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Knock-out of the histidine decarboxylase gene modifies the repertoire of natural autoantibodies

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Abstract

Natural antibodies (NA) are antibodies produced in the absence of known immunization with specific antigens. NA are found in the blood of healthy humans and mice. Histamine influences many aspects of the immune response, including antibody production. However, the role of histamine in the generation of NA has not yet been studied. In this work, we used an ELISA assay to characterize the self-antigen binding repertoires of NA in wild type (WT) mice and in histidine decarboxylase knock-out (HDC-KO) mice, unable to synthesize histamine. We now report that HDC-KO and WT mice differed in the patterns of autoreactivity of their IgM and IgG NA. The NA in HDC-KO sera manifested a larger repertoire of IgM autoantibodies than did the WT sera. The self-antigens bound by IgM from HDC-KO mice included structural proteins, enzymes associated with cellular metabolism, double-stranded and single-stranded DNA, and tissue-specific antigens like insulin. There were relatively fewer differences in the NA repertoire of IgG autoantibodies of the mice: notably, the HDC-KO sera reacted with glutamic acid decarboxylase (GAD), an antigen associated with autoimmune diabetes. These results demonstrate that endogenous histamine can influence the self-reactivity of the NA repertoire.

Keywords: Autoantibodies; Histamine; Histidine decarboxylase knock-out; Autoimmunity

1. Introduction

Healthy humans and mice harbour natural antibodies (NA), immunoglobulins reactive with self or foreign molecules detectable in the absence of immunization with the target antigens [1]. Human and murine NA are thought to perform several functions, recently reviewed by Lacroix-Desmazes et al. [2]. These functions include the control of autoreactivity and immune homeostasis in healthy individuals [2–7]. NA can be found in the cord blood of newborns suggesting that their synthesis is independent of stimulation by foreign antigens [8,9] and is controlled by genetic factors [8–11]. In addition, an individual's specific repertoire of NA might reflect susceptibility to develop certain autoimmune diseases [12,13]; we, for example, have found that NA IgG to the self-antigen acetylcholine receptor indicates susceptibility to the induction of experimental autoimmune myasthenia gravis (EAMG) [12]. The mechanisms, however, which regulate the NA repertoire are not fully understood.

Histamine is synthesized from L-histidine by an enzymatic reaction catalyzed by the L-histidine decarboxylase (HDC) enzyme. We have recently developed a histidine decarboxylase knock-out (HDC-KO) mouse, which exhibits HDC and histamine levels close to zero in almost all its organs [14]. Moreover, the specialized secretion granules that store histamine in mast cells seem to be empty or present smaller granular contents in

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Table 1
Antigens used

Group	Function/structure	Antigen	Antigen number	Catalogue
Cellular structure	Cytoskeleton	Actin	1	A3653
		Tubulin	2	T4925
		Myosin	3	M6643
		Tropomyosin	4	T4770
		Vimentin	5	V4383
	Extracellular matrix	Fibronectin	6	F0895
		Collagen I	7	C7774
		Collagen II	8	C7806
		Collagen III	9	C4407
		Collagen IV	10	C7521
		Collagen V	11	C3657
		Heparin	12	H2149
		Laminin	13	L6274
		Collagenase	14	C9891
Cellular membranes	Phospholipids	Cardiolipin	15	C5646
		Glucocerebroside	16	G9884
		Phosphatidylethanolamine	17	P9137
		Cholesterol	18	C1145
Cellular metabolism	Glucose	Enolase	19	E0379
		Aldolase	20	A8811
		Acid phosphatase	21	P1774
	Apoptosis	Annexin 33 kDa	22	A9460
		Annexin 67 kDa	23	A2824
		Cytochrome P450C	24	C3131
	Monooxigenases	Catalase	25	C9322
		Peroxidase	26	P6782
		Tyrosinase	27	T 7755
	Others	Ribonuclease	28	R4875
Nucleus	Protein DNA	Histone II A	29	H 9250
		DsDNA	30	D1501
		SsDNA	31	D1501
Plasma proteins	Carriers	Transferrin	32	T4132
		Fetuin	33	F2379
		Human serum albumin	34	A8763
		Bovine serum albumin	35	A9647
		Ovoalbumin	36	A5378
	Coagulation	Factor II	37	F5132
		Factor VII	38	F6509
		Fibrin	39	F5386
		Fibrinogen	40	F4883
	Complement	C 1	41	C2660
		C 1 q	42	C0660
Immune system	Cytokines	Interleukin 2	43	I2644
		Interleukin 10	44	I9276
		Interleukin 4	45	I4269
	Antibodies	Human IgG	46	I8640
		Human IgM	47	I8260
Tissue antigens	Heat shock	HSP60	48	[a]
	Proteins	p277	49	[b]
		HSP70	50	[c]
	Islet antigens	GAD	51	G2126
		Insulin	52	I0259
	CNS	Human MOG	53	[d]
		Human MOG p94–116	54	[d]
		Murine MOG	55	[d]
		Rat MOG p35–55	56	[d]
		MBP	57	[e]
		Brain extract	58	B1877
	Muscle and skeleton	AchR	59	[f]
		Myoglobulin	60	M6036
		Cartilage extract	61	C5210
	Thyroid	Thyroglobulin	62	T1001
	Blood cells and platelets	Hemoglobin A	63	H0267
		Spectrin	64	S3644

