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REVIEW

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The major histocompatibility complex of the rat (*Rattus norvegicus*)

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Abstract This review of the *RT1* complex, the major histocompatibility complex (MHC) of the rat, focuses on genetic, genomic, evolutionary, and functional aspects at the molecular level. The class I, class II, and framework genes are listed. The physical map of the *RT1* complex as revealed by analysis of clonal contigs is compared with the human and mouse MHC, and the degree of orthologous relationship is outlined. Elucidation of the *RT1* complex provides important information for using the rat as a model of experimental transplantation and complex diseases.

Keywords MHC · Rat · Evolution · Disease models · Transplantation

The major histocompatibility complex (MHC) of the rat (*Rattus norvegicus*), the *RT1* complex, has been detected in the course of serological and transplantation studies (Aizawa et al. 1965; Bogden and Aptekman 1960; Křen et al. 1960; Palm 1962). Histocompatibility research was a major stimulus to analyze this gene system and to establish inbred, *RT1* congenic, and *RT1* recombinant strains. Further major findings on the functional role of the rat MHC were the control of antigen-specific immune responsiveness (Würzburg 1971) and of disease susceptibility, first shown for experimental allergic encephalomyelitis (EAE) (Gasser et al. 1973; Williams and Moore 1973).

Like the MHC of other species (Parham 1999), the *RT1* complex represents a group of closely linked genes, among which the class I and class II genes are the most characteristic. These genes function by presenting antigenic peptides, and thereby control antigen-specific, adaptive immune responses. Further genes of the MHC control antigen processing and loading or play a role during antigen-nonspecific and innate reactions of the immune system. Numerous other genes are also located in the MHC that do not appear to be involved in immune responsiveness.

The *RT1* complex is of particular interest because the rat plays a dominant role in experimental transplantation and provides several very useful disease models. Furthermore, it contributes to phylogenetic understanding of the MHC. The best-studied examples are the MHC of human and mouse. Rat and mouse represent two related species that diverged about 20–40 million years ago, as determined by molecular data (Kumar and Hedges 1998; O'hUigin and Li 1992). The evolutionary distance to humans is about 100 million years, although a more rapid evolutionary change is assumed to occur in rodents compared to primates and has to be taken into account (Li et al. 1990).

This review will focus on the genomic, molecular, and comparative aspects of the rat MHC, paying particular attention to the homologous systems, *H2* in the mouse and *HLA* in humans.

The *RT1*-carrying chromosome

The *RT1* complex has been assigned to rat chromosome (RNO) 20 (Locker et al. 1990) and fine-mapped by fluorescence in situ hybridization to the telomeric part of the short arm of this chromosome (Helou et al. 1998; Fig. 1a). The orientation of the *RT1* complex with respect to the centromer is the same as for the *H2* and *HLA* complexes. Differences are found for the genes flanking the MHC (Fig. 1b). Thus *Cryaa* maps centromeric from the MHC in rat and mouse, but to a different chromosome, HSA21q22.3, in human (Hawkins et al. 1987). *RFP*, *HFE*, and the histone cluster are located telomeric from the MHC in humans, but are found on RNO17 and MMU13 in the rat and mouse, respectively. Genetic, radiation hybrid (RH) and combined maps of RNO20 have been published (Dracheva et al. 2000 http://www.nih.gov/niams/scientific/ratgbase/index.htm;

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Kawahito et al. 1998b; Masuyama et al. 2000; McCarthy et al. 2000 http://www.well.ox.ac.uk/rat_mapping_resources; Steen et al. 1999 http://rgd.mcw.edu/maps/; Watanabe et al. 2000 http://ratmap.ims.u-tokyo.ac.jp/). Sets of congenic strains are available in which the *RT1* complex has been isolated on different genetic backgrounds such as ACI, BN, DA, LEW, PVG, or WKA (Hedrich 1990b).

Genetic structure and polymorphism of the *RT1* complex

The genetic structure of the rat MHC has been elucidated on the basis of *RT1* recombinant haplotypes that were identified in segregating hybrids of established inbred strains (Figs. 1b, 2). Some recombinations have served to distinguish certain regions in the *RT1* complex. The major regions (Figs. 1b, 2) are *RT1-A* (the centromeric class I region), *RT1-B/D* (the class II region), class III region, and *RT1-C/E/M* (the telomeric class I region). The latter has been divided into *RT1-C/E* (also called *RT1-C/E/grc*) and *RT1-M* on the basis of recombination r38 (Lambracht et al. 1995). Most recombinations turned out not to define exactly the classical class I, II, and III regions. For example, recombinations that were initially thought to separate the class III and *RT1-C/E* regions could be later fine-mapped into the class III region itself (Fig. 2). MHC regions corresponding to the centromeric class I, class II, class III and telomeric class I regions are found in the same order in the mouse, and, excepting the rat- and mouse-specific centromeric class I region, in the human MHC as well (Fig. 1b).

Among the more than 200 inbred rat strains (Hedrich 1990b; http://ratmap.gen.gu.se/ratfesting/strainframe.html) a limited number of different standard *RT1* haplotypes such as *a*, *b*, *c*, *d*, *f*, *g*, *h*, *k*, *l*, *m*, *n*, *q*, *s*, or *u*, and derivative *RT1* haplotypes ("natural recombinants") like *e*, *i*, *j*, *o*, or *p* have been defined on the basis of serological and histogenetic typing (Hedrich 1990a). They represent combinations of standard *RT1-A* regions (*a*, *b*, *c*, *d*, *f*, *g*, *h*, *k*, *l*, *m*, *n*, *q*, *s*, *u*) and standard *RT1-B/D* regions (*a*, *b*, *c*, *d*, *f*, *h*, *k*, *l*, *m*, *n*, *u*) (Hedrich 1990a). In $RT1^{o}$, for example, $RT1\text{-}A^{d}$ and $RT1\text{-}B^{a}D^{a}$ are combined. Histogenetic analysis of strains that initially appeared to be *RT1* identical by RT1-A and RT1-B/D typing often revealed mutual histoincompatibility that could be assigned to the *RT1-C/E/M* region, so that *RT1* variant haplotypes can

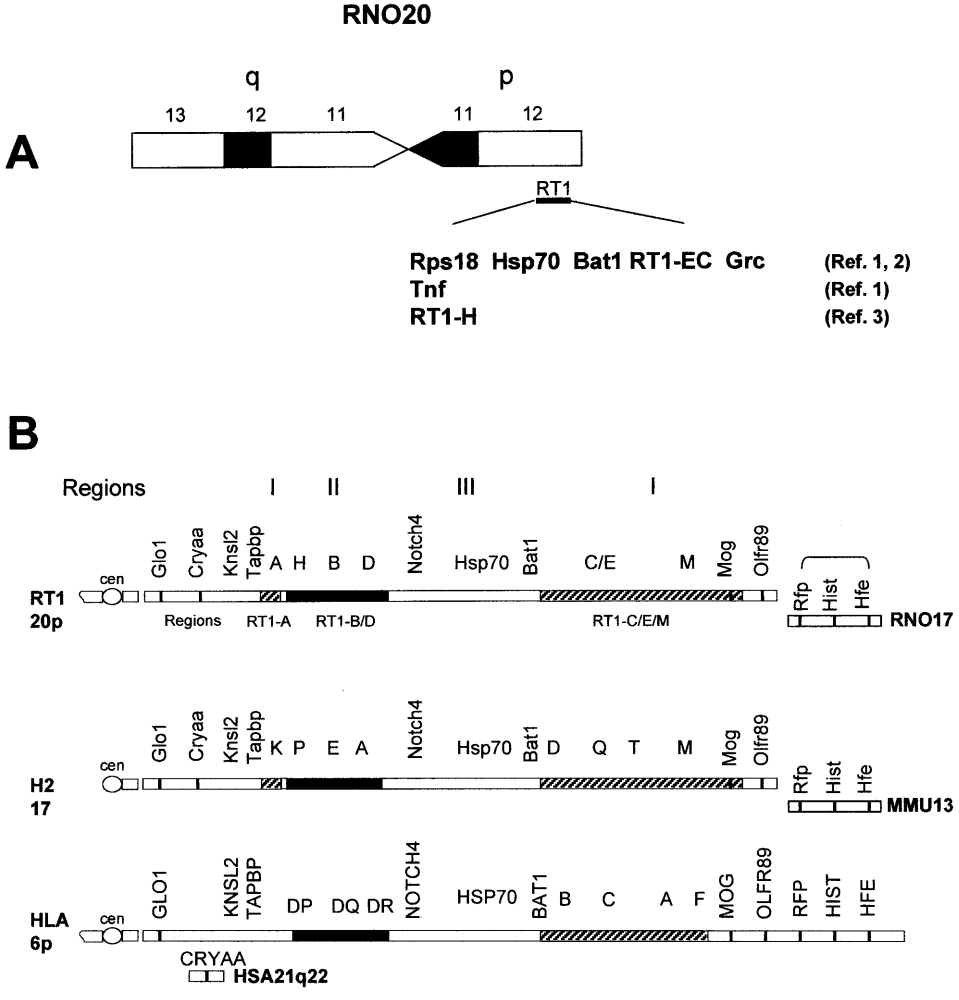


Fig. 1a,b Cytogenetic localization and schematic structure of the rat MHC. **a** Chromosome RNO20, localization of the *RT1* complex (*bar*) and of genes that have been located to the MHC by fluorescence in situ hybridization (FISH) (*Ref. 1, 2* Helou et al. 1998, 1999; *Ref. 3* Andoh et al. 1998). *D20Kyo3* (Andoh et al. 1998) and *Glp1r* (Szpirer et al. 2000) have been also mapped to RNO20p by FISH, but their relative cytogenetic position to the MHC genes is not known. **b** Comparative scheme of the MHC chromosomal regions in rat, mouse, and human. Included are genes that are useful for demarcation of MHC regions. The *bracket* indicates that the order of *Rfp* (Szpirer et al. 1997), histone genes (indicated as Hist) (Walter et al. 1996a, 1996b) and *Hfe* (Table 1) is not yet known in the rat. The scheme is not to scale and the telomeric class I region is not subdivided into class I and framework gene clusters as in Figs. 2, 3, and 4

