Exp. Anim. 67(3), 301–312, 2018

—Review—

Comparative immunity of antigen recognition, differentiation, and other functional molecules: similarities and differences among common marmosets, humans, and mice

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Abstract: The common marmoset (CM; *Callithrix jacchus*) is a small New World monkey with a high rate of pregnancy and is maintained in closed colonies as an experimental animal species. Although CMs are used for immunological research, such as studies of autoimmune disease and infectious disease, their immunological characteristics are less defined than those of other nonhuman primates. We and others have analyzed antigen recognition-related molecules, the development of hematopoietic stem cells (HSCs), and the molecules involved in the immune response. CMs systemically express Caja-G, a major histocompatibility complex class I molecule, and the ortholog of HLA-G, a suppressive nonclassical HLA class I molecule. HSCs express CD117, while CD34 is not essential for multipotency. CD117+ cells developed into all hematopoietic cell lineages, but compared with human HSCs, B cells did not extensively develop when HSCs were transplanted into an immunodeficient mouse. Although autoimmune models have been successfully established, sensitization of CMs with some bacteria induced a low protective immunity. In CMs, B cells were observed in the periphery, but IgG levels were very low compared with those in humans and mice. This evidence suggests that CM immunity is partially suppressed systemically. Such immune regulation might benefit pregnancy in CMs, which normally deliver dizygotic twins, the placentae of which are fused and the immune cells of which are mixed. In this review, we describe the CM immune system and discuss the possibility of using CMs as a model of human immunity.

Key words: antigen recognition, common marmoset, hematopoietic stem cell, immune system

(Received 26 November 2017 / Accepted 16 January 2018 / Published online in J-STAGE 8 February 2018)

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Introduction

Nonhuman primates (NHPs) play a pivotal role in basic brain science and clinical research of the central nervous system. They have also been used as infectious disease models and in research on reproduction. However, the immune system has not been as well studied as the nervous system in NHPs at the molecular level. Using rodents as experimental animals, many molecular aspects of the human immune system have been explained and predicted, but it has also been clarified that the human and mouse have significant differences [48]. The reason why the research concerning immunity in NHPs, which are more akin to humans, is behind that in rodents is mainly the level of research tools. For example, there are many inbred lines for rodents, specifically mice, that possess a homozygous background for not only major histocompatibility complexes (MHCs) but also for genes encoding other proteins. Immune research in rodents involves a large number of analytical tools, such as specific antibodies against NHP species-specific antigens. Without these tools, no classical transplantation experiments would be successful. NHPs for which completely genotypically homozygous animals have not been established cannot match the extent to which rodents are used in immunology research. This might be a major reason why extensive comparisons of NHP immune function with mouse and human immune function have not been conducted, especially for the function of immune regulation. Cynomolgus monkeys are one of the most extensively studied NHPs. Recently, MHC-identified monkeys were obtained [2, 5, 37]. This made transplantation-based immunological research possible [36, 51]; however, MHC-homologous animals are very limited, so researchers cannot frequently use them for transplantation-based immunological research. Molecularly targeted drugs, such as neoantigen-specific monoclonal antibodies, require preclinical studies involving NHPs. However, even among primates, antigen-recognizing molecules are highly evolved and branched. Therefore, responses do not completely mimic the human response [85]. These limitations for the prediction of antigen recognition by human immune cells using NHPs may lead to low reliability when using them as a model for human immunology. Therefore, while the importance of NHPs for preclinical studies of moleculary targeted drugs is increasing, our understanding of the basis of molecular immunity is still relatively immature. To better understand the immunological characteristics of human immune responses to molecularly targeted drugs, we must select adequate species among the various experimental animals, which will enable reliable translational research. Thus, it is urgent to clarify the characteristics of the immune system of each primate species and to select adequate species for various types of studies.