Table 1 (*continued*)

Group	Function/structure	Antigen	Antigen number	Catalogue
Pathogens	Proteins and peptides	TB PPD	65	[g]
		HSP65	66	[h]
		pEC27	67	[i]
		pMt278	68	[j]
		GST	69	[a]
		KLH	70	[k]
		Pepstatin	71	P5318
		pR13	72	[l]
	Others	LPS	73	L3755
Synthetic polymers	Poly amino acids	Poly arginine	74	P3892
		Poly lysine	75	P4408
		Poly aspartic	76	P6762
		Poly glutamic	77	P4636
	Oligonucleotides	Poly A	78	[m]
		Poly T	79	[n]
		Poly C	80	[o]
		Poly G	81	[p]
		Poly ATA	82	[q]
		Poly TAT	83	[r]

The name, number, catalogue number of Sigma (Rehovot, Israel) and source of each of the antigens used are indicated.

[a] Purified as described [51].
[b] p277: VLGGGVALLRVIPALDSLTPANED.
[c] Recombinant human HSP70 was purchased from StressGen (San Diego, CA, USA), catalogue number SPP-755.
[d] Kindly provided by Prof. Avraham Ben Nun, The Weizmann Institute, Israel. Human MOG p94–116: GGFTCFFRDHSYQEEAAMELKVE, rat MOG p35–55: MEVGWYRSPFSRVVHLYRNGK
[e] Kindly provided by Dr Felix Mor, The Weizmann Institute, Israel.
[f] Kindly provided by Prof. Sara Fuchs, The Weizmann Institute, Israel.
[g] Produced at the Statens Seruminstitut, Copenhagen, Denmark.
[h] Kindly provided by Prof. Ruurd van der Zee, University of Utrecht, The Netherlands.
[i] pEC27: KKARVEDALHATRAAVEEGV.
[j] pMt278: EGDEATGANIVKVALEA.
[k] Purchased from Pierce (Oud Beijerland, The Netherlands), catalogue number 77153.
[l] pR13: EEEDDDMGFGLFD.
[m] Poly A: A_{20}.
[n] Poly T: T_{20}.
[o] Poly C: C_{20}.
[p] Poly G: G_{20}.
[q] Poly ATA: $AT_{18}A$.
[r] Poly TAT: $TA_{18}T$.

HDC-KO mice [14]. Compared to wild type (WT) mice, HDC-KO mice display changes in their levels of IL-6 and the IL-6 receptor [15], acute phase proteins [16], development of mast cells [17] and osteoclasts [18], histamine receptor expression [19], and androgen hormone [20].

Histamine is involved in the regulation of several aspects of the immune response, including antibody production following immunization [21–23]. However, the role of histamine in the generation of NA has not yet been studied. In this work, we analyze the role of histamine in the generation of the NA repertoire.

2. Materials and methods

2.1. Mice

The generation of the HDC-KO strain has been described elsewhere [14]. Three- to four-month-old male or female wild type (WT) and HDC-KO mice (both with the CD1/129sv background) were used in the experiments. HDC deficient ($HDC^{-/-}$) and wild type ($HDC^{+/+}$) animals were litter-mates in a segregating F2 population, and were fed a histamine-free diet. Serum samples from five animals per group were collected from the retro-bulbar venous plexus and stored at −20 °C until tested.