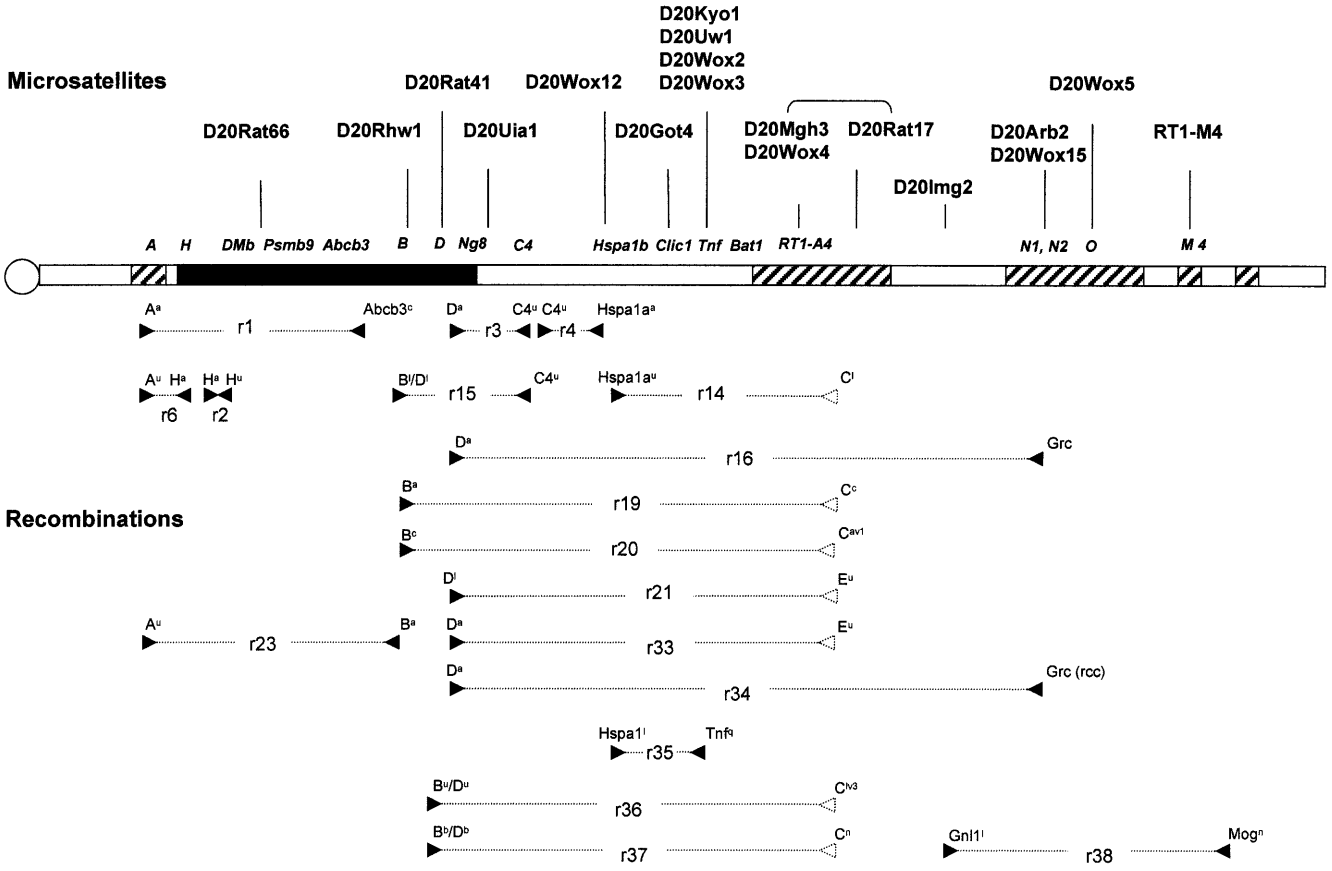


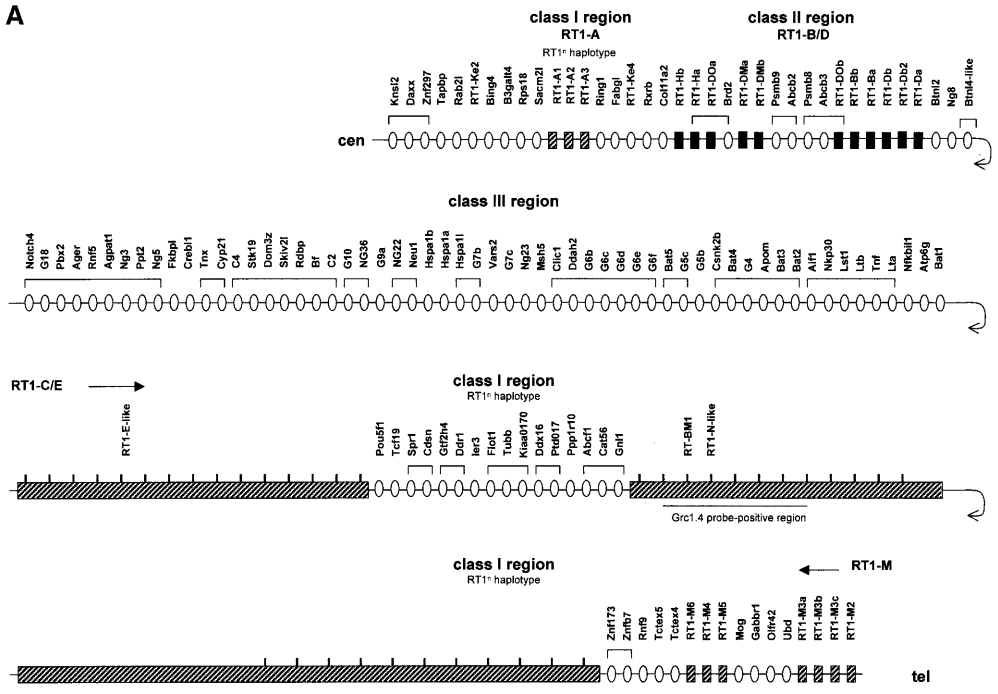
Fig. 2 Genetic structure of the *RT1* complex with the positions of microsatellites and some intra-*RT1* recombinations. For references of *D20Rhw1* and *Tnf* markers see http://ratmap.gen.gu.se. Microsatellites *D20Arb2* (Kawahito et al. 1998b), *D20Got4*, *D20Rat17*, *D20Rat41*, *D20Rat66*, *D20Uia1* (Masuyama et al. 2000), *D20Mgh3*, *D20Wox4*, *D20Wox5* (Watanabe et al. 1999), *D20Wox12*, *D20Wox15* (Gauguier et al. 1999), *D20Img2* (Ioannidu et al. (2001), and that in the *RT1-M4* gene (Lambracht-Washington et al. 1998) have been mapped according to the position of the gene sequence (see Fig. 3) from which the microsatellite sequence was derived or by direct P1-derived artificial chromosome (PAC) mapping (Ioannidu et al. 2001). *D20Mgh3* and *D20Wox4* are identical, except for an incomplete overlap of the 3′ primer. Similarly, *D20Arb2* and *D20Wox15* refer to the same microsatellite, and the primers overlap partially. The position of *D20Rat17* relative to *D20Mgh3*/*D20Wox4* is not known as indicated by the *bracket*. It is noteworthy that *D20Mgh3*, *D20Wox4*, *D20Arb2*, *D20Wox4*, and *D20Rat17* might occur at several positions in the *RT1-C/E* region due to duplication (Ioannidu et al. 2001; own unpublished data). The microsatellite in sequence X67504 ("clone G8") derived from the *RT1-C113* gene (Rothermel et al. 1993) and described by Fakhrai-Rad and co-workers (1999) is found at several positions in the *RT1-A* and *RT1-C/E* regions. Microsatellites *D20Rat46*, *D20Rat71*, and *D20Got2* have been co-localized with *Tnf* by linkage analysis (Masuyama et al. 2000), but have not yet been assigned genomically. The scheme is not to scale. *Triangles* at the ends of *dotted lines* indicate the maximal range where the respective recombination could be mapped; an *open symbol* indicates that this position could not yet be assigned to a precisely mapped gene (for references see Günther 1996)

be distinguished. For example haplotype $RT1^{av1}$ of DA rats is an *RT1-C/E/M* variant of the $RT1^{a}$ haplotype of LEW.1A rats, and $RT1^{lv1}$ of F344 is an *RT1-C/E/M* variant of $RT1^{l}$ of LEW rats. Furthermore, Southern blot analysis showed that several strains assumed to be *RT1-C/E/M* identical differ for the *RT1-M* region at the telomeric end of the rat MHC (Lambracht et al. 1993).

Studies of wild rats designed to examine the degree of *RT1* polymorphism under natural conditions are rare. Serological and mixed lymphocyte reaction typing as well as determination of *RT1*-controlled immune responsiveness to synthetic polypeptides indicated that allelic diversity of class I and class II genes is restricted, and that the class Ia and class II gene products detected by these typing methods in wild rats closely resembled those known from standard inbred strains (Cramer et al. 1978; Günther 1979; Shonnard et al. 1976, 1979). No sequence-based information about class I and class II gene polymorphism is available for wild rats.

Genomic organization of the *RT1* complex

A synopsis of the present physical map of the rat MHC is depicted in Fig. 3. It incorporates data obtained from different *RT1* haplotyes by pulsed-field gel electrophoresis (Carter et al. 1994; Lund et al. 1994; Vardimon et al. 1992) and by analyses of phage clones (Arimura et al. 1995a, 1995b), cosmid clonal contigs (Diamond et al.



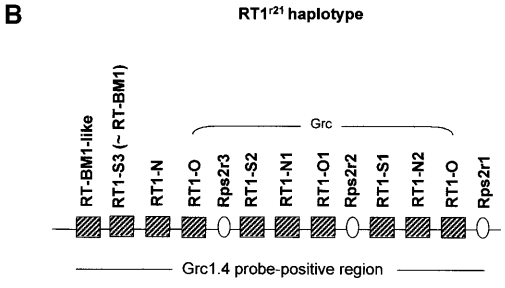
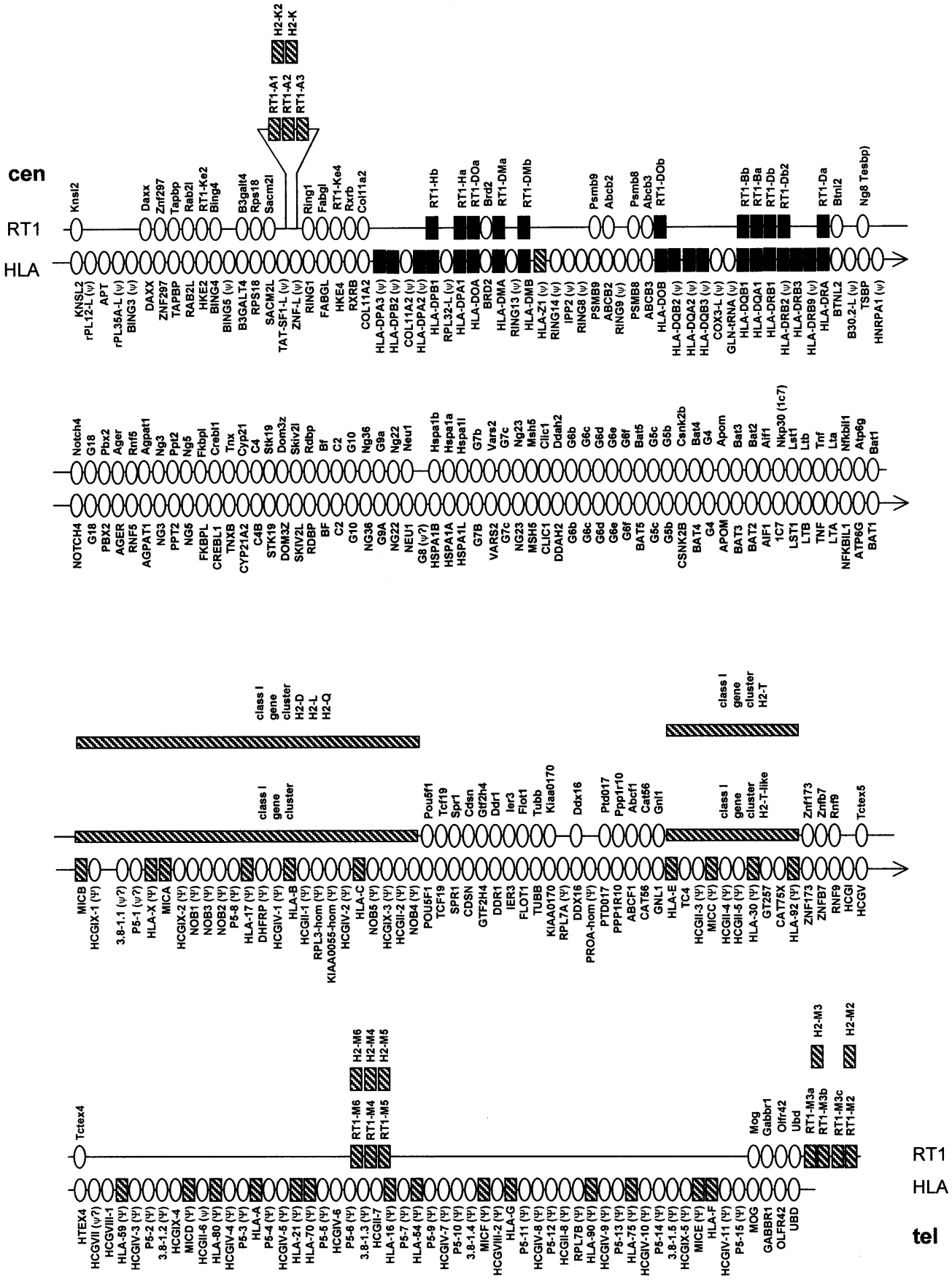