Callithrix jacchus is conventionally known as the common marmoset (CM) [43, 44] and is a New World monkey for which colonies have been established via planned breeding. Closed CM colonies have been maintained in Japan for approximately 50 years. CMs diverged from humans approximately 33 million years ago (MYA), which was after the divergence of rats and mice (diverged by 96 MYA) and before the divergence of macaques (diverged by 23 MYA), which are the most widely used model species in the study of motor systems [54, 87]. CMs are small and possess a high reproductive capacity, conceiving 2–3 offspring per pregnancy twice a year. Because of these advantages, Japanese researchers at the Central Institute for Experimental Animals (CIEA, Kawasaki, Japan) succeeded in the establishment of transgenic animals and in performing gene targeting of these animals [72, 73]. Transgenic CMs have shown promise in playing an important role in primate brain research and research on neuronal diseases because the CM brain is the simplest and smallest among the available experimental primates [49, 57].

With regards to CM immunity, there are several previously reported research models. For example, there are models of infectious diseases [15, 62], autoimmune disorders [1, 6, 30, 84], and transplantation immunology [64, 86]. CMs are susceptible to natural infections with particular strains of bacteria, which are thought to be caused by their diminished MHC class II repertoire [3, 18, 83]. However, these factors, which result in a unique immune system, have not been well characterized. *Caja-G* genes were identified as the main *MHC* genes of CMs, and a polymorphism indicates that Caja-G plays a role in the activation of cytotoxic T cells in a manner similar to classical MHC class I molecules, which are known to activate cytotoxic T cells that specifically react to infectious microbes. However, polymorphic MHC molecules might not recognize the T cell receptor (TCR) of CMs in a manner similar to class I HLAs, including HLA-A, HLA-B, and HLA-C, as Caja-G is an ortholog of HLA-G, an immune suppressing nonclassical HLA. Thus, the

susceptible nature of CMs to some strains of bacteria may also indicate that the function of the CM immune system is dampened not only by malfunctioning MHC class II molecules but also by its unique MHC class I structure.

Because CMs are New World monkeys that diverged relatively early in primate evolution, they possess one of the oldest sets of immune characteristics common in primates. On the other hand, protein sequences included in CM immunity shares only a limited similarity with humans. We and others have examined the cross-reactivities of various anti-human monoclonal antibodies and demonstrated that a large part of the antibodies did not react with CM antigens [7, 26, 29]. To identify molecules useful for examining the immune system, we prepared CM antigen-specific monoclonal antibodies and simultaneously identified the immune-related cDNAs [33, 39]. Subsequently, we performed analyses of CM immunity. Limitations in analytical tools prevent a more detailed analysis of the CM immune system; however, we obtained some intriguing results. In this review, we will describe the CM immune system and discuss its potential as an experimental animal, which thus far mimics human immunity.

Homology of Immune-related Genes

The evolution of immune system-related genes is relatively unique because it involves not only various functional molecules but also MHC molecules, TCRs, and immunoglobulins (Igs), which all evolved rapidly in divergent directions [19, 69]. While the variability of effector molecules, including cytokines and surface receptors such as cytokine receptors, toll-like receptors, and integrins, reflects the complexity of the immune function of a species, the variability of MHC molecules, TCRs, and Igs determines the capacity for antigen recognition. These molecules are indices of what type of antigen the species can recognize and what kind of regulatory systems the species possesses to recognize antigens. Primates are not an exception. As MHC molecules, TCRs and Igs have evolved in order to recognize non-self antigens, it is possible that environmentally closely related species possess more highly conserved sequences. Collectively, the molecules involved in immune effector functions and those involved in antigen recognition should be analyzed independently. The structures of these molecules also suggest that while molecules working on immune effector function include various families and can be discussed in parallel with other nonimmune molecules, the molecules involved in antigen recognition have unique and repetitive sequences and should be evaluated independently.

