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Short communication

Are rats more human than mice?

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ABSTRACT

In contrast to rats, mouse models are nowadays generally used for the investigation of immune responses and immune-mediated diseases, there are many different strains and mouse-specific tools available, and it is easy to generate transgenic and constitutive or inducible knockout mice for any gene. Many immune markers and mechanisms have been detected in mice and have been introduced as gold standard in immunology, however, some turned out to be not unconditionally transferable to the human immune system.

Rats have been used more frequently in former days but are mostly outstripped by mice due to the fact that fewer strains are available, they need more space than mice, are more expensive to maintain and breed, and it is extremely difficult to generate transgenic or ko-rats. Consequently, the choice of rat-specific diagnostic tools like antibodies is quite poor and most researchers have switched to mouse models for the investigation of immune mechanisms, while rats are still widely used for toxicology by the pharmaceutical industry. However, it should be taken into consideration that there are some immunological similarities between rats and humans that are not presented in mice. Some of them like MHC class II and Foxp3 expression by activated effector T cells we have detected during our research on the immune response of rat models of experimental autoimmune uveitis.

1. Introduction

Rats, especially Lewis rats are highlysusceptible for the induction of autoimmune diseases, therefore they were also used for the induction of experimental autoimmune uveitis (EAU), an inflammatory disease of the inner eye, which was induced by immunizing Lewis rats with retinal S-Antigen (S-Ag) or interphotoreceptor retinoid-binding protein (IRBP) and complete Freund's adjuvant. They are the best-characterized and most used autoantigens for experimental uveitis (Wacker and Kalsow, 1973; Wacker et al., 1977; de Kozak et al., 1981; Gery et al., 1986; Donoso et al., 1988). The characterization of the most pathogenic epitopes on both molecules allowed us to switch to synthetic peptides as autoantigens, PDSAg (S-Ag, aa 345-354) and R14 (IRBP, aa 1169-1191) (Gregerson et al., 1986; Donoso et al., 1988; Sanui et al., 1989; Wildner and Thurau, 1994; Thurau et al., 2004; Diedrichs-Möhring et al., 2005).

Using these two peptides we detected that they induce different types of disease, immunization with PDSAg induces a clinically monophasic disease that chronically progresses subclinically, inducing the growth of new blood vessels, while immunization with R14 results in a spontaneously relapsing-remitting uveitis (Diedrichs-Möhring et al., 2008; von Toerne et al., 2010; Kaufmann et al., 2012). The latter is a very useful tool to study the effects of therapies in an already ongoing autoimmune response instead of the usual preventive intervention (Diedrichs-Möhring et al., 2015; Huber et al., 2015; Diedrichs-Möhring et al., 2018). Although there are murine models of relapsing disease, they can only be induced in strains that are different from acute models. In the rat model of EAU the different disease courses are induced in the same strain, allowing for comparison of immunological mechanisms and gene regulation far beyond genetic background differences. When we started to analyze the underlying immune mechanisms of monophasic/chronic and relapsing-remitting uveitis, we first investigated the differences in gene- and protein-expression of T cell lines specific for these two peptides (von Toerne et al., 2010; Wildner and Kaufmann, 2013; Diedrichs-Möhring et al., 2018). We found expression differences in 29 genes and/or proteins, 28 were up-regulated in R14-specific T cells (relapsing EAU), and only vascular endothelial growth factor (VEGF) was secreted by PDSAg-specific, but not R14-specific T cells. The latter explains the neovascularization observed in the later phase of PDSAg- induced EAU, since no new vessel growth is seen in R14-induced uveitis (Diedrichs-Möhring et al., 2015; Diedrichs-Möhring et al., 2018). IFN-γ turned out to play a crucial role in relapsing disease, and all regulated genes in R14-specific T cells

Abbreviations: APC, antigen-presenting cell; BRB, blood-retina-barrier; EAU, experimental autoimmune uveitis; Foxp3, forkhead box protein 3; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IFN, interferon; IRBP, interphotoreceptor retinoid-binding protein; MHC, major histocompatibility complex; NKT, natural killer T cells; RPE, retinal pigment epithelium; S-Ag, retinal soluble antigen; TCRT, cell receptor; Teff, effector T cell; Treg, regulatory T cell; VEGF, vascular endothelial growth factor