Fig. 3a, b Preliminary physical map of the *RT1* complex. The size of the regions is roughly to scale, but distances between genes are not. The individual genes are listed in Table 2. *Oval symbols* represent framework genes, *striped symbols* indicate class I genes (*RT1-A*) or regions of class I exon 4 cross-hybridizing sequences (symbolized by *spikes* on the striped bars), *black rectangles* represent class II genes. *Brackets* indicate that exact relative positions of these genes are not yet known. In the case of *Btnl4*, several copies appear to be present. **a** *RT1* complex. The scheme summarizes data from different sources and *RT1* haplotypes, but is mainly based on the results obtained with the PAC library of $RT1^n$ origin. The number of class I genes varies between haplotypes; presence of three *RT1-A* class I genes is $RT1^n$ haplotype specific (see text). The sources of the data are: *Knsl2* to *RT1-DMb*, PAC contig (Walter and Günther 2000); *RT1-Hb* to *RT1-DOa*, phage clones ($RT1^u$) (Arimura et al. 1995a) and PAC contig (L. Walter and co-workers, unpublished data); *RT1-DOb* to *RT1-Da*, cosmid contigs ($RT1^{av1}$, $RT1^c$; Diamond et al. 1989) and PAC contig (L. Walter and co-workers, unpublished data); *Notch4* to *Tnf*, pulsed-field gel electrophoresis analysis (Lund et al. 1994) and PAC contig (L. Walter and co-workers, unpublished data); *Tnf* to *RT1-M2*, PAC contig (Ioannidu et al. 2001) and yeast artificial chromosome clones ($RT1^{lv1}$) (Lambracht et al. 1995, 1997; Lambracht-Washington et al. 1999). **b** *Grc* region. Genomic structure of the *RT1-C/E* interval that includes the *Grc* region, based on a cosmid contig of the $RT1^{r21}$ haplotype (Salgar et al. 1997; Yuan et al. 1999b)

1989; Jameson et al. 1992; Yuan et al. 1999a), yeast artificial chromosome (YAC) clones (Lambracht et al. 1997; Lambracht-Washington et al. 1999) and, in particular, a P1-derived artificial chromosome (PAC) clonal contig that encompasses the entire rat MHC of the $RT1^n$ haplotype (Ioannidu et al. 2001; Walter and Günther 2000; L. Walter et al., unpublished data). On the basis of these data, the physical length of the complete *RT1* complex is expected to be 3–4 Mb, similar to the mouse and human MHC. The availability of large-insert YAC libraries from inbred strains F344 ($RT1^{lv1}$; Haldi et al. 1997) and SHRSP ($RT1^k$; Cai et al. 1997), as well as PAC (Woon et al. 1998) and BAC (http://www.chori.org/bacpac/) libraries from inbred strain BN ($RT1^n$) has contributed decisively to large-scale genomic analysis of the rat MHC.

The *RT1-A* region has been cloned as part of a PAC contig of about 300 kb that is anchored in the class II region (Walter and Günther 2000). The class II and class III regions have been partially described by cosmid clone analysis (Diamond et al. 1989) and pulsed-field gel electrophoresis (Carter et al. 1994; Lund et al. 1994), and a complete PAC contig of both regions has now been established (L. Walter and co-workers, unpublished data). For the *RT1-C/E/M* region, several YAC contigs have been described (Lambracht-Washington et al. 1999), and this region has been cloned completely in a single PAC contig (Ioannidu et al. 2001). It encompasses at least 2 Mb from *Bat1* to *Mog* and includes additional *RT1-M* genes telomeric from *Mog* (Fig. 3a). The genomic structure of a part of the *RT1-C/E* region, designated Grc, has been analyzed by cosmid clones of the $RT1^{r21}$ haplotype (Yuan et al. 1999a) and is shown in Fig. 3b.


cen
RT1
HLA
H2-K2
H2-K
RT1-A1
RT1-A2
RT1-A3
Knsl2
Daxx
Znf297
Tapbp
Rab2l
RT1-Ke2
Bing4
B3galt4
Rps18
Sacm2l
Ring1
Fabgl
RT1-Ke4
Rxrb
Col11a2
RT1-Hb
RT1-Ha
RT1-DOa
Brd2
RT1-DMa
RT1-DMb
Psmb9
Abcb2
Psmb8
Abcb3
RT1-DOb
RT1-Bb
RT1-Ba
RT1-Db
RT1-Db2
RT1-Da
Btnl2
Ng8 Tesbp)
KNSL2
rPL12-L (ψ)
APT
rPL35A-L (ψ)
BING3 (ψ)
DAXX
ZNF297
TAPBP
RAB2L
HKE2
BING4
BING5 (ψ)
B3GALT4
RPS18
SACM2L
TAT-SF1-L (ψ)
ZNF-L (ψ)
RING1
FABGL
HKE4
RXRB
COL11A2
HLA-DPA3 (ψ)
HLA-DPB2 (ψ)
COL11A2 (ψ)
HLA-DPA2 (ψ)
HLA-DPB1
RPL32-L (ψ)
HLA-DPA1
HLA-DOA
BRD2
HLA-DMA
RING13 (ψ)
HLA-DMB
HLA-Z1 (ψ)
RING14 (ψ)
IPP2 (ψ)
RING8 (ψ)
PSMB9
ABCB2
RING9 (ψ)
PSMB8
ABCB3
HLA-DOB
HLA-DQB2 (ψ)
HLA-DQA2 (ψ)
HLA-DQB3 (ψ)
COX3-L (ψ)
GLN-tRNA (ψ)
HLA-DQB1
HLA-DQA1
HLA-DRB1
HLA-DRB2 (ψ)
HLA-DRB3
HLA-DRB9 (ψ)
HLA-DRA
BTNL2
B30.2-L (ψ)
TSBP
HNRPA1 (ψ)
Notch4
G18
Pbx2
Ager
Rnf5
Agpat1
Ng3
Ppt2
Ng5
Fkbpl
Creb1
Tnx
Cyp21
C4
Stk19
Dom3z
Skiv2l
Rdbp
Bf
C2
G10
Ng36
G9a
Ng22
Neu1
Hspa1b
Hspa1a
Hspa1l
G7b
Vars2
G7c
Ng23
Msh5
Clic1
Ddah2
G6b
G6c
G6d
G6e
G6f
Bat5
G5c
G5b
Csnk2b
Bat4
G4
Apom
Bat3
Bat2
Aif1
1C7
Nkp30 (1c7)
Lst1
Ltb
Tnf
Lta
Nfkbil1
Atp6g
Bat1
NOTCH4
G18
PBX2
AGER
RNF5
AGPAT1
NG3
PPT2
NG5
FKBPL
CREBL1
TNXB
CYP21A2
C4B
STK19
DOM3Z
SKIV2L
RDBP
BF
C2
G10
NG36
G9A
NG22
NEU1
G8 (ψ?)
HSPA1B
HSPA1A
HSPA1L
G7B
VARS2
G7C
NG23
MSH5
CLIC1
DDAH2
G6b
G6c
G6d
G6e
G6f
BAT5
G5c
G5b
CSNK2B
BAT4
G4
APOM
BAT3
BAT2
AIF1
1C7
LST1
LTB
TNF
LTA
NFKBIL1
ATP6G
BAT1
class I gene cluster H2-D H2-L H2-Q
class I gene cluster H2-T
class I gene cluster
class I gene cluster H2-T-like
Pou5f1
Tcf19
Spr1
Cdsn
Gtf2h4
Ddr1
Ier3
Flot1
Tubb
Kiaa0170
Ddx16
Ptd017
Ppp1r10
Abcf1
Cat56
Gnl1
Znf173
Znfb7
Rnf9
Tctex5
MICB
HCGIX-1 (Ψ)
3.8-1.1 (ψ?)
P5-1 (ψ?)
HLA-X (Ψ)
MICA
HCGIX-2 (Ψ)
NOB1 (Ψ)
NOB3 (Ψ)
NOB2 (Ψ)
P5-8 (Ψ)
HLA-17 (Ψ)
DHFRP (Ψ)
HCGIV-1 (Ψ)
HLA-B
HCGII-1 (Ψ)
RPL3-hom (Ψ)
KIAA0055-hom (Ψ)
HCGIV-2 (Ψ)
HLA-C
NOB5 (Ψ)
HCGIX-3 (Ψ)
HCGII-2 (Ψ)
NOB4 (Ψ)
POU5F1
TCF19
SPR1
CDSN
GTF2H4
DDR1
IER3
FLOT1
TUBB
KIAA0170
RPL7A (Ψ)
DDX16
PROA-hom (Ψ)
PTD017
PPP1R10
ABCF1
CAT56
GNL1
HLA-E
TC4
HCGII-3 (Ψ)
MICC (Ψ)
HCGII-4 (Ψ)
HCGII-5 (Ψ)
HLA-30 (Ψ)
GT2B7
CAT75X
HLA-92 (Ψ)
ZNF173
ZNFB7
RNF9
HCGI
HCGV
Tctex4
RT1-M6
RT1-M4
RT1-M5
H2-M6
H2-M4
H2-M5
Mog
Gabbr1
Olfr42
Ubd
RT1-M3a
RT1-M3b
RT1-M3c
RT1-M2
H2-M3
H2-M2
HTEX4
HCGVII (ψ?)
HCGVIII-1
HLA-59 (Ψ)
HCGIV-3 (Ψ)
P5-2 (Ψ)
3.8-1.2 (Ψ)
HCGIX-4
MICD (Ψ)
HCGII-6 (ψ)
HLA-80 (Ψ)
HCGIV-4 (Ψ)
P5-3 (Ψ)
HLA-A
P5-4 (Ψ)
HCGIV-5 (Ψ)
HLA-21 (Ψ)
HLA-70 (Ψ)
P5-5 (Ψ)
HCGIV-6
P5-6 (Ψ)
3.8-1.3 (Ψ)
HCGII-7
HLA-16 (Ψ)
P5-7 (Ψ)
HLA-54 (Ψ)
P5-9 (Ψ)
HCGIV-7 (Ψ)
P5-10 (Ψ)
3.8-1.4 (Ψ)
MICF (Ψ)
HCGVIII-2 (Ψ)
HLA-G
P5-11 (Ψ)
HCGIV-8 (Ψ)
P5-12 (Ψ)
HCGII-8 (Ψ)
RPL7B (Ψ)
HLA-90 (Ψ)
HCGIV-9 (Ψ)
P5-13 (Ψ)
HLA-75 (Ψ)
HCGIV-10 (Ψ)
P5-14 (Ψ)
3.8-1.5 (Ψ)
HCGIX-5 (Ψ)
MICE (Ψ)
HLA-F
HCGIV-11 (Ψ)
P5-15 (Ψ)
MOG
GABBR1
OLFR42
UBD
RT1
HLA
tel