2.2. Antigen set

The antigens used in these studies are shown in Table 1. These antigens were chosen from among the proteins, nucleotides and phospholipids reported to interact with autoantibodies. The antigens are classified in different groups according to their cellular localization, tissue distribution or function in the organism.

2.3. Measurement of total serum IgM and IgG

Since the individual antibody reactivities were measured by an ELISA assay, we tested whether the WT and HDC-KO mice differed in their total IgM and IgG levels using a capture ELISA procedure. Briefly, flat-bottom microtiter plates (Maxisorb, Nunc, Denmark) were coated with unlabelled antibodies specific for IgM or IgG (Jackson ImmunoResearch, USA). Non-specific binding to the ELISA plates was blocked with bovine serum albumin (BSA) 1%, and the serum samples were added for incubation at a 1/100 dilution for 3 h at 37 °C. Bound IgM or IgG antibodies were detected using mouse IgM or IgG-specific detection antibodies conjugated to alkaline phosphatase (Jackson ImmunoResearch, USA) together with a substrate for alkaline phosphatase (Sigma, Rehovot, Israel). The total IgM or IgG values are expressed as the readings of optical density at 405 nm.

2.4. Study of the repertoire of serum IgM and IgG antibodies

The serum levels of autoantibodies directed against a panel of antigens previously described by Quintana et al. [13] were determined by ELISA as described [13,24]. Serum levels of anti-cholesterol antibodies or antibodies against human 70 kDa heat shock protein (HSP70) were measured as described previously [25,26].

The results represent the mean ± SD of three independent assays; each assay was done in duplicate. The average variation of OD values between assays of the same sera on different days was less than 10%. The background OD obtained in antigen-free wells incubated with sera was subtracted from each experimental value. When appropriate, threshold cut-off values were calculated. We used threshold values of 0.4 and 0.3 for IgM and IgG antibodies, respectively.

2.5. Statistical analysis

Differences between mean values of antibodies between different mouse strains were calculated by the unpaired *t*-test by using the GraphPad Prism V 3.00 for Windows software package (GraphPad Software, San Diego, CA, USA).

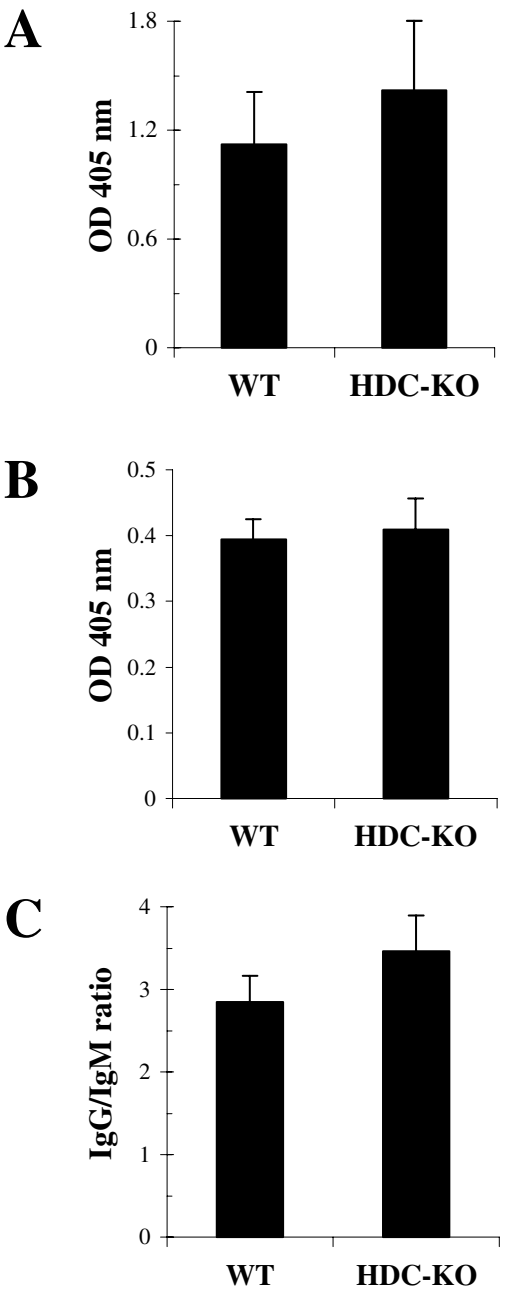

Fig. 1. Total serum IgM and IgG antibody levels in HDC-KO and WT mice. The levels of total IgM (A) and IgG (B) antibodies were compared by a capture ELISA method, and the IgG to IgM ratio (C) was computed. The antibody levels are expressed as OD units at 405 nm; the results are presented as the mean (±SD) of each experimental group (n=5).