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belong to different signal transduction pathways up- or downstream of IFN-γ. Among the regulated genes we found upregulation of MHC class II molecules (RT1.B, the rat equivalent of HLA-DQ and RT1.D equivalent to HLA-DR) and Foxp3 on both, mRNA and protein expression levels, in activated, R14-specific T cells inducing relapses. These observations can only be made with human and rat T cells, but not in mice, and it should be taken into consideration that for the investigation of certain immune mechanisms rat models are more useful than mice, since they are better representing the human situation. In addition, the rats provide the opportunity to investigate two typical courses of human autoimmune diseases, a chronic progressive and a relapsing-remitting type, in the same strain; and we can dissect the immune responses directed against two different autoantigen peptides, which is not feasible in mice, since they only respond to one autoantigen/-peptide in EAU.

2. Activated T cells in humans and rats, but not in mice, express MHC class II molecules

It is already known for decades that, in addition to professional antigen-presenting cells (APC) like dendritic cells and macrophages, also B and T cell can express MHC class II. The class II expression of T cells was primarily found on activated human T cells (Diedrichs and Schendel, 1989; Gansbacher and Zier, 1989; LaSalle et al., 1992; Taams et al., 1999) and later also on rat, but not mouse T cells (Wildner et al., 2004; von Toerne et al., 2010; Wildner and Kaufmann, 2013). The function of class II expression by T cells is not yet clear. The potential antigen-presentation of T cells to other T cells is lacking accessory molecules and induces anergy rather than activation of the antigen-recognizing T cell. This led to the hypothesis that antigen-presentation from T cell to T cell via MHC class II might play a regulatory role (LaSalle et al., 1992). Recently, Hua et al. showed in an in vitro suppression assay that human T cells expressing HLA-DR had the highest suppression index and the highest impact to suppress the cytokine genes of Th1, 2 and 17 cells (Hua et al., 2015).

We have contributed to this hypothesis with data from autoantigen peptide-specific γδ TCR+ cells, induced by oral application of antigen in rats. We have used oral tolerance as a treatment for experimental autoimmune uveitis and found that γδ T cells play a pivotal role as regulatory cells in oral tolerance, since their adoptive transfer can suppress uveitis in the recipient rats (Wildner et al., 1996, 2004). Moreover, we have shown that these γδ T cells proliferate in vitro in response to activated, irradiated αβ TCR+ cells and the respective antigen peptide, but not to a control peptide. Interestingly, this proliferation could be inhibited by antibodies to the CD8α and β chains (the γδ T cells were CD8+), but also with an antibody (Ox6) to the peptide-presenting rat MHC class II molecule RT1.B, which blocks the recognition of the presented antigen (Fig. 1A). The antibody blocking the non-presenting MHC class II molecule RT1.D had no inhibitory effect on the proliferation of the regulatory γδ T cells. The anti-rat γδ TCR antibody V65 has a stimulatory rather than inhibitory effect on T cells, therefore we could not block the γδ TCR to prove whether it recognizes the peptide antigen. Peptide recognition by γδ T cells has been described in several cases, but so far, the evidence that the γδ TCR recognizes antigen presented by MHC is missing (Born et al., 2011). The proliferation of γδ T cells was inhibited by antibodies against CD8α and CD8β chains, which would suggest a recognition of the peptide antigen presented on MHC class I, however, Straube and Hermann have shown that the structure of the CDR3 region of the γδ TCR prevents its binding to MHC class I (Straube and Herrmann, 2000). Furthermore, blocking MHC class II molecules by antibodies also inhibited the peptide-specific proliferation of the γδ T cells. These data would point to the γδ T cell recognition of the specific antigen peptide presented by MHC class II of the activated effector T cells. It is not yet proven how the γδ TCR sees its peptide antigen on the antigen-specific αβ T cells, the inhibitory effect of anti-CD8 and anti-MHC class II could be due to steric inhibitions of