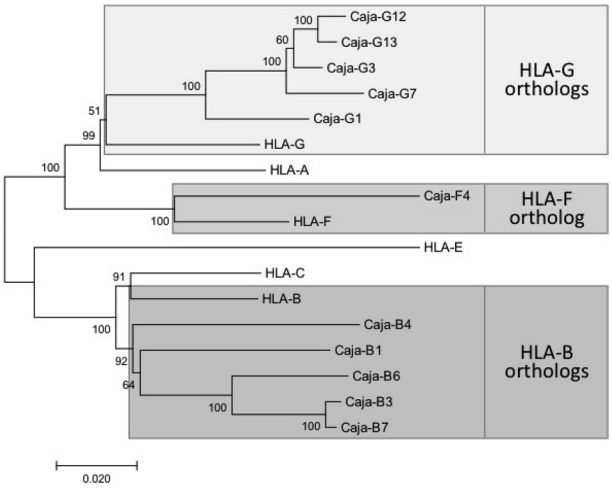

Fig. 1. Phylogenetic tree of MHC class I molecules in humans and common marmosets. HLA-G orthologs (beige squares), HLA-F orthologs (pale blue squares), and HLA-B orthologs (pink squares) are shown in the phylogenetic tree. The LBP and the scale of the substitutions/site are shown. Caja-G, HLA-G, and HLA-A diverged recently.

Therefore, we first analyzed the cDNA sequences for these molecules, which have immune effector functions that involve cytokines, and we compared their homologies with mouse and human sequences [39]. From our results, an 86 ± 5.5% homology was observed between CM and human cDNA sequences. The homology of the same gene set between humans and mice was 61 ± 13% and that between CMs and mice was 60 ± 13%; therefore, CM genes appear to be much closer to human genes than to mouse genes.

As for the MHC molecules of CMs, *Caja* genes, which are equivalent to *HLA* class I genes, contain *Caja-B, Caja-G, and Caja-F* loci [77]. Shiina *et al*. determined the structure of *Caja-B* and *Caja-G* genes. The *Caja-G* gene cluster contains 14 loci, and at least 5 loci express functional gene products [40]. It has recently been shown that multiple alleles can be found at these loci [3, 9, 53, 83]. Examining the homology of *Caja* genes and *HLA* genes shows that *Caja-G* has a high homology with *HLA-G*, suggesting that they are evolutionarily closely related, as shown in Fig. 1. Similarly, *Caja-F* is highly related to *HLA-F*, and *Caja-B* is related to *HLA-B*, while

HLA orthologs have not been identified in rodents.

It is well known that HLA-G is a nonclassical MHC molecule, and is represented by only one locus in humans, with a low number of alleles, and is expressed mainly on the placenta and by regulatory T cells. HLA-G is reported to suppress the immune system [10]. In contrast to HLA-G, Caja-G is systemically expressed and polymorphic, similar to the characteristics of human classical class I HLAs. This raises the question of what function Caja-G molecules perform. While the peptide presentation of the HLA-G and the ortholog has now been identified [50, 53], it is unclear if it possesses a sufficient repertoire to interact with anchoring peptides derived from numerous pathogens. Therefore, it may be helpful to examine the following three hypotheses. (1) Because HLA-G has the potential to present many types of peptides, Caja-G, as the ortholog of HLA-G, may present such peptides and activate the immune system in a manner similar to classical MHC class I molecules. (2) Caja-G may suppress the immune system in a manner similar to HLA-G through orthologs of HLA-G ligands. (3) Caja-G may contain both classical class I-like loci and nonclassical class I-like loci, and their functions may be divergent. Clarifying the functions of Caja-G is one of the most important issues for understanding the acquired immune system of CMs. For example, it would be beneficial to better identify the MHC molecules exclusively expressed on trophoblasts of the placenta because, in humans, HLA-G is mainly expressed on extravillous trophoblasts and prevents maternal immunity from rejecting the semi-allogeneic fetus [16].

In CMs, the presence of the genes for LILRB1 and LILRB2 orthologs, which are HLA-G ligands [12–14, 67], is predicted. These ligands might interact with HLA-G and suppress the activation of T cells and natural killer (NK) cells [12, 14]. However, the ortholog of KIR2DL4, which plays a pivotal role in the placenta, has not been predicted [68]. Thus, the identification of loci for *Caja-G*, the products of which suppress immune function in a manner similar to HLA-G, as well as the identification of relevant ligands, is important. If immune-suppressive MHC molecules are located on all tissues, we would not be able to use CMs as a model animal for research on human transplantation immunology.