3. Results

3.1. Total serum IgM and IgG in HDC-KO and WT mice

The total levels of serum IgM or IgG in HDC-KO and WT mice were compared using a capture ELISA procedure. Fig. 1 shows that there were no significant differences in the levels of total IgM or IgG, nor in the IgG/IgM ratio between the two strains of mice. Thus, the endogenous levels of histamine do not affect the total levels of serum IgG or IgM detectable in the ELISA assay we used.

3.2. Repertoire of IgM NA in HDC-KO and WT mice

Fig. 2 shows the reactivity of serum IgM from HDC-KO and WT against the panel of antigens listed in

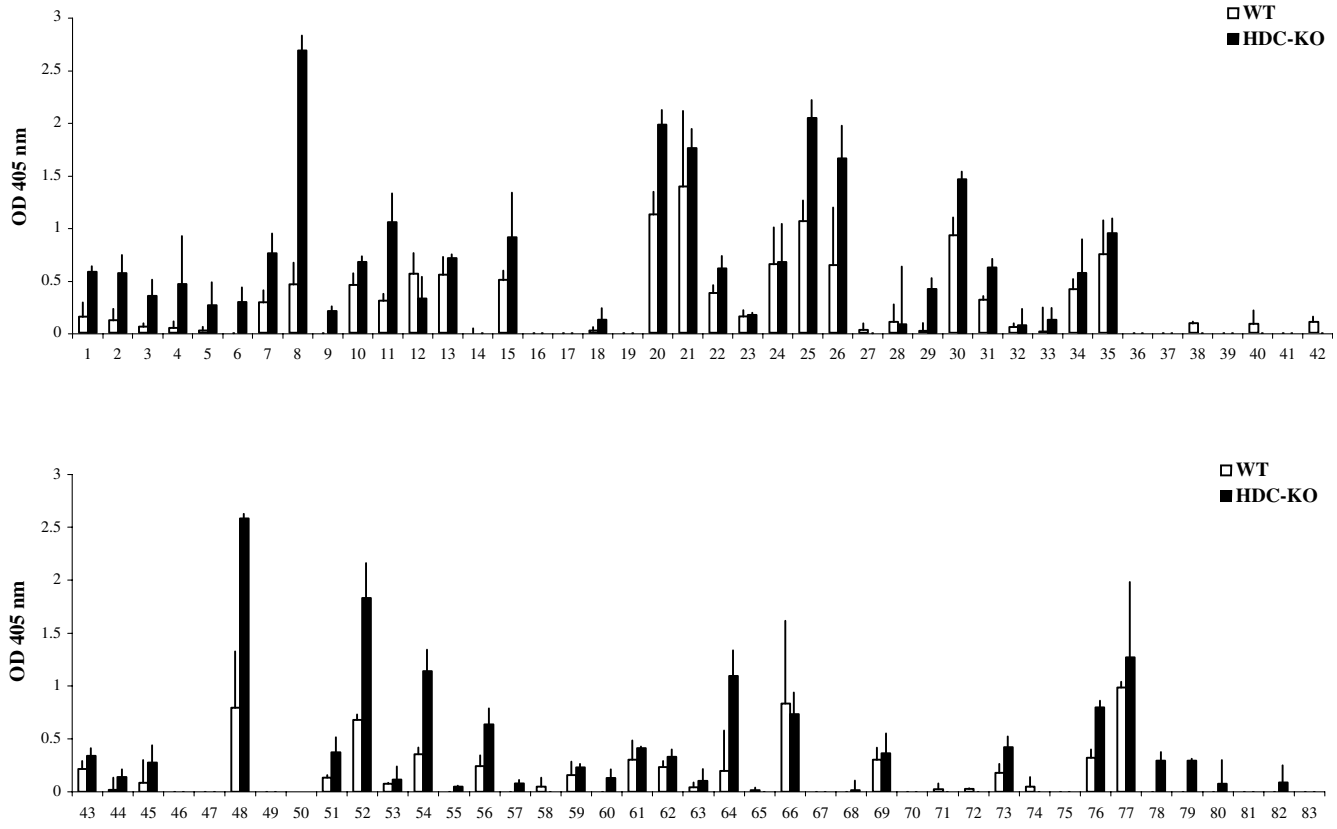

Fig. 2. Natural serum IgM antibodies from HDC-KO and WT mice.