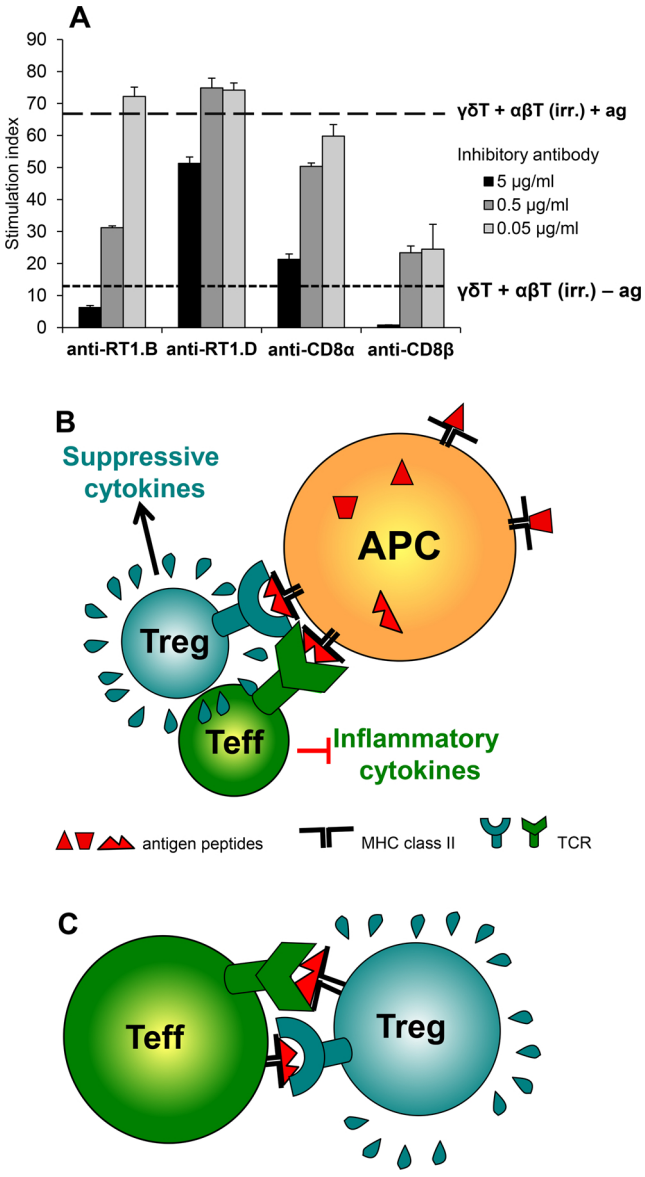

Fig. 1. A) Lewis rats were orally tolerized with retinal autoantigen peptide PDSAg; regulatory γδ-T cells were isolated from spleens of tolerized rats and coincubated with PDSAg-activated, irradiated αβ TCR+ effector-T cells and peptide of PDSAg. Antibodies to rat MHC class II RT1.B (HLA-DQ equivalent) and RT1.D (HLA-DR equivalent) and to the CD8α or CD8β chain were added to the cultures in various concentrations (Wildner et al., 2004). Anti-CD8β most efficiently inhibited proliferation of γδ T cells, followed by anti-RT1.B, which blocks the PDSAg-presenting MHC class II molecule. Also anti-CD8α could inhibit the proliferation of γδ T cells, while addition of anti-RT1.D had only a marginal effect. The dotted lines show the γδ T cell proliferation in response to αβ T cells and the antigen (upper line), or the co-incubation of γδ T cells with αβ T cells without addition of antigen (lower line). We have previously shown that γδ T cells can proliferate in response to αβ T cells with the same antigen specificity even without addition of the antigen, since they seem to present the antigen peptide they have taken up during previous restimulations. B) Treg and Teff present antigen to each other. Activation of the Treg by antigen presented on the MHC class II of the effector cell, resulting in the production of suppressive cytokines or induction of anergy of the effector T cell by recognizing antigen presented by the Treg. Even both mechanisms could be used simultaneously. C) Hypothesis: antigen-recognition of effector (Teff) and regulatory T cells (Treg). Teff and Treg in close vicinity both see antigen presented by (the same?) professional APC, resulting in bystander regulation by suppressive cytokines secreted from the Tregs.

molecule complexes within the lipid raft but might not be directly involved in the specific antigen recognition.

The function of CD8αβ is – besides a stabilization of the MHC/peptide/TCR complex – thought to contribute to the recruitment of the TCR/CD3 complex to the lipid raft (Arcaro et al., 2001; Parel and Chizzolini, 2004). Huang et al. have reported that especially CD8αβ can bind to MHC class I in a TCR- and peptide-independent manner, underlining its role in the raft (Huang et al., 2007). So far, we can only speculate that blocking CD8 disrupts the interaction between CD8 and MHC I and weakens the interaction between the responding and presenting T cells, disturbing the recognition of the antigen peptide.