In human, the *KNSL2* (*HSET*) gene (Fig. 1b) is presently often taken as the centromeric end of the MHC (Stephens et al. 1999; The MHC Sequencing Consortium 1999), because of the break of syntenic homology between mouse and human and changes in chromatin structure found near *KNSL2*. Furthermore, with this boundary definition, the *TAPBP* gene, whose product is involved in peptide loading of class I molecules, is still included in the MHC. The interval between *KNSL2* and the classical class II region, which starts with the *HLA-DP* genes, is called the extended class II region in humans. The boundary between the class II and class III regions is assigned to *NOTCH4*, and that between the class III and class I regions to *BAT1*. The telomeric border of the human MHC is usually assigned to *HLA-F*, mapping close to *MOG*, or to the class I-like *HFE* gene about 4 Mb telomeric from *HLA-F*. The *MOG/HFE* interval is also called the extended class I region (or extended MHC) in humans.

The structure of the rat and mouse MHC is superimposable on the human MHC with respect to *Knsl2*, the *RT1-H* genes (orthologous to the *HLA-DP* and *H2-P* genes), *Notch4*, *Bat1*, and *Mog* (Figs. 1, 4). At variance with humans, the extended class II region of the rat and mouse harbors the centromeric class I region, *RT1-A* and *H2-K*, respectively. Furthermore, the telomeric part of the MHC differs between the rat and mouse compared to humans. In the rat and mouse, but not humans, class I genes are found immediately telomeric from *Mog* (Fig. 3a), and most of the extended class I region as defined in humans is not located on the MHC-bearing chromosome but on RNO17 and MMU13, respectively (Fig. 1b).

Figure. 3a shows that the class I genes occur in clusters which are embedded in between groups of genes, most of which are unrelated to the immune system. The latter genes have also been called framework or anchor genes (Amadou 1999). This architecture is found for the *RT1-A* region, located between *Sacm2l* and *Ring1*, and in the *RT1-C/E/M* region, where at least four class I clusters and respective framework gene subregions can be distinguished. The first class I cluster is located between *Bat1* and *Pou5fl*, the second between *Gnl1* and *Znf173*, the third between *Tctex4* and *Mog*, and the fourth extends telomerically from *Ubd* (Fig. 3). In the mouse, the class I genes are found similarly grouped together in four clusters (Amadou et al. 1999) that are located in the same genomic intervals as in the rat MHC (Fig. 4). In the *HLA* class I region, the class I genes occur also only in distinct subregions that are again defined by the *BAT1*/*POU5FL*, *GNL1*/*ZNF173*, and *HTEX4*/*MOG* genes as in the rat and mouse (Fig. 4). The reason for this conserved pattern is not clear. The class I gene-carrying genomic intervals might have been particularly receptive for the class I genes that evolved there, undergoing further expansion and contraction due to duplication and unequal crossover.

A number of polymorphic microsatellites, which are useful markers for genetic analysis, have been fine-mapped in the *RT1* complex as shown in Fig. 2.

Several *RT1* framework genes or the corresponding expressed sequence tags (ESTs) have been mapped in RHs. Of note is that the gene order obtained by RH mapping (http://ratmap.ims.u-tokyo.ac.jp/cgi-bin/Mapview_rat.pl?RNO20, http://ratest.eng.uiowa.edu/cgi-bin/map-info?chr=20) still differs in some cases from that established by PAC cloning and shown in Fig. 3.

◀ **Fig. 4** Alignment of rat and human framework MHC genes and of rat, mouse, and human class I gene regions. The scheme is based on the genes mapped in humans according to The MHC Sequencing Consortium (1999; update http://www.sanger.ac.uk/HGP/Chr6/current_MHC_gene_list.shtml) and Forbes and Trowsdale (1999). It is noteworthy that the genomic organization of the region including *HCGV*, which corresponds to *Tctex 5* in the mouse (Giffon et al. 1996), is more complex than shown and contains further genes (Coriton et al. 2000; Fan et al. 2000). Gene designations are updated according to LocusLink where possible. RT1 data and symbols correspond to Fig. 3. Rat genes not yet mapped with respect to each other (Fig. 3) are aligned according to the order in humans. For *TC4* see text. The presence of *HLA* genes *APT*, *GT257*, *CAT75X*, *HCGI*, *HCGVIII-1*, *HCGIX-4*, *HCGIV-6*, *HCGII-7* has not yet been tested for in the rat. The mouse data are from Amadou and co-workers (1999) and Allcock and co-workers (2000)

Class I genes

According to expression pattern, polymorphism, and function, MHC class I genes (Table 1) are usually divided into the class Ia and class Ib subfamilies. Class Ia genes are highly polymorphic and show nearly ubiquitous expression with high cell surface density, notably on lymphoid cells. Polymorphism occurs mainly in the peptide-binding region (PBR) and is due to balancing selection at the population level (Hughes and Yeager 1998). The function of class Ia gene products resides in the presentation of peptides to αβ T lymphocytes. Class Ib genes are mono- or oligomorphic, have restricted tissue distribution with low cell surface expression, and an antigen presentation function has been shown only for some of them.

Table 1 Class I and class I-related genes described in the rat. References for rat genes: class Ia, class Ib genes and absence of MIC, see text; *Hfe* and *Fcgrt*, own unpublished data; *Cd1d*, Matsuura and co-workers (1999); *Mr1*, Walter and Günther (1998); *Azgp1*, http://ratmap.ims.u-tokyo.ac.jp/cgi-bin/Mapview_rat.pl?RNO12. For mouse genes see http://www.informatics.jax.org/. For human genes see http://www.ncbi.nlm.nih.gov/LocusLink/index.html and http://gdbwww.gdb.org

Gene(s)	Chromosome		
	Rat	Mouse	Human
Class Ia	20p12 (MHC)	17 (MHC)	6p21.3 (MHC)
Class Ib	20p12 (MHC)	17 (MHC)	6p21.3 (MHC)
Hfe	17	13 (15 cM)	6p22.1–21.3 (extended MHC)
Cd1d	2q34	3 (48 cM)	1q22–23
Mr1 [a]	13	1	1q25.3
Fcgrt (*Fcrn*)	1 (13.2–18.5 cR)	7 (23 cM)	19q13.3
Azgp1	12	5 (78 cM)	7q22.1

[a] Official symbol in human *HLALS*, in mouse *H2ls*

Similar to the mouse, class Ia gene products encoded in the MHC might be involved in controlling kin selection in the rat. Thus, polymorphic class Ia molecules that are excreted in the urine and possibly associated with certain odorous molecules can be distinguished by smelling among *RT1-A* congenic strains (Brown et al. 1987; Singh et al. 1987, 1988).

Class Ia genes

So far, a class Ia-like function could be assigned only to the *RT1-A* region (Günther and Wurst 1984) with a single exceptional case, in which peptide presentation has been attributed to the *RT1-C/E/M* region (Wang et al. 1991). In particular, no genes corresponding functionally to the *H2-D/L* class Ia genes of the mouse have been found in the *RT1-C/E/M* region.

The number of class I genes in the *RT1-A* region (Table 2) can vary between one and three (*RT1-A1*, *A2*, *A3* genes) depending upon the *RT1* haplotype (Joly et al. 1996). The class Ia-like nature and function of the *RT1-A1* and *A2* genes has been established, but is not yet fully evaluated for *RT1-A3*. The A region of the $RT1^k$ haplotype contains one class Ia gene according to analysis of an *RT1-A*-carrying YAC clone (Walter and Günther 2000), haplotype *c* carries two class Ia genes mapped to the *RT1-A* region (Joly et al. 1996), and haplotype *n* contains three *RT1-A* genes according to PAC clone analysis (Walter and Günther 2000). By PCR cloning of expressed class I genes, the sequences from several other *RT1* haplotypes have been assigned to the *RT1-A1*, *A2*, and *A3* types, respectively (Joly et al. 1998; Table 2). The presence of only one class Ia gene, as appears to be the case in the *a*, *k*, *l*, and presumably further haplotypes, is unusual in comparison to the mouse, where at least two class Ia genes, *H2-K* and *H2-D*, are found, and with regard to humans, where three class Ia genes, *HLA-A*, *B*, and *C*, are regularly present.

Peptide-binding motifs are known for the $RT1\text{-}A^a$- (Powis et al. 1996; Speir et al. 2001; Stevens et al. 1998a), $RT1\text{-}A1^c$- (Stevens et al. 1998a, 2000a), $RT1\text{-}A^l$- (Reizis et al. 1997), and $RT1\text{-}A^u$-encoded molecules (Stevens et al. 1998a, 2000b). Distinct peptide length preferences have been observed for the gene products of $RT1\text{-}A^a$ (9–15mers), $RT1\text{-}A^c$ (9–12mers), and $RT1\text{-}A^u$ (9–12mers) (Stevens et al. 1998b, 2000b). The $RT1\text{-}A^a$-encoded molecule has been co-crystallized with a natural ligand (MTF-E) of 13 amino acid residues that bulges out of the peptide-binding groove and can adopt different conformations (Speir et al. 2001). MTF-E is derived from mitochondrial ATPase6 that functions as a maternally transmitted minor histocompatibility antigen (Bhuyan et al. 1997).

The *RT1-A* genotype affects the αβ T-cell receptor (TCR) repertoire in an allele-specific manner. This is evident by overrepresentation ("overselection") of TCRVB16 in $CD8^+$ lymphocytes of the $RT1\text{-}A^u$ genotype (Torres-Nagel et al. 1994) and by a still stronger overselection of TCRVA8S2 in $CD8^+$ lymphocytes of the $RT1\text{-}A^f$ genotype (Torres-Nagel et al. 2001). In alloresponses of $RT1^f$-negative rats, the TCRVA8S2$^+$ $CD8^+$ lymphocytes are preferentially expanded by $RT1^f$ stimulator cells (Torres-Nagel et al. 2001).