Although we have not analyzed MHC class II molecules, Antunes and colleagues reported that HLA-DR and HLA-DQ of CMs are functional but that their diversity is small [3]. Plasad *et al*. reported the divergence of *Caja-DRB* and, specifically, the identification of *DRB*W16* [64, 65]. Similar to Caja-B, as reported by Shiina *et al.* [77], classical HLA class II orthologs in CMs also appear to function similarly to human HLAs.

In contrast to these findings, the homology of the TCR repertoire is high between CMs and humans. Dr. Suzuki's group reported that most of the genes for TCR repertoires possessed a greater than 90% homology in the CDR3-FR4 region, and none of the repertories possessed less than 80% homology in the CDR3-FR4 region between CMs and humans [38, 46]. No reports have yet identified the sequence homology of Igs.

Collectively, (1) individual molecules related to immune function in CMs show a greater homology to humans than to mice; (2)*Caja* genes in CMs have been identified as orthologs of HLAs but are unique in having more loci and fewer alleles than those in humans; and (3) the TCR in CMs is evolutionarily close to that in humans. In other words, the factors of immune function common in both mice and humans are also common in CMs, while the molecular structures of antigen-recognizing molecules in CMs are more closely related to humans.

Differentiation of Immune Cells

To characterize immune cells, identification of the developmental pathway is important. Hematopoietic cells of humans and rodents have been identified using an SRC assay in immunodeficient mouse systems [17, 41, 61, 89]. Subsequently, evidence has been accumulating for the repopulation and development of human immune cells. CD117 and Sca-1 are hematopoietic stem cell (HSC) markers in mice, and CD34 has been revealed to be an HSC marker in humans [22, 56]. CD34 is also expressed on hematopoietic progenitor cell lines in mice [4]. However, HSCs of New World monkeys have not been identified. Therefore, we established an anti-CM CD34 monoclonal antibody and anti-CM CD117 monoclonal antibody, and identified CD117 as a CM HSC marker using these antibodies [29, 33]. Next, we examined if the multipotency and developmental pathway of CM HSCs were similar to those of humans by transplanting the cells into severely immunodeficient NOG mice [27, 55, 78]. CM bone mallow cells were collected from newborn CMs that were abandoned due to a birth of triplets. The cells were stained with monoclonal antibod-

ies, which we established [33], anti-CD117, as a mouse HSC marker, and anti-CD34, as a human HSC marker [24, 48, 56, 59]. The cells were sorted in accordance with the expression of both markers using a cell sorter and subjected to a colony or SRC assay using immunodeficient NOG mice [27, 28, 32, 45]. The engrafted cells were analyzed using flow cytometry, and their engraftment capacity and ability to differentiate were measured. Consequently, we found that (1) CM CD117+ cells developed into erythroid and myeloid lineages when the colony assay was conducted, independent of CD34 expression. (2) The SRC assay revealed that CD117+ cells developed into T cells and B cells in NOG mice. (3) CD117+ cells developed into mast cells both *in vitro* and in NOG mice [55, 78], (4) CD8 T cells but not B cells predominantly developed after HSC transplantation, and (5) multipotency, evaluated by SRC assay, showed that total engraftment in NOG mice after HSC transplantation was enhanced by CD34 expression. No CD4 T cells were observed in the SRC assay. As previously reported, when human HSCs were transplanted into NOG mice, B cell development preceded T cell development, and CD4 T cells and CD8 T cells developed simultaneously [27, 32, 45, 90]. This evidence suggests that the developmental pathways are different between CMs and humans. NOG mice developed not only CM lymphoid cells but also CM myeloid cells, represented by mast cells, early after the transplantation of HSCs into NOG mice [78]. The CM-transplanted NOG mice expressed the cDNAs of various CM cytokines, suggesting that these CM cells were somewhat functional.