The direct interaction between effector and regulatory cell might be a clue for the antigen-specific regulation, since the usual idea is that effector and regulatory cells would see the same antigen presented by a conventional APC, ideally being in close vicinity at this APC to gain an efficient down regulation of the effector cell by suppressive cytokines secreted from the neighboring regulatory T cell (Treg) (Fig. 1B, C). The mutual antigen presentation is easy to explain when both, Teff and Treg are activated αβ TCR + cells expressing antigen-presenting MHC class II molecules.

These observations could never be made in mouse models, since activated mouse T cells do not express MHC class II molecules. Therefore, the rat models are very important to further investigate the role of direct T-T interactions for an antigen-specific regulation of T cell responses, especially for in vivo experiments.

3. Only activated T cells of humans and rats transiently express Foxp3

Fifteen years ago, the transcription factor Foxp3 was first published to be expressed in regulatory T cells, and it was a highly desired marker to distinguish regulatory from effector T lymphocytes (Teff) (Hori et al., 2003; Kasprowicz et al., 2003). The idea mainly came from the IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), presenting multiorgan human autoimmune diseases, allergy and inflammatory bowel disease, and is genetically determined and X-linked. A mouse strain, Scurfy, which displays similar symptoms, has shown mutations in the transcription factor Foxp3, and also patients with IPEX syndrome carry mutations in the gene coding for this molecule. These findings started the era of Foxp3 as the primary marker of regulatory cells, followed by many publications of experiments mainly performed in mice. However, already 2 years after the first publication of Foxp3 as a Treg marker Morgan et al. showed that Foxp3 is not an exclusive marker for regulatory T cells, but in humans also transiently expressed in activated effector T cells (Morgan et al., 2005), which was later confirmed by others (Gavin et al., 2006; Allan et al., 2007; Pillai et al., 2007; Wang et al., 2007; Kmieciak et al., 2009). Since it was not found in mice and thus could not be experimentally reproduced in vivo, this finding from the human system was widely ignored, and the proof of Foxp3-expression was demanded to identify Tregs for the following years.

Another three years later activated, autoimmune rat T cells were investigated for gene and protein expression, and they also expressed Foxp3, demonstrated by qPCR and Western blot (von Toerne et al., 2010; Wildner and Kaufmann, 2013). Thus, it turned out to be difficult to distinguish between just activated effector cells and regulatory T cells by Foxp3-expression only, when tissue-resident T lymphocytes from target organs during autoimmune diseases were investigated (Kaufmann et al., 2012). Foxp3 expression that defines Treg activity needs to sustain within a cell but looking at Foxp3 expression by intracellular staining of a freshly isolated cell is only a snapshot of the cell's life and does not allow any prediction on its fate and its assignment to any cell type, and in addition, effector T cells also express CD4 and CD25, the other commonly used Treg markers.

In a rat model of monophasic experimental autoimmune uveitis, where the disease shows only one clinically visible course of intraocular inflammation, Foxp3 + cells in the affected eyes slightly but significantly increase from onset via peak disease to resolution. In contrast, Foxp3-expressing T cells from the eyes of spontaneously relapsing uveitis in rats are lowest at peak disease and high (about 7% of all intraocular lymphocytes) at onset, resolution and during the relapses (Kaufmann et al., 2012). So, it can be speculated whether the increasing Foxp3 + cells in the monophasic disease are regulatory cells, while the increased numbers of Foxp3-expressing cells during resolution and relapses are probably representing both, Teff and Treg cells.

Ectopic expression of Foxp3 has been described in tumor-infiltrating T cells as well as in tumor cells but can also be observed at the anatomical border to the immune privileged organ eye. Retinal pigment epithelium (RPE) cells, which are part of the blood-retina-barrier (BRB) and protect the eye from spontaneous incursions and more or less accidental attacks of the immune system, have immunoregulatory abilities (Takenaka et al., 2013; Busch et al., 2017). RPE cells belong to the outer BRB, which is an educational barrier, converting aggressive cell types to a repairing, friendly phenotype (Shechter et al., 2013). Cocultivation of lymphocytes with RPE cells has induced Foxp3 expression in T cells, converting them to Tregs that could help maintain the immune privilege of the eye (Vega et al., 2010; Imai et al., 2012). Moreover, we have recently shown expression of Foxp3 in RPE cells, so far only in humans and rats. Stressed (here: treated with the anaphylatoxins C3a or C5a) human RPE cells in vitro show expression of Foxp3, and also rat RPE cells in inflamed eyes with uveitis can upregulate Foxp3 (Busch et al., 2017). The function of this ectopic Foxp3 expression is not yet clear, and so far we can only speculate that the Foxp3 expression in RPE cells could be induced by autocrine activation of the RPE with TGF-β, which is produced by these cells (Tran, 2012; Ogawa et al., 2014).

