNF-β is made principally by T lymphocytes and is identical to lymphotoxin [98]. Although TNF-α and TNF-β are different proteins, they bind to the same receptor and, for the most part, elicit the same responses [97]. TNF-α production at a site of injury may function both to recruit and activate macrophages [96]. In addition to the direct actions of TNF-α, its interaction with other cytokines including IL-1 and IFN-γ allows it to play an even more powerful role in the regulation of cell growth and function [96].

There have been no reports concerning the properties of feline TNF. However, as is consistent with other reports concerning the similaritites of TNF-α among different animal species [98-100], cats are responsive to human TNF. Carotid arteries of cats respond to human TNF in vitro by producing proteins that inhibit the release of endothelium-derived relaxing factor [101]. Also, human TNF in combintion with 2’,3’-dideoxycytidine and human IFN-α inhibit feline leukemia virus proliferation in feline cell cultures more dramatically than the drug or human IFN-α alone [91].

VI. MAJOR HISTOCOMPATIBILITY COMPLEX

Both class I and II major histocompatibility complex (MHC) antigens are polymorphic in most outbred species [102]. However, the grafting of feline tissues and organs has been reported to be less dependent on the feline MHC or feline leukocyte antigen (FLA) than that of other animals. Feline skin allografts last somewhat longer than acutely rejected grafts in other animals [103, 104]. Feline kidney transplantation has been remarkably successful even though attempts have not been made to match tissue compatibilities between donor and recipient or to provide immunosuppression [105]. Furthermore, cats fail to develop lymphocytotoxic antibodies after pregnancy or transfusions [106].
It thus has been speculated that cats may have limited polymorphism at their MHC loci [102, 106, 107].

Other studies have shown that cats may have a more typical MHC. Allogeneic skin transplantation in cats has been shown to cause the production of cytotoxic antibodies against the donor's lymphocytes [108, 109]. Also there is some controversy as to the lack of polymorphism of FLA reported by some workers using mixed lymphocyte reactions [106, 107, 110-112]. Using gel electrophoresis of homogenized feline lymphocytes followed by Western blot analysis and immunochemical staining with antibodies directed against human class I and II MHC antigens, feline lymphocytes were found to bear determinants that are as polymorphic as human lymphocytes [113]. Monoclonal antibodies against human class II I-A antigens bind to the majority of feline lymphocytes suggesting that the expression of class II I-A-like antigens in unstimulated feline lymphocytes is unusually elevated [113, 114]. In contrast, feline class II I-E-like molecules can be detected using anti-mouse I-E antibody only when lymphocytes are pre-activated with lipopolysaccharide [115].

Cats have been shown to possess a minimum of 20 class I loci and 5 class II genes per haploid genome in experiments that employed molecular probes for human and murine MHC [116]. DNA sequence analysis of feline MHC class I genes has shown similarities with human and murine MHC loci in both the nucleotide sequence and functional organization [117, 118]. Both feline class I and II genes have been genetically mapped to chromosome B2 which is homologous to human chromosome 6 and mouse chromosome 17 [116]. Genetic characterization using cytotoxic allo-antibodies has given an additional demonstration of the existence of polymorphisms in FLA [108].

VII. DELAYED-TYPE HYPERSENSITIVITY

Cats can develop delayed-type hypersensitivity reactions to foreign proteins, and this sensitivity is transferable only with lymphocytes [119, 120]. Delayed-type hypersensitivity reactions in cats are not as intense or consistent as those in guinea pigs, and cats have not been found to respond to some proteins such as bovine serum albumin [121]. In cats with intact cellular immunity, lymphocytes migrate to the site of stimulation within 24 h and reach maximal numbers in 48–72 h [122]. Delayed-type hypersensitivity to feline infectious peritonitis virus antigens is associated with an increased level of resistance to this virus infection in cats [123, 124].

VIII. CONCLUSIONS

In general, there is less known about the immune system of the cat than that of humans, mice or other domestic animals. A considerable amount of effort has been directed towards the characterization of feline immunoglobulins and the feline MHC. However, the identification of feline lymphocyte markers is still in its infancy. Feline IL-1, IL-2, IL-6, IFN-α, IFN-β and IFN-γ have been partially characterized. There is virtually nothing known about the properties of feline TNF-α, TNF-β and those interleukins other than IL-1, IL-2 and IL-6. Future work will probably be directed, in part, towards identifying feline immune system components that are truly unique to the cat. Ultimately, it is hoped that as more is known about the feline immune system and as more reagents become available for cats that the feline immune system will become as well understood as that of other domestic animals.
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