A study of HSC development from embryonic stem cells (ESCs) was reported by Sasaki *et al*. [71]. They introduced *Tal1/Scl* genes, which encode essential transcription factors in normal and malignant hematopoiesis in humans [63] into CM ESCs, and found that the cells highly expressed CD34. Although CD34 is not an HSC marker of CMs, according to our results, it is probable that *Tal1/Scl*-transfected ESCs have characteristics of a hematopoietic lineage and contain HSCs. In parallel with these results, Izawa *et al*. (2004) [29] and our group (2008) [78] observed the multilineage differentiation of CD34+ cells in NOD/SCID and NOG mice. Schrimpf *et al*. succeeded in the development of neutrophils from induced pluripotent stem (iPS) cell-derived hematopoietic cells expressing CD34 [75]. The function of CD34 has been studied, and functions correlated with adhesion and proliferation inhibition have been reported [81]. However, the function of CD34 in hematopoiesis has not been completely described until recently. Therefore, it is difficult to interpret the meaning of the differences in CD34 expression among mice, CMs, and humans. The mechanisms of migration and localization of HSCs might be different among species.

On the other hand, immune cells are nearly completely deficient in NOG and NSG mice [27], both of which lack IL-2Rγ signaling in the NOD/SCID background. IL-2Rγ plays a pivotal role in the development of lymphocytes [42]. However, if a mouse has only *IL-2Rγ* gene deficiency [8, 9] but is not bred in the NOD/SCID background, then the effect is less severe, although B cell development is suppressed and T cell development is delayed. Sato and our group established *IL-2Rγ*-knockout (KO) CMs using a genome-editing method and found that *IL-2Rγ*-KO CMs showed a deficiency in IL-2Rγ chain-related cytokine signaling, which induced a less severe immunodeficiency in CMs than in humans, and T cells developed later, similar to findings in *IL-2Rγ*-KO mice [73]. B cells were not observed in adult peripheral blood mononuclear cells (PBMCs) of *IL-2Rγ*-KO CMs. T cells expressed the molecule, which cross-reacted with a human CD56 antibody. Wild-type CMs also expressed a CD56-like molecule, and the expression level of each cell was higher than in KO CMs. Although it is unclear why the cells expressed the CD56-like molecule, these features might be important in CM immune function.

These results suggest that CD117 is expressed on HSCs of CMs, which is similar to mice, but the fact that CD34-expressing cells possess high potential for engraftment indicates a similarity with humans. Therefore, CM IL-2Rγ possesses a function similar to that in mice, although there have been reports of patients with severities of immunodeficiency similar to those observed in mice and CMs [74]. Collectively, in the mouse environment, CM HSCs showed a unique development of lymphoid cells, as B cell development in CMs is delayed compared with that in humans.

Function of Immune Cells

In CM PBMCs, both helper T (Th) cells and cytotoxic T (Tc) cells exist similarly to those in mouse and human PBMCs. However, the ratio of Tc cells tends to be high, as is frequently observed in other NHPs. Most of the cytokines produced by mice and humans are observed in CMs, and the production of the mRNAs is

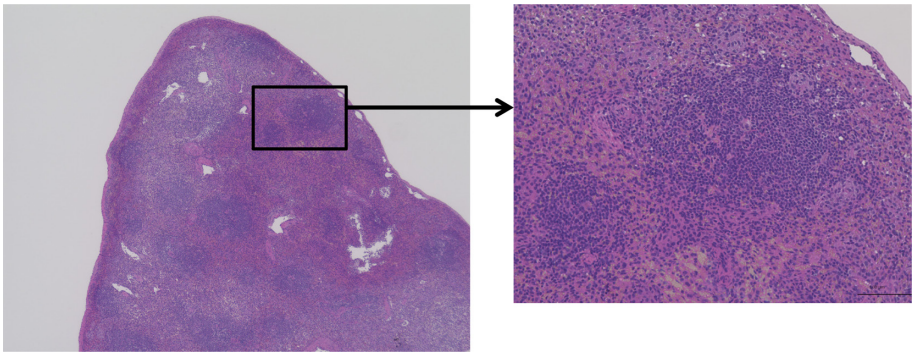

Fig. 2. HE staining of common marmoset spleen tissue. Representative data of a hematoxylin-eosin-stained spleen section (6-year-old female CM). The right panel shows a magnified image of the left panel (black open square). No clear germinal centers were observed in the spleen section.

enhanced after T cell stimulation. CM PBMCs were prepared and stimulated with PMA/ionomycin or the super-antigen toxic shock syndrome toxin-1 (TSST-1) [79]. Before and after stimulation, mRNA levels were measured by quantitative RT-PCR. Consequently, the transcription of most of the cytokines was enhanced [21, 33]. However, in CMs, the increase in *IL-4* mRNA levels was lower than in humans, and the *IFN-γ* levels were higher, suggesting that immunity shifted to cellular immunity or a Th1-type response. From this perspective, the CM cytokine environment preserves a type typical of NHPs and is different from that of modern humans [31].