4. Human and rat CD4 + /CD8 + macrophages

The first evidence for CD4-expression on human monocytes/macrophages was published in the early 1980ies (Moscicki et al., 1983), which gained more interest when CD4 turned out to be an essential component of the HIV receptor and thus could explain why these cells serve as a reservoir for HI virus (Dalgleish et al., 1984). So far, the immunological function of the CD4 molecule on monocytes/macrophages is not elucidated, but meanwhile also the expression of CD8 and even coexpression of CD4 and CD8αβ are detected on human and rat, but not mouse macrophages (Crocker et al., 1987; Baba et al., 2006; Gibbings et al., 2007; Gibbings and Befus, 2009). Coexpression of CD4 and CD8 is usually observed on T cells in the thymus during T cell maturation, but also in the periphery, mainly on activated human and rat T cells e.g. in autoimmune diseases (Parel and Chizzolini, 2004; Huber et al., 2015). We have shown TCRαβ + and TCRγδ + cells from mesenteric lymph nodes of rats with experimental autoimmune uveitis that coexpress CD4 and CD8 expanded upon autoantigen stimulation in vitro (Huber et al., 2015).

The lineage assignment of cells expressing molecules regarded typical for T cells has further been undermined after human and mouse macrophages were found with surface expression of T cell receptors and recombination of their TCR genes (Chávez-Galán et al., 2015). The latter argues against a simple membrane acquisition of TCR from T cells during cell-cell contact (Fuchs et al., 2013; Kaminski et al., 2013; Fuchs et al., 2015). TCRs consisting of αβ or γδ chains are found on macrophages, they are associated with the CD3 complex and their activation leads to different responses, depending on the expressing cell type and the recognized antigen/activated TCR. TCR expression is not only a feature of macrophages, but also detected on neutrophil and eosinophil granulocytes. These TCRs are variable and there is no restricted use of certain TCR chains as found in NKT cells (Beham et al., 2011).

T cells can recognize antigen presented on MHC molecules of other T cells, so maybe macrophages could also present antigen to each other and recognize it via their TCR. Macrophages coexpressing CD4 and CD8

could recognize antigen presented on MHC class I and II molecules and might be the counterpart of crosspresenting APCs. All these mechanisms are lacking in the mouse.

5. Discussion

The validity of animal models for human diseases and/or therapeutic approaches is always under discussion. There is no doubt that animal models are very important for the investigation of complex interactions of cells, soluble factors and various organs (immune or non-immune), since there is no possibility to fully imitate the induction and regulation of an organ-specific (auto)immune response with the interaction of different cells of the immune system and the target organ in vitro. However, the choice of the animal model is crucial and often dependent on its availability and the questions to be answered. In autoimmune diseases the questions concerning immune regulation are a major challenge, and especially for this topic models should be chosen that are closest to the human situation. Due to their lack of MHC class II-expression on T cells, mouse models exclude the direct, antigen-specific interaction between the T lymphocytes, which we could previously describe as a mechanism of antigen-specific interaction between effector and regulatory T cells in rats.

Transient expression of Foxp3 and its ectopic expression on RPE cells that are part of the border between immune system and the immune privileged eye might be a clue that goes far beyond the function of Foxp3 as a simple marker of regulatory T cells. Thus, Foxp3 expression might enable any cells (also tumor cells) to downregulate aggressive immune responses in their vicinity.

The coexpression of CD4 and CD8 molecules on macrophages with a cytotoxic phenotype defines a new cell type that could be a left over from the evolution of the immune system and might be a link between innate and adaptive immunity, located between macrophages, NK cells and/or cytotoxic T cells, an "ancient" cell type that is still found in rats and humans, but is probably lost in mice. Whenever only mouse models are considered for the investigation of immune regulation, certain reactions or mechanisms cannot be seen and taken into consideration and could lead to bad surprises e.g. when therapeutic approaches aiming at immune regulation are transferred to patients.

Conflict of interest

None.

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