Class Ib genes

Whereas one to three class I genes have been identified and mapped to the *RT1-A* region, a large number of class I genes, mostly of the class Ib type, has been estimated to occur in the *RT1-C/E/M* region. On the basis of cosmid clone analysis, Jameson and co-workers (1992) determined the number of class I genes or class I gene fragments in the $RT1^{av1}$ haplotype to be at least 61. Yuan and co-workers (1996) estimated this number to be more than 62 in the $RT1^{r21}$ haplotype. Forty-five or more class I genes and gene fragments were extrapolated following the PAC clone analysis of the $RT1^n$ haplotype (Ioannidu et al. 2001). Thus, the number of class Ib genes appears to be at least in the range known for the *H2* complex and larger than in the *HLA* complex. The exact number of class I genes and gene fragments will become known only on the basis of the MHC sequence.

Different *RT1* haplotypes are expected to vary in the number of class I gene sequences present in the *RT1-C/E/M* region, as can be extrapolated from Southern blot data. Furthermore, examples of *RT1-C/E/M* class I loss mutants have been reported. By typing a closed colony, the Grc$^-$ mutant was described that lacks about 50 kb including *RT1-N*, *O*, and *S* class I genes (Salgar et al. 1997; Yuan et al. 1999b). Several *RT1-C/E/M* mutants could be identified when typing F2 hybrids between established inbred strains. The lm1 deletion mutant lacks about 100 kb including at least one expressed class I gene (Wurst et al. 1989), and the lm2 (Lambracht et al. 1990) and lm3 (Lambracht et al. 1993) mutants lack certain expressed class I genes. Analysis of these mutants by serology, cytotoxic T lymphocytes (CTLs), and skin grafting led to the identification of an $RT1\text{-}C^l$-encoded antigen (Lambracht and Wonigeit 1995; Wurst et al. 1989) and the antigens RT1-L (Wonigeit and Hänisch 1991) and RT1-R (previous designation RT1-M; Wonigeit and Hänisch 1991). The mutants mentioned can be bred as homozygotes, except that Grc$^-$ males are sterile. Evidently, evolution of class I genes is a still ongoing process and loss of class Ib genes need not have obvious adverse effects.

The sequences of *RT1-C/E/M* region genes reported so far can be placed into at least three groups on the basis of gene tree analysis and homology to *H2* genes: (1) genes that are most similar to *RT1-A* class Ia genes, like *RT1-E* (Salgar et al. 1995), *RT1-U* (Leong et al. 1999), *RT1-Clw2* (Walter et al. 1994) or the *RT1-EC* genes (Yuan et al. 1999a); (2) genes resembling *H2-T* genes, like *RT-BM1* (Carter et al. 1994) and *RT1-N1* (Kirisits et al. 1994); (3) genes most similar to *H2-M* genes, like *RT1-M3* (Wang et al. 1995). These three types can be as-

Table 2 Genes in the *RT1* complex. Not included are genes for which sequence information is lacking, such as class I genes *RT1-F* (Misra et al. 1985), *RT1-G* (Kunz et al. 1989), *RT1-L* (Wonigeit and Hänisch 1991), *RT1-M6* (Lambracht et al. 1995), *RT1-N* (Yuan et al. 1996), *RT1-O1* (Yuan et al. 1999b), *RT1-R* (formerly *RT1-M*) (Wonigeit and Hänisch 1991), class II gene *RT1-Db2* (Diamond et al. 1989), and non-class I/non-class II genes *ft*, *dw3*, *rcc* (Melhem et al. 1993)

Gene	Allele	Accession number	Reference	Designation
Class I genes				
RT1-A [a]	A^{av1}	M31018	Rada et al. 1990	
	$A1^{b}$	AJ249704, U38970	Joly et al. 1998; Wang et al. 1996a	
	$A2^{b}$	AJ249705	Joly et al. 1998	
	$A1^{c}$	X90370	Joly et al. 1998	
	$A2^{c}$	X90371, U38971	Joly et al. 1998; Wang et al. 1996a	
	A^{f}	Y14014	Joly et al. 1998	
	$A1^{f}$	X99767	Joly et al. 1998	
	$A2^{f}$	Y13579	Joly et al. 1998	
	A^{g}	Y08532	Joly et al. 1998	
	$A1^{h}$	AJ249698	Joly et al. 1998	
	$A2^{h}$	AJ249699	Joly et al. 1998	
	$A1^{k}$	AJ249702, AJ243580	Joly et al. 1998; Walter and Günther 2000	
	A^{l}	AF025309, L26224	Lambracht and Wonigeit 1995; Salgar et al. 1994	
	$A1^{n}$	X90375	Joly et al. 1998 (clone 12: Wang et al. 1996b)	
	$A2^{n}$	X90376	Joly et al. 1998	
	$A3^{n}$	AJ277139	Walter and Günther 2000	
	$A1^{o}$	X90373	Joly et al. 1998	
	$A2^{o}$	X90372	Joly et al. 1998	
	$A3^{o}$	X90374	Joly et al. 1998	
	$A1^{q}$	AJ249700	Joly et al. 1998	
	$A2^{q}$	AJ249701	Joly et al. 1998	
	A^{u}	X82106, X82669, U38972	Joly et al. 1995; Walter et al. 1995; Wang et al. 1996a	
RT1-A^{k} [b]		AJ249703	Joly et al. 1998	
RT1-C113		X67503, X67504	Rothermel et al. 1993	
RT1.Cl		AF025308	Lambracht and Wonigeit 1995	
RT1-Clw2		X70066	Walter et al. 1994	
RT1-E	E^{u}	L40365, AJ306619	Salgar et al. 1995; Deverson (EMBL GenBank database)	
	E^{g}	AJ243338	Le Rolle et al. 2000	
	E^{l}	AJ276126	Le Rolle et al. 2000	
RT1-EC1		AF074607	Yuan et al. 1999a	
RT1-EC2		AF074608	Yuan et al. 1999a	
RT1-EC3		AF074609	Yuan et al. 1999a	
RT1-K		M25319	Radojcic et al. 1989	
RT1-M2		AJ319593	Walter et al., unpublished data	
RT1-M3		U16025, AJ249342	Wang et al. 1995; Joly (EMBL GenBank database)	
RT1-M4		AF024712	Lambracht et al. 1995	
RT1-M5		AF055667	Lambracht et al. 1995	
RT1-N1		M74822	Kirisits et al. 1992	
RT1-N2		L23127	Kirisits et al. 1994	
RT1-N3		L23128	Kirisits et al. 1994	
RT1-O		L16012	Rushton et al. 1994	
RT1-P1		AB002169	Matsuura et al. 1997	
RT1-P2		AB002170	Matsuura et al. 1997	
RT1-S1		L81134	Salgar et al. 1997	
RT1-S2		L81135	Salgar et al. 1997	
RT1-S3		AF029240, AF029241	Salgar et al. 1998 (see below: *RT-BM1*)	
RT1-U1	$U1^{f}$	AJ004889	Leong et al. 1999	
	$U1^{g}$	Y08530	Leong et al. 1999 (see below: *RT1.A-1*)	
RT1-U2		Y13890	Leong et al. 1999	
4B2/3.7		AF074610	Yuan et al. 1999a	
Clone 3.6		M31038	Rada et al. 1990; *RT1.Aw2* according to Remmers et al. 1995	

Table 2 (continued)

Gene	Allele	Accession number	Reference	Designation
Clone 9.5		AJ004887	Leong et al. 1999	
Clone 9.6		AJ004888	Leong et al. 1999	
Clone 109		U50449	Wang et al. 1996b; *RT1-U1*^{n} according to Leong et al. 1999	
Clone 119		L40362	Salgar et al. 1995	
Clone 149		L40364	Salgar et al. 1995	
Clone cc1		AJ005022	Leong et al. 1999	
Clone cc9		AJ005023	Leong et al. 1999	
Clone cc22		AJ005024	Leong et al. 1999	
Clone cc23		AJ005025	Leong et al. 1999	
RT12.5		X79721	Lambracht and Wonigeit 1995	
RT21		M24024	Mauxion et al. 1989	
RT(2.1)		L16013	Rushton et al. 1994	
RT16		M24023	Mauxion et al. 1989 (see above: *RT1-A*^{l})	
RT44		M24026	Mauxion et al. 1989	
RT1.A-1 [b]		M11071	Kastern 1985; *RT1-U1*^{g} according to Leong and co-workers (1999) and Le Rolle and co-workers (2000)	
RT1.A-2 [b]		M10094	Kastern 1985	
RT1.A-4 [b]		M64795, M34659	Kryspin-Sorensen et al. 1991	
RT1.Aw3 [b]		L40363	Salgar et al. 1995	
RTA		M24025	Mauxion et al. 1989	
RT-BM1	*BM1*^{av1}	X16979, AJ243974	Parker et al. 1990; Lau et al. 2000	
	BM1^{c}	AJ243975	Lau et al. 2000	
	BM1^{k}	AJ243973	Lau et al. 2000	
	BM1^{n}	AJ243976	Lau et al. 2000	
	BM1^{r21} (*RT1-S3*)	AF029240, AF029241	Salgar et al. 1998	
RTS		M24324	Mauxion et al. 1989	
Class II genes				
RT1-Ba	*Ba*^{av1}	L11342	Holmdahl et al. 1993	
	Ba^{c}	L11337	Holmdahl et al. 1993	
	Ba^{d}	L11338	Holmdahl et al. 1993	
	Ba^{f}	L11339	Holmdahl et al. 1993	
	Ba^{l}	L11340, X14879	Holmdahl et al. 1993; Syha et al. 1989	
	Ba^{n}	L11341	Holmdahl et al. 1993	
	Ba^{u}	K02815	Wallis and McMaster 1984	
RT1-Bb	*Bb*^{a}	M76779, M767780	Fujii et al. 1991	
	Bb^{b}	M36151, M76777, M76778, U65218	Figueroa et al. 1988; Fujii et al. 1991	
	Bb^{d}	M76783, M76784	Fujii et al. 1991	
	Bb^{k}	M76785–M76787	Fujii et al. 1991	
	Bb^{l}	M76773–M76776, X56596, AF113922	Fujii et al. 1991; Noris et al. 1999; Syha-Jedelhauser et al. 1991	
	Bb^{n}	M76781, M76782	Fujii et al. 1991	
	Bb^{u}	M24930, M76770, M76771	Chao et al. 1989; Fujii et al. 1991	
RT1-Da	*Da*^{a}	AJ002991	Vestberg et al. 1998	
	Da^{b}	AJ002992	Vestberg et al. 1998	
	Da^{c}	AJ002993	Vestberg et al. 1998	
	Da^{d}	AJ002994	Vestberg et al. 1998	
	Da^{f}	AJ002995	Vestberg et al. 1998	
	Da^{h}	AJ002996	Vestberg et al. 1998	
	Da^{k}	AJ002997	Vestberg et al. 1998	
	Da^{l}	AJ002998	Vestberg et al. 1998	
	Da^{m}	AJ002999	Vestberg et al. 1998	
RT1-Da	*Da*^{n}	AJ003000	Vestberg et al. 1998	
	Da^{u}	M15562, Y00480, AJ003001	Holowachuk et al. 1987; Vestberg et al. 1998	

Table 2 (continued)