We also analyzed the phenotype of NK cells [88]. If we accept the cross-reactivity of human anti-CD56 monoclonal antibodies in CMs, CD56 molecules were not expressed on resting NK cells, and after stimulation with IL-2, activated NK cells expressed CD56. These cells also expressed NKG2D and possessed killer activity. These results suggested that NK cells are prepared for activation in the CM immune response. Moreover, there is another class of NK cells, known as uterine NK (uNK) cells, that have no cytotoxic activity but secrete cytokines and are involved in the development of placental cells. They react with unique ligands such as KIR2Dl4 in humans. However, as we described above, genes for *KIR2DL4 orthologs* have not been identified, indicating the absence of this molecule in CMs. These findings suggest that CMs do not preserve the function to remodel blood vessels of the placenta as observed in humans [68]. Thus, CM uNK cells might be different from those of humans and other primates [60].

Normally, humoral immunity involves complements and Igs. Complements are categorized as natural immunity-related molecules, and Igs are categorized as acquired immunity-related molecules. Interestingly, CM plasma contains complement components according to an LC/MS analysis (report in preparation). Moreover, they were detected in the lesions of CMs with experimental autoimmune encephalomyelitis (EAE) [82] Therefore, natural humoral immunity in CMs might be similar to that in other primates and rodents. Moreover, the acquired humoral immunity of CMs is highly unique. The amount of Igs in the plasma is extremely low, as Igs were hardly detected by LC/MS (report in preparation), although a significant amount of B cells was detected in PBMCs. Importantly, IgG was scarcely observed, although some IgM was detected, while human and mouse sera contain detectable levels of IgG. Moreover, germinal centers were not observed in the spleen or lymph nodes (LNs) (Fig. 2), while it is well known that several germinal centers are detectable in the head of the spleen in mice under specific pathogen-free conditions. This evidence is comparable with the findings reported by Quint *et al.* showing that IgG levels were much lower than IgM levels after xeno-stimulation *in vitro*, even if antibody production was somewhat enhanced. Such evidence is not similar to findings for humans and mice [66]. For NHP vaccination models, macaques are usually used because they can secrete antigen-specific IgGs. However, CMs might not be suitable for use as a vaccination model in place of macaques. This does not conflict with the fact that many infection models have been established using CMs but that the vaccinations tested were not effective. Griffiths *et al.* reported vaccination-induced antigen-specific IgM and IgG production,

Table 1. Comparison of immune-related molecules among human/CM/mouse species

	human	CM	mouse	reference for CM	reference for mouse and human (review)
Antigen Recognition limit					
classical MHC class I	HLA-A,B,C	Caja-B, G (?)	H-2K,D,L	[9, 40, 53, 77, 83]	[47, 76]
non-classical MHC class I	HLA-E,F,G	Caja-F,G (?)	Qa-1, 2	[40, 53]	[10, 16, 50, 76]
class II MHC	HLA-DR, DQ	Caja-DRB	I-A, E	[3, 64, 65]	[47, 76]
TCR	(+)	(+)	(+)	[38, 46]	[11]
Serum IgM	(+)	(+)	(+)	[66]	[58]
Serum IgG	(+)	(±)	(+)	[66, 73]	
functional molecules for immune activation					
LILRB1	(+)	(+) predicted	NKG2A	*XM_017967588.1 *XM_017967590.1 *XM_017967591.1 *XM_017967592.1 *XM_017967589.1	[12-14, 52, 67, 68]
LILRB2	(+)	(+) predicted		*XM_017969139.1	
NKG2D	(+)	(+)	(+)	[88]	
KIR2DL4	(+)	(−)	(−)	No predicted sequences were found in NCBI	
complement	(+)	(+)	(+)	[82]	[20, 70]
Differentiation					
HSC marker	CD34	CD117	CD117	[29, 78]	[17, 22, 41, 56, 61, 89]
IL-2Rg KO effect	severe T/B deficiency	B cell deficiency	B cell deficiency	[73]	[8, 9, 74]
B cell /T cell order	B prior to T	simultaneous (CD8Tl)		[78]	[27, 32, 45, 90]