Table 2
Serum IgM autoantibodies in wild type (WT) and histidine decarboxylase knock out (HDC-KO) mice

Group	Antigen	Mean OD 405 nm ± SD		
		WT	HDC-KO	*P* value
Structural components	Collagen I	0.30 ± 0.12	0.76 ± 0.19	0.0016
	Collagen II	0.46 ± 0.21	2.68 ± 0.14	<0.0001
	Collagen V	0.31 ± 0.07	1.05 ± 0.27	0.0004
Cellular metabolism	Aldolase	1.13 ± 0.21	1.98 ± 0.14	<0.0001
	Catalase	1.06 ± 0.2	2.04 ± 0.17	<0.0001
	Peroxydase	0.64 ± 0.55	1.66 ± 0.31	0.0068
Nucleous	dsDNA	0.31 ± 0.04	0.62 ± 0.09	0.0002
	ssDNA	0.92 ± 0.17	1.46 ± 0.07	<0.0001
	HSP60	0.79 ± 0.53	2.58 ± 0.05	<0.0001
	Insulin	0.68 ± 0.05	1.83 ± 0.33	<0.0001
Tissue antigens	Human MOG p94–116	0.35 ± 0.07	1.14 ± 0.20	<0.001
	Rat MOG p35–55	0.24 ± 0.24	0.64 ± 0.15	0.0152
	Spectrin	0.20 ± 0.38	1.09 ± 0.25	0.0022
Synthetic polymers	Poly aspartic	0.32 ± 0.08	0.78 ± 0.01	<0.0001

dsDNA, double stranded DNA; ssDNA, single stranded DNA; HSP, heat shock protein; GAD, glutamic acid decarboxylase; rat MOG p35–55, peptide 35–55 of rat myelin oligodendrocyte glycoprotein; human MOG p94–116, peptide 94–111 of human myelin oligodendrocyte glycoprotein.

Table 1. Table 2 summarizes the significant differences in the mean OD values (± SD) of the IgM NA detected in the sera of HDC-KO and WT mice. In the cell structure group of antigens, serum IgM levels to collagen I, II and V and were significantly higher in the HDC-KO mice than in the WT mice, whereas no significant differences in their IgM autoantibodies against other antigens of the structural components group were found. Significant differences in IgM levels between the KO and WT mice were found in three out of the ten antigens of the cellular metabolism group: aldolase, catalase and peroxidase. Antibodies binding to both double-stranded or