Gene	Allele	Accession number	Reference	Designation
RT1-Db	*Db*^{a}	AJ003226	Vestberg et al. 1998	
	Db^b	AJ003227	Vestberg et al. 1998	
	Db^c	AJ003228	Vestberg et al. 1998	
	Db^d	AJ003229	Vestberg et al. 1998	
	Db^f	AJ003230	Vestberg et al. 1998	
	Db^h	AJ003231	Vestberg et al. 1998	
	Db^k	AJ003232	Vestberg et al. 1998	
	Db^l	M24934, X53054	Chao et al. 1989; Syha-Jedelhauser and Reske 1990	
	Db^m	AJ003233	Vestberg et al. 1998	
	Db^n	AJ003234	Vestberg et al. 1998	
	Db^u	M12382, M24933	Robertson and McMaster 1985; Chao et al. 1989	
RT1-Ha		D42013–D42015, S80409	Arimura et al. 1995b	
RT1-Hb		D42016–D42019	Arimura et al. 1995b	
RT1-DMa		U31598, Z49761	Hermel and Monaco 1995; Reske (EMBL GenBank database)	
RT1-DMb		U31599, Z49762	Hermel and Monaco 1995; Reske (EMBL GenBank database)	
RT1-DOa		D45240, D45241	Arimura et al. 1995a	
RT1-DOb		M15561	Schøller and Lernmark 1985	
Non-class I/non-class II genes[c]				
Abcb2 (*Tap1*)	*RT1*^{av1}	X57523		ATP-binding cassette, subfamily B (MDR/TAP), member 2
	RT1^c	Y10230		
	RT1^{dv1}	Y10231		
	RT1^k	Y10232		
	RT1^l	Y10233		
	RT1^n	Y10234		
	RT1^u	Y10235		
Abcb3 (Tap2)	*RT1*^{av1}	X63854		ATP-binding cassette, subfamily B (MDR/TAP), member 3
	RT1^c	X75306		
	RT1^l	X75305		
	RT1^u	X75307		
Abcf1 (*Abc50*)		AF293383		ATP-binding cassette, subfamily F (GCN20), member 1
Ager (*Rage*)		L33413		Advanced glycosylation end product-specific receptor
Agpat1 (*G15*)				1-acylglycerol-3-phosphate O-acyltransferase 1
Aif1 (*G1*)		U17919, AB000818		Allograft inflammatory factor 1
*Apom** (*G3a*)		AF207821		Apolipoprotein M
Atp6g		AJ314857		ATPase, H^+-transporting, lysosomal (vacuolar proton pump)
B3galt4		AB003478		UDP-Gal:betaGlcNAc beta1,3-galactosyltransferase, polypeptide 4
*Bat1**		M75168		D20H6S81e (putative nuclear RNA helicase)
*Bat2** (*G2*)				D20H6S51e
*Bat3** (*G3*)		AB018791		D20H6S52e
*Bat4** (*G5*)				D20H6S54e
*Bat5** (*Ng26*)				D20H6S82e
Bf				B-factor, properdin
*Bing4**				Unknown function
Brd2 (*Ring3*, *Rnf3*)				Bromodomain-containing 2 (mitogen-activated nuclear kinase, homologous to *Drosophila fsh*)
Btnl2 (*Ng9*)				Butyrophilin-like 2 (MHC class II associated)
*Btnl4** (*Ng11*)				Butyrophilin-like 4
C2				Complement component 2
C4				Complement component 4
*Cat56**				Unknown function
Cdsn				Corneodesmosin

Table 2 (continued)

Gene	Allele	Accession number	Reference	Designation
Clic1 (G6)				Chloride intracellular channel 1
Col11a2		X95869, X95872, X95873		Collagen, type XI, alpha 2
Crebl1 (G13)				cAMP responsive element binding protein-like 1
Csnk2b		L15619		Casein kinase 2 beta polypeptide
Cyp21		U56853		Cytochrome P450, subfamily XXI (steroid 21-hydroxylase)
Daxx				Death-associated protein 6
Ddah2 (G6a, Ng30)				Dimethylarginine dimethylaminohydrolase 2
Ddr1 (Cak)		L26525		Discoidin domain receptor family, member 1 (cell adhesion kinase)
Ddx16 (Dbp2)				DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 16 (RNA helicase)
Dom3z (Dom31, Ng6)				DOM-3 (C. elegans) homolog Z
Fabgl (Ke6, Ring2)		X95870		FabG (beta-ketoacyl-[acyl-carrier-protein] reductase, E. coli)-like
Fkbpl (Ng7)				FK506-binding protein-like
Flot1		U60977		Flotillin 1
*G4**				unknown function
*G5b**				unknown function
G5c (Ng33)*				unknown function
G6b (Ng31)*				unknown function
G6c (Ng24)*				unknown function
G6d (Megt1, Ng25)*				Megakaryocyte enhanced transcript 1 protein
*G6e**				putative Ly-6 superfamily member
G6f (Ng32)*				identical to G6D according to LocusLink, but non-identical according to http://www.sanger.ac.uk/HGP/Chr6/current_MHC_gene_list.shtml
*G7b**				U6 snRNA-associated Sm-like protein
G7c (Ng37)*				unknown function
G9a (Bat8)*				Ankyrin repeat-containing protein
G10 (Ng35)*				unknown function
G18 (Ng1)*				unknown function
Gabbr1		AB016161		Gamma-aminobutyric acid (GABA) B receptor, 1
Gtf2h4				General transcripton factor IIH, polypeptide 4
Gnl1 (Hsr1, Gna-rs1)				Guanine nucleotide binding protein-like 1
Hspa1a (Hsp70-2)		X77208		Heat shock 70 kD protein 1a
Hspa1b (Hsp70-1)		L16764, X74271, X75357, X77207		Heat shock 70 kD protein 1b
Hspa1l (Hsp70-3)		X77209		Heat shock 70 kD protein-like 1
ler3 (Dif2, Prg1)		X96437		Immediate early response 3
*Kiaa0170**				similar to D. melanogaster calphotin
Knsl2 (Hset)				Kinesin-like 2
Lst1 (B144)*		AF208230		Leucocyte specific transcript 1, identical to NKP30/1C7 (designated LY117) according to LocusLink, but non-identical according to http://www.sanger.ac.uk/HGP/Chr6/current_MHC_gene_list.shtml
Lta (Tnfb)		L00981		Lymphotoxin alpha (Tnf superfamily, member 1)
Ltb				Lymphotoxin beta (Tnf superfamily, member 3)
Nkp30 (1c7)*				NK cell receptor; according to LocusLink identical to LST1/B144 and designated LY117
Mog		M99485, L21995		Myelin oligodendrocyte glycoprotein
Msh5				Muts (E. coli) homolog 5
Neu1 (G9)		AB035772		Sialidase 1 (lysosomal sialidase)
Nfkbil1		AJ314857		Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1
*Ng3**				unknown function
*Ng5**				unknown function
Ng8 (Tesbp)*				testis specific basic protein

Table 2 (continued)

Gene	Allele	Accession number	Reference	Designation
*Ng22**				Unknown function
*Ng23**				Unknown function
*Ng36**				Unknown function
*Nkp30** (*1c7*)				NK cell receptor; identical to *LST1*/*B144* (designated *LY117*) according to LocusLink, but nonidentical according to http://www.sanger.ac.uk/HGP/Chr6/current_MHC_gene_list.shtml
Notch4 (*Int3*)				Notch (*Drosophila*) homologue 4
*Olfr42** (*D20M17Tu42*)				Olfactory receptor 42
Pbx2 (*G17*)				Pre-B-cell leukemia transcription factor 2
Pou5f1 (*Oct3*, *Otf3*)				POU domain, class 5, transcription factor 1
Ppp1r10 (*Fb19*, *Pnuts*)		AF040954		Protein phosphatase 1, regulatory subunit 10
Ppt2		AF061971		Palmitoyl-protein thioesterase 2
Psmb8 (*Lmp7*)				Proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional protease 7)
Psmb9 (*Lmp2*)		D10757		Proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional protease 2)
*Ptd017**				Unknown function
Rab2l (*Rgl2*)				Rab2, member Ras oncogene family-like
*Rdbp** (*Rd*)				RD RNA-binding protein
Ring1		X95474, AJ243579		Ring finger protein 1
Rnf5 (*G16*, *Ng2*, *Ring5*)				Ring finger protein 5
Rnf9 (*Rfb30*)				Ring finger protein 9
Rps2r1		L81136		Ribosomal protein S2
Rps2r2		L81137		Ribosomal protein S2 pseudogene
Rps2r3		L81138		Ribosomal protein S2 pseudogene
Rps18 (*Ke3*)		X57529, AJ223831		Ribosomal protein S18
RT1-Ke2				Orthologue of human *HKE2* and mouse *H2-Ke2*
RT1-Ke4				Orthologue of human *HKE4* and mouse *H2-Ke4*
Rxrb		X95868		Retinoid X receptor, beta
Sacm2l		AJ223830		SAC2 (suppressor of actin mutation 2, yeast, homologue)-like
Skiv2l				Superkiller viralicidic activity 2 (*Saccharomyces cerevisiae* homologue)-like
*Spr1**				Unknown function
Stk19 (*G11*)				Serine/threonine kinase 19
Tapbp		AJ400732		TAP-binding protein (tapasin)
Tcf19				Transcription factor 19 (Sc1)
Tctex4				Unknown function
Tctex5				Unknown function
Tnf (*Tnfa*)		D00475		Tumor necrosis factor (TNF superfamily, member 2)
Tnx		U24489		Tenascin X
Tubb		AB011679		Tubulin, beta polypeptide
*Ubd**		AJ312394		Diubiquitin, ubiquitin D
Vars2 (*G7a*, *Bat6*)				Valyl-tRNA synthetase 2
Znf173 (*Zfp173*)				Zinc finger protein 173
Znf297 (*Bing1*)				Zinc finger protein 297
*Znfb7**				Zinc finger protein

[a] The *RT1*^{c} haplotype carries two (*A1*, *A2*) and the *RT1*^{n} haplotype three (*A1*, *A2*, *A3*) class Ia genes according to genetic mapping and sequence analysis (Joly et al. 1996; Walter and Günther 2000). For some haplotypes, assignment to *A1*, *A2*, *A3* has been reported on the basis of sequence homology (Joly et al. 1998; GenBank entries). The *RT1-A*^{o} region corresponds to *RT1-A*^{d} (see text)

[b] Designation does not imply mapping to *RT1-A* region

[c] Gene symbols and designations follow official human nomenclature, while some alternative symbols are given in *parentheses*. Symbols that are not approved are indicated by an *asterisk*. Where available, the accession number of the rat sequence (cDNA and genomic sequences, but not expressed sequence tags) is listed. For references see http://ratmap.gen.gu.se, http://rgd.mcw.edu, and http://www.ncbi.nlm.nih.gov/LocusLink/index.html.

signed to the different class I clusters of the *RT1-C/E/M* region (Fig. 3). (1) At least some of the *RT1-A*-like genes map to the first cluster, but are not orthologous to *H2-D* or *H2-Q* genes. The similarity between these *RT1-C/E* and the RT1-A genes is reflected by cross-reactivity between *RT1-A* and *RT1-C/E/M* region gene products at the CTL (see e.g., Stephenson et al. 1985) and serological (see e.g., Leong et al. 1999) level. (2) *RT-BM1*, assumed to be orthologous to *H2-T23*^{d} (Parker et al. 1991), and *RT1-N1*, assumed to be orthologous to *H2-T11*^{d}/*H2-T22*^{d} (Kirisits et al. 1992), map to the second cluster. Consequently, the centromeric part of the second class I

cluster will be *H2-T* orthologous. In accordance with this assignment, the grc1.4 probe that locates the *Grc* region to the second cluster (Ioannidu et al. 2001), cross-hybridizes with the *H2-T22*^{d}*–T23*^{d} interval in the mouse (Hunt et al. 1993). (3) The *H2-M* homologous genes identified belong to the third and fourth clusters. At least for the *M2*, *M3*, *M4*, *M5* and *M6* genes, rat/mouse orthology has been shown (Lambracht et al. 1995; Lambracht-Washington et al. 1998; own unpublished data). Of note is that the rat *M3* gene is triplicated in the *RT1*^{n} haplotype (*M3a*, *M3b*, *M3c)* (Ioannidu et al. 2001), whereas *M3* is a single-copy gene in the mouse *H2*^{b} haplotype.