*NCBI reference sequence.

but they also reported that the antigen types that induced an immune response were limited [23]. It is a unique condition compared with conventional primate and rodent acquired immunity. For example, robust antibody production was observed against an anthrax protective antigen and a whole-cell pertussis vaccine, while weaker responses were obtained against cholera and typhoid vaccines. Moreover, the increase in titers was not always extensive. Thus, the overall efficiency of the immune response of CMs might be considered to be significantly lower than in humans.

To investigate the mechanism underlying multiple sclerosis (MS), a CM EAE model was established [34]. After extensive analysis of this useful model, the importance of B cells was suggested by treatment with an anti-human CD20 monoclonal antibody [35], although the model showed a heterogeneous response to the treatment due to its outbred nature. The specific role of B cells in this process has yet to be clarified.

Collectively, immune function in the periphery of CMs might be different from that of humans and mice. They may have a unique function of immune suppression, specifically in their humoral immunity.

Discussion and Perspective

We summarized the characteristics of CM immune factors in Table 1. CM immune function is predicted to be evolutionally intermediate to that of mice and humans as far as the homology of immune-related genes except antigen recognition-related genes (MHC molecules, Igs and TCRs) was concerned. Genes for these antigen-recognizing molecules have evolved uniquely. They have many loci, but their diversity in CMs is rather small compared with that in humans. The nonclassical *HLA-G* ortholog has many loci and is expressed in the body. The developmental process of lymphocytes is also unique, as B cell development is suppressed or delayed in immunodeficient NOG mice compared with that in humans. Moreover, Tc cells tend to be more abundant than Th cells. However, these findings do not conflict with the fact that humoral immunity related to Th2 cytokines is down-regulated in the periphery of CMs. The delay of B cell development and the suppression of Th cells might reduce B cell activation, reducing the secretion of antigen-specific antibodies and class switching of IgM antibodies to IgG and IgE antibodies, resulting in the suppression of IgG-based humoral immunity. Moreover, if

Caja-G, which is expressed throughout the body, induces suppressive signals into immune cells, as does HLA-G, these peripheral immune functions might be suppressed systemically.

This finding might correlate with the uniqueness of pregnancy in CMs, which normally deliver dizygotic twins [25]. The placentae of these twins are fused, and their immune cells are mixed with each other, but no rejection of the two allogeneic sets of tissue is induced [80]. The detailed mechanism for this is unclear. If the CM immune system cannot reject any allogeneic tissues, then fusion and maintenance of the allogeneic placentae may be possible.

This evidence suggests that wild-type CMs in a closed colony may not easily be developed as a model relevant to Th2 immunity. If we need such models, the establishment of Th2 cytokine-overexpressing transgenic CMs, such as *IL-4*-Tg-expressing animals, may help to lead to a breakthrough. Otherwise, we need to more strictly select the target phenomenon or disease. Macaques and other Old World monkeys may have an immune system more closely related to the human immune system. However, the molecules for antigen recognition have diverged from those of humans, like those of CMs. Moreover, fertility is less efficient than in CMs, which is a limitation of Old World monkeys as experimental animals. These findings should be considered when using NHP species. The characteristics of NHPs, including CMs, should be studied in greater detail to select the experimental animals beneficial for the preclinical examination of molecularly targeted drugs.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science by a Grant-in- Aid for Scientific Research (C) (grant number 25430095 to Yoshie Kametani), a Tokai University Grant-in-Aid to Yoshie Kametani (2013–2014), and the MEXT-Supported Program for the Strategic Research Foundation at Private Universities (2012–2016).

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