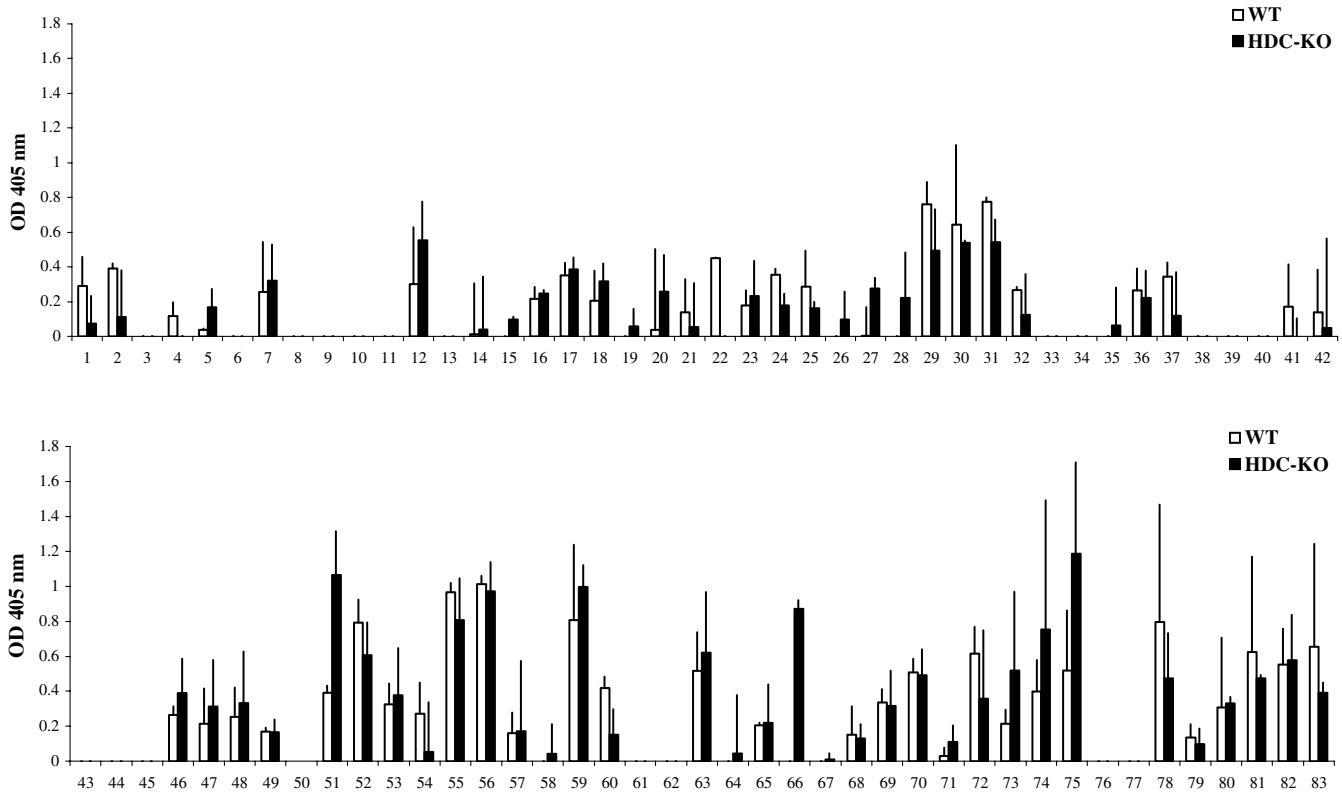

Fig. 3. Natural serum IgG antibodies from HDC-KO and WT mice.

Table 3
Serum IgG autoantibodies in wild type (WT) and histidine decarboxylase knock out (HDC-KO) mice

Group	Antigen	Mean OD 405 nm ± SD		
		WT	HDC-KO	*P* value
Cellular metabolism	Annexin 33	0.45 ± 0.01	0	0.004
Tissue antigens	GAD	0.39 ± 0.04	1.06 ± 0.25	0.0003
Pathogens	HSP65	0	0.88 ± 0.05	<0.0001

HSP65, mycobacterial 65 kDa heat shock protein.

single-stranded DNA were significantly higher in the HDC-KO than in the WT mice. Six other antigens also showed significantly higher levels of autoantibodies in HDC-KO mice: HSP60, insulin, rat MOG p35–55, human MOG p94–116, spectrin and poly aspartic. Overall, IgM autoantibodies were more prevalent in the HDC-KO mice.

3.3. Repertoire of IgG NA in HDC-KO and WT mice

The study of IgG NA revealed a different situation (Fig. 3 and Table 3). Significant differences between HDC-KO and WT mice were found related to only two autoantigens (annexin 33 and GAD), and to *Mycobacterium tuberculosis* HSP65. WT mice showed higher levels of antibodies to annexin 33, while HDC-KO mice manifested higher levels of IgG antibodies to the two other antigens.

4. Discussion

Our present findings indicate that endogenous histamine does not influence the total levels of serum IgM and IgG (Fig. 1), but has a marked effect on the repertoire of murine NA (Figs. 2 and 3, Tables 2 and 3). This effect is most prominent in the IgM repertoire. Serum levels of IgM autoantibodies are significantly higher in HDC-KO mice for 14 antigens, whereas only the levels of IgG autoantibodies to annexin 33, GAD and HSP65 were modified in HDC-KO mice.