The *RT1-EC* genes and related genes of the *RT1*^{r21} haplotype have been physically mapped in a cosmid contig of about 150 kb and partially sequenced (Yuan et al. 1996, 1999a; see also Joly 1997). The *RT1-N*, *RT1-O*, *RT1-S*, and *RT-BM1* genes of the same haplotype have been physically mapped in a further cosmid contig of about 110 kb (Fig. 3b; Salgar et al. 1998; Yuan et al. 1996, 1999a). Part of this contig includes sequences cross-hybridizing with the grc1.4 probe (Yuan et al. 1996, 1999a, 1999b). The *RT1-N* and *RT-BM1* class I genes and the *Grc*-cross-hybridizing sequences map to the second class I cluster of the *RT1*^{n} PAC contig (Fig. 3a).

Polymorphisms have been described for some *RT1-C/E* class Ib genes like *RT1-U* (Leong et al. 1999) and *RT1-E* (Le Rolle et al. 2000). One cannot exclude, however, that actually pseudoallelism occurs due to the presence of a variable number of only slightly different copies of a gene. The *RT1-N*-type genes of the *r21* haplotype are an example of a group of very closely related neighboring class I genes (Kirisits et al. 1994).

Orthology between certain rat and mouse genes of the *H2-T* and *H2-M* families, respectively, is primarily deduced from the fact that the rat sequence is more similar to the respective mouse sequences than to other rat class I sequences. Orthology of *H2-T*- and *H2-M*-like genes between rat and mouse could imply that not all rat class I genes have been homogenized by gene conversion, as has been postulated by Rada and co-workers (1990). *H2-T*- and *H2-M*-like genes are missing in the human MHC, whereas the class Ib genes of the MHC class I chain-related (MIC) type occur in the human MHC, but are absent from the rat and mouse MHC (Bahram et al. 1994; Ioannidu et al. 2001).

The lack of orthology between rat and human class Ib genes is in accordance with the general observation that no orthologous relationship exists between class Ib genes of different orders (Hughes and Nei 1989). Of interest in this context is that mouse *H2-Qa1*, which is encoded by the *RT-BM1* orthologous gene *H2-T23*^{d}, and human *HLA-E* carry out a similar function in that both present class I leader peptides and inhibit natural killer (NK) cells, suggestive of orthology. The homology between the PBRs of *H2-Qa1* and *HLA-E*, however, has been shown to be due to convergent evolution and, thus, does not reflect an orthologous genetic relationship between the genes (Yeager et al. 1997). A comparison between rat and mouse class I genes demonstrates that even between species that are relatively closely related, orthology need not exist, as is illustrated by genes in the first class I cluster of the *RT1-C/E/M* region.

The expression profiles of individual class Ib genes have not yet been analyzed systematically. RNA expression data show that *RT1-N* is highly expressed in the thymus (Kirisits et al. 1992), and *RT1-U* in nerve cells (Lidman et al. 1999).

Ligands of NK cell receptors

Class I gene products do not only interact with αβ TCRs, but serve also as ligands for NK cells. Human and mouse class I genes can inhibit or stimulate NK cell function by binding to special NK cell receptors. Class Ia molecules encoded by *RT1-A1*^{c} *(*Naper et al. 1999; Stevens et al. 2000a), *RT1-A*^{l} (Kraus et al. 1996), *RT1-A1*^{n} (Bäckman-Petersson et al. 2000), and *RT1-A*^{u} (Jonges et al. 2000) have been described as inhibiting NK cells. The NK cell receptor for the *RT1-A1*^{c}-encoded molecule has been identified as the Ly49 family member STOK2. Its expression is controlled by the *RT1* complex (Naper et al. 1998, 1999). Stimulation of NK cells that are alloreactive against lymphoid cells has been assigned to the *RT1-C/E* region, notably to *RT1-C*^{l}-(Rolstad et al. 1997) and *RT1-E*^{u}-encoded molecules (Petersson et al. 1999). The inhibitory stimulus by RT1-A molecules is dominant over the activating effect of the *RT1-C/E* gene products (Naper et al. 1996). Interestingly, NK-mediated alloreactivity can be stimulated by alloimmunization leading to differentiation, proliferation, recruitment, and increased lytic activity of a subset of NK cells (Petersson and Hedlund 1999). Thus, these NK cells exhibit features of an adaptive immune response.

Non-MHC-linked class I-like genes

Among the genes with low but significant similarity to class I genes (Hughes et al. 1999) that map outside the MHC, *Azgp1*, *Cd1d*, *Fcgrt*, *Hfe*, and *Mr1* have also been identified in the rat (Table 1). In fact, the *Fcgrt* gene was first described in the rat (Simister and Mostov 1989). Some of these genes have acquired a new function unrelated to antigen presentation (see Shinkai and Locksby 2000). The non-MHC-linked class I-like genes map to chromosomal regions that show homology of synteny in rat, mouse, and human. Exceptions are *Cd1d* and *Mr1*. In humans, the *CD1D* and *MR1* genes are linked to each other on HSA1, but in the rat (as in the mouse) they map to two separate chromosomes, *Cd1d* to RNO2 and *Mr1* to RNO13 (Table 1).

Class II genes

Three prototypes of class II molecules, each composed of an α and β chain, are encoded in the human MHC and designated *HLA-DPA*/*B*, *HLA-DQA*/*B* and *HLA-DRA*/*B*. Their function is to present peptides to CD4^{+} T lympho-

cytes. The human *DP* and *DQ* genes are duplicated, one copy of each being functional, whereas *DRB* can occur in several copies depending upon the *HLA* haplotype, and *DRA* is a single-copy gene. The corresponding genes are also present in the rat MHC (Arimura et al. 1995b; Diamond et al. 1989; Fujii et al. 1989, 1991; Watters et al. 1987). The *RT1-H* genes are orthologous to *HLA-DP* (and *H2-P*), the *RT1-B* genes to *HLA-DQ* (and *H2-A*), and the *RT1-D* genes to *HLA-DR* (and *H2-E*). The order of the class II genes is colinear in rat, mouse, and human (Fig. 3), but gene copy number and functional status differ between rat and human, and resemble more closely the mouse pattern. The *DPA* and *DPB*-like rat genes, *RT1-Ha* and *RT1-Hb*, respectively, occur as single copies and *RT1-Hb* is a pseudogene (Arimura et al. 1995b; Fujii et al. 1991). For *RT1-B*, only one copy of the *Ba* and *Bb* genes is present. In the case of *RT1-D*, a single *RT1-Da* gene and two *RT1-Db* genes are found, the *RT1-Db2* copy presumably being nonfunctional (Diamond et al. 1989).

Comparison of class II genes (Table 2) revealed that the extent of allelic variability is small in terms of the number of nucleotide exchanges. Furthermore, exon 2 sequences, in particular of *RT1-D* genes, appear to be shared among several haplotypes. *RT1-Da* exon 2 of *RT1* haplotypes *a*, *d*, *f*, and *l*, as well as of *c* and *k* carry identical nucleotides, and *RT1* haplotypes *a*, *c*, *d*, *f*, *k*, *l* and *m* encode identical amino acid sequences (Vestberg et al. 1998). Similarly, exon 2 of *RT1-Db* shows identical nucleotide and amino acid sequences in haplotypes *a*, *c*, *d*, *f*, and *m*, as well as in *h* and *n* (Vestberg et al. 1998). In the case of *RT1-Ba* (Holmdahl et al. 1993), exon 2 sequences of *RT1* haplotypes *a*, *d*, *f*, *l*, and *n* are different, whereas that of haplotype *c* is like *a*. *RT1-Bb* exon 2 of haplotypes *a*, *b*, *d*, *l*, *n*, and *u* differ at the amino acid level in contrast to *b* and *k* (comparison based on sequences in the database; see Table 2).

Both, RT1-B and RT1-D molecules appear to be regularly expressed with the exception of BDIX rats ($RT1^{dv1}$). In this strain, no *RT1-B* gene product could be detected at the cell surface (Male et al. 1987) in spite of mRNA expression (Fujii et al. 1991). Differential modulation of RT1-B and RT1-D molecules by cytokines and other agents has been reported (Roos et al. 1998). The peptide-binding motif has been described so far only for the $RT1\text{-}B^{l}$-encoded class II molecule (Reizis et al. 1996; Wauben et al. 1997).

The class II genotype has been shown to control *V* gene usage of the αβ TCR in $CD4^+$ lymphocytes. $CD4^+$ cells of the $RT1\text{-}B/D^{u}$ haplotype reveal a haplotype-specific overrepresentation of TCRVA4 (Torres-Nagel et al. 1994).

RT1 genes controlling antigen processing and peptide loading

Several genes have been identified in the MHC that control antigen processing [*Psmb9* (*Lmp2*), *Psmb8* (*Lmp7*)] peptide transport [*Abcb2* (*Tap1*), *Abcb3* (*Tap2*)], and peptide loading [*Tapbp* (*tapasin*)] in the class I presentation pathway. The *Abcb2*, *Abcb3*, *Psmb8*, and *Psmb9* genes are located in the class II region (Fig. 3), *Tapbp* is located centromeric from the *RT1-A* region. Each of these genes maps at orthologous positions with respect to the mouse and human homologues (Figs. 3, 4).

The *Abcb3* (*Tap2*) gene is polymorphic (Joly et al. 1994), giving rise to a functional dimorphism of two types of transporter molecules, TAP-A and TAP-B. They differ with respect to the nature of the peptides transferred from the cytosol to the endoplasmic reticulum (Joly et al. 1998). Whereas TAP-A transports peptides that can bear various C-terminal residues, TAP-B is more restricted in this respect, prefering to transport peptides with hydrophobic C-terminal residues. In most *RT1* haplotypes, transporter specificity fits to the peptide-binding specificity of the F pocket of the *RT1-A*-encoded class Ia molecule(s) of that haplotype (Joly et al. 1998; Speir et al. 2001). This kind of cis-association, e.g., between *TAP-A* group alleles with $RT1\text{-}A^{a}$ or *TAP-B* group alleles with $RT1\text{-}A1^{c}$, is a strong argument for natural selection favoring certain MHC haplotype constellations by co-evolution and, more generally, close linkage of certain MHC genes (Joly and Butcher 1998; Joly et al. 1998). The association between the class Ia and TAP specificities might be facilitated by the proximity between the *RT1-A* and *Abcb2/Abcb3* (*Tap1*/*Tap2*) genes, which are about 150 kb apart. In humans, the class Ia and *TAP* genes are separated by about 1.5 Mb, whereas in the mouse, class Ia genes do not only occur as close to the Tap genes (*H2-K*) as in the rat, but also telomeric from the class III region (*H2-D/L*), more than 1 Mb away. In humans, TAP specificity resembles rat TAP-A, and in the mouse it is like rat TAP-B. No functional TAP polymorphism has been reported in other species than the rat, but it might occur in the Syrian hamster (Lobigs et al. 1995).