Four histamine receptors have been described. Histamine receptor type-1 (H1R) and histamine receptor type-2 (H2R) have been both shown to mediate the effects of histamine on the immune response (reviewed in [21,23]), however, little information is available about the role played by the histamine receptors type-3 or type-4 in immunity. Moreover, it is difficult to achieve complete and long lasting elimination of histamine in vivo by the administration of HDC blockers like α-fluoromethyl histamine (α-FMH), as discussed by Ohtsu and co-workers [14,27]. We have therefore studied the influence of histamine on the repertoire of NA using HDC-KO mice, to cover the physiological

activities of histamine mediated by all of its receptors. In addition, our approach should not be biased by histamine receptor activation triggered by yet unknown endogenous ligands, different from histamine.

Direct and indirect mechanisms might be the cause of the altered NA repertoire of HDC-KO mice. Histamine has direct effects on B-cell activation [28,29]. However, only certain autoantibodies were modified in the HDC-KO mice NA repertoire (Figs. 2 and 3, Tables 2 and 3), but not the total levels of IgM or IgG (Fig. 1). Contrary to what has been shown for the mast cell compartment [14,17,30], endogenous histamine does not influence the whole B-cell compartment. Its effects are rather antigen specific and strikingly restricted to autoantibodies; the antibodies directed against non-self antigens were not affected.

How could then histamine modify the levels of autoantibodies? At the moment we can only speculate. The interaction with self-antigens seems to be necessary for the induction of mature B-cell clones [31]. Thus, the effects of NA might be due to modification of the levels or site of expression of certain self antigens, and/or the modification of the DC that activate antigen-specific T [32] or B [33–35] cells. Indeed, histamine has been shown to modify surface expression of co-stimulatory molecules and dendritic cell function [36–39], and our preliminary results suggest that HDC-KO mice have an enhanced ability to present self-antigens (László et al., unpublished observations). Further studies should study the mechanism of action of histamine in the NA repertoire, including serum samples taken from H1R or H2R to pinpoint the contribution of the signalling pathway associated with each of these receptors.

High levels of IgG autoantibodies might reflect a high frequency of activated autoimmune T cells. HDC-KO mice show increased levels of IgG NA to GAD (Fig. 3, Table 3). Moreover, HDC-KO mice have high serum leptin and insulin levels and impaired glucose tolerance [20]. Immunity to GAD characterizes type I insulin-dependent diabetes mellitus in the human [40], and spontaneous [41] and cyclophosphamide-accelerated diabetes [42] in NOD mice. Thus, higher levels of IgG antibodies to GAD in HDC-KO mice might reveal an increased susceptibility to autoimmune diabetes. Indeed, natural IgG autoantibodies have been associated with susceptibility to induced or spontaneous autoimmune diseases [12,13,24].

However, note that no spontaneous autoimmune disease was observed in the HDC-KO mice, suggesting that the GAD-reactive B and Tcells of the natural repertoire are efficiently controlled by regulatory mechanisms [43–45]. The onset of autoimmune disease is a complex mechanism that involves both the induction of pathogenic immunity and the overcoming of regulatory mechanisms. Several experimental procedures have been shown to elicit the autoimmune potential of animals prone to develop autoimmune disease. We are currently studying the susceptibility to low-dose streptozotocin diabetes of HDC-KO mice [46]. Further studies in HDC-KO mice might shed light on the mechanisms that control or trigger autoimmune disease.

HDC-KO mice also had significantly higher levels of IgM NA binding to 16 self-antigens (Fig. 2, Table 2). Natural IgM autoantibodies have been implicated in immune regulation [1,47,48], and IgM deficiency predisposes to the development of IgG autoantibodies [49]. But, on the other hand, increased IgM levels might indirectly facilitate the induction of IgG autoantibodies, since they probably reflect higher frequencies of activated autoreactive B cells. Indeed, natural IgM antibodies have been shown to facilitate the induction of IgG antibodies upon immunization [50]. The biological significance of the increased levels of IgM antibodies in HDC-KO mice is not known and requires further investigation.

Nevertheless, our work demonstrates that histamine influences the repertoire of NA; changes in the endogenous levels of histamine might be reflected as changes in the repertoire of NA. Thus, the detailed characterization of the repertoire of natural autoantibodies in humans, the immunological homunculus [3,4], may lead to the identification of patterns of autoantibodies associated with increased susceptibility to allergy, even before the onset of any anaphylactic reaction.

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