A group of MHC gene products known from human and mouse to be involved in peptide loading of class II molecules in endosomal compartments are the class II-like molecules DMA, DMB, DOA, and DOB. The corresponding genes are also present in the rat and located in the *RT1* class II region at similar, presumably orthologous positions with respect to mouse and human (Figs. 3, 4). In contrast to the mouse, only a single *DMb* gene is found in the rat (Hermel and Monaco 1995).

The diubiquitin (*Ubd*) gene has been shown in the mouse to be expressed in dendritic cells, B cells, and endothelial cells and is inducible by interferon-γ and tumor necrosis factor-α, suggesting involvement in antigen processing (Raasi et al. 1999).

Class III and further genes in the *RT1* complex

The first non-class I/non-class II genes detected in the MHC were mapped between the class II and (telomeric) class I regions. They were grouped together as class III genes and the corresponding MHC region was designated the class III region. Class III genes include members of the complement system (*C4*, *Bf*, *C2*), the tumor necro-

sis factor cytokine gene family (*Tnf*, *Lta*, *Ltb*), and the heat shock protein (Hsp)70 family (*Hspa1a*, *Hspa1b*, *Hspa1l*). The function of these genes documents that the MHC is also involved in controlling antigen-nonspecific and innate immune mechanisms, in addition to antigen-specific (adaptive) immune responsiveness. All class III genes identified in the *HLA* complex are also present in the rat (and mouse) MHC and show a colinear order in these three species (Table 2, Figs. 3, 4). The extent to which the group of *Cyp21*, *C4*, and neighboring genes that can occur module-like in several copies in the human and mouse MHC (Yu et al. 2000) is present in more than one copy in the *RT1* is still unclear.

Apart from the class III region, the other MHC regions also contain genes that are structurally and functionally unrelated to class I and class II genes (Figs. 3, 4, Table 2). Many of these genes have been identified or mapped to the MHC only after the complete sequence of the human MHC was determined. Nearly each functional non-class I/non-class II gene that has been identified in the *HLA* complex can be found at an orthologous position in the *RT1* complex (Fig. 4). A few genes of the *HLA* complex that are classified as functional have not yet been identified in the *RT1* complex. An example is *TC4*, which, however, could be a processed pseudogene, and this explanation might also apply for other discrepant genes.

Beside the class I and class II multigene families and the expressed framework genes, a large number of gene sequences present in the *HLA* complex represent pseudogenes, some of the processed type and derived from transcripts of non-class I/non-class II genes residing outside the MHC. They occur preferentially in the *HLA* class I region. The same processed pseudogenes are unlikely also to be present in the rat MHC. Sequencing will reveal which pseudogenes occur in the *RT1* complex and whether they are preferentially found in *RT1-C/E/M*, the region homologous to the *HLA* class I region. An example of a gene sequence present in the rat that is missing in the *HLA* complex is *Btnl4* (*Ng11*), a putative pseudogene of the butyrophilin-like gene family (Fig. 3) that occurs at an orthologous position in the mouse (Stammers et al. 2000).

Evolutionary relationship between the two class I regions, *RT1-A* and *RT1-C/E/M*

The *RT1-A* region is usually interpreted as being the result of a translocation of *RT1-C/E* region genes into that centromeric part of the MHC which is defined as the extended class II region in humans. This translocation model is supported by promoter sequence data showing that the *RT1-A* class I genes contain the same type of an 11-bp deletion as do *RT1-C/E* region class I genes (Lambracht-Washington et al. 2000). Since the 11-bp deletion is not found in mouse class I genes, the translocations leading to *RT1-A* and *H2-K* are hypothesized to have occurred in rat and mouse separately and not in a common ancestor species (Lambracht-Washington et al. 2000). Further support of this model was seen in the presence of an 18-bp insertion in exon 5 of most rat class I genes (Rada et al. 1990). An earlier hypothesis, based on the few rat class I sequences then available postulated two translocations, one in a common mouse/rat ancestor (Hughes 1991). The high sequence similarity between class I genes in the *RT1-A* region and in the first class I cluster of the *RT1-C/E/M* region (Ioannidu et al. 2001) suggests that the latter could have been the source of the *RT1-A* genes. The interpretation of the class I sequence relationship might be biased by concerted evolution due to species-specific homogenization as suggested to occur in rat class I genes by Rada and coworkers (1990).

Sequence information of the *Sacm2l/RT1-A* and *RT1-A/Ring1* intervals indicates that the *RT1-A* and *H2-K* regions were inserted at the same positions relative to the *Ring1* and *Sacm2l* genes in rat and mouse, respectively (Walter and Günther 2000). At first sight, these data favor a single translocation event that predated separation of mouse and rat. However, the possibility cannot be excluded that the MHC interval harboring *RT1-A* or *H2-K* is particularly permissive for the integration of class I translocations, so that insertions could have occurred at the same genomic location on different occasions.

One has also to consider that the location of the *H2-K* and *RT1-A*-encoded class Ia genes in the vicinity of genes controlling antigen processing and peptide transport might reflect the original genomic situation, so that the human order of these genes developed secondarily due to loss of the centromeric class I genes. This possibility is noteworthy because of the association between the rat class Ia/transporter specificities discussed above and because in several nonmammalian species, the genes controlling antigen processing and transport map close to the class I genes (Flajnik et al. 1999).

RT1 complex and transplantation

Being the MHC in the rat, the *RT1* complex is the main genetic system that determines histocompatibility in this species (for a review see Günther 1998). The histoincompatibility reaction is elicited by the alloantigenic class I and class II molecules of the donor and exerted by the immune response of the host against these molecules. By analysis of *RT1* recombinant strains, graft rejection has been assigned to the *RT1-A*, *RT1-B/D*, and *RT1-C/E/M* regions. The individual class I genes of the *RT1-C/E/M* region that encode histoincompatibility-inducing molecules have not yet been identified. The strength of the histoincompatibility effect varies for the different types of graft like skin, kidney, liver, heart, pancreas, islets, or bone marrow. It also depends on the haplotypic or allelic combination, giving rise to “weak” and “strong” MHC combinations with respect to the survival time of skin or organ grafts. In the case of bone marrow grafting, alloreactive NK cells that recognize *RT1-A* and *RT1-C/E/M* gene products are involved (Engh et al.

1998; Rolstad et al. 1997). The rat is the main experimental model for organ transplantation (Timmermann et al. 1998), since it combines suitability for microsurgery with availability of inbred strains and tools for immunologic and genetic analysis.

RT1 control of disease susceptibility

Spontaneous diseases for which susceptibility has been described in the rat to be MHC controlled are type I diabetes mellitus (Colle et al. 1981) and thyroiditis (Awata et al. 1995; Pettersson et al. 1995) occurring in the BB strain. Diabetes of the BB rat closely resembles type I diabetes in humans and in the NOD mouse. Susceptibility is associated with the $RT1^u$ haplotype (Colle et al. 1981; Ellerman and Like 2000). The corresponding MHC-linked quantitative trait locus (QTL), *Iddm1*, maps to the class II region according to analysis of *RT1* recombinant strains (Colle et al. 1988; Günther et al. 1991). In humans, a strong association between susceptibility to type I diabetes and the *HLA* complex is found for *HLA-DQB* alleles that encode valine, serine or alanine instead of aspartic acid at position 57. In the BB rat, the $RT1\text{-}Bb^u$ gene encodes the susceptibility-conferring serine residue at this position, which is, however, also found in other *RT1-Bb* alleles (Chao et al. 1989).

The rat is a very useful model for several experimentally induced autoimmune diseases. Mostly tissue extracts, and tissue-specific proteins or peptides are used together with adjuvants to elicit the disease. Certain autoimmune syndromes can be induced by chemicals like mercury ($HgCl_2$) or gold salts (aurothiopropanolsulfonate). In each of the experimental autoimmune diseases for which the genetic basis has been studied, the *RT1* complex has turned out to play a major role in controlling susceptibility. Table 3 lists the diseases for which *RT1* association has been proven by genetic analysis. Inducibility of other autoimmune diseases is expected to be *RT1* associated as well, but pertinent genetic data are missing. Among the best-studied and most relevant experimental rat diseases are various types of EAE and arthritis, which are models for human multiple sclerosis and rheumatoid arthritis, respectively. Of note is that the MHC not only controls resistance or susceptibility to the disease, but also the course of the disease, as demonstrated for the acute, chronic, and relapsing forms of myelin oligodendrocyte glycoprotein (MOG)-induced EAE (Weissert et al. 1998).

The importance of the type of antigen chosen for eliciting the disease is illustrated by the EAE model. LEW

Table 3 RT1-disease associations

Disease	Mode of induction, strain (selected references); quantitative trait locus or gene
Type I diabetes mellitus	Spontaneous, BB (Colle et al. 1981), LETL, LETL-KDP (Komeda et al. 1998), LEW.1AR1-iddm (Wedekind et al. 2001); *Iddm1*
Experimental allergic encephalomyelitis (EAE)	Myelin basic protein (Williams and Moore 1973); myelin oligodendrocyte glycoprotein (Stefferl et al. 1999; Weissert et al. 1998); rat spinal cord (Bergsteinsdottir et al. 2000; Dahlman et al. 1999; Gasser et al. 1973); *Eae1*
Experimental allergic uveitis (EAU)	Retinal S protein, interphotoreceptor retinoid-binding protein (Hirose et al. 1991)
Experimental arthritis	
AIA	Freund's adjuvant (Kawahito et al. 1998a); *Aia1*
OIA	Oil (Lorentzen et al. 1998); *Oia1*
CIA	Collagen of bovine, chick, pig or rat origin (Griffiths et al. 1992, 2000); *Cia1*, *Ciaa1*
PIA	Pristane (Vingsbo et al. 1996); *Pia1*
AvIA	Avridine (Vingsbo et al. 1995)
Cartilage oligomeric matrix protein-induced arthritis	Cartilage oligomeric matrix protein (Carlsen et al. 1998)
Relapsing polychondritis	Matrilin (Hansson et al. 1999)
Experimental nephritis	
Anti-tubular basement membrane interstitial nephritis	Tubular basement membrane (Neilson et al. 1983)
Autoimmune complex nephritis	Tubular antigen (Stenglein et al. 1975)
Anti-glomerular basement membrane-mediated glomerulonephritis	$HgCl_2$ (Druet et al. 1977)
Immune complex-type glomerulonephritis	$HgCl_2$ (Sapin et al. 1982)
Immune complex glomerulonephritis	Glomerular basement membrane (Stuffers-Heiman et al. 1979)
Glomerulonephritis, increased IgE levels	Aurothiopropranolsulfonate (Kermarrec et al. 1996); *Atps1*
Thyroiditis	Spontaneous, BB (Awata et al. 1995; Pettersson et al. 1995)
Experimental allergic thyroiditis	Thyroglobulin (Penhale et al. 1975)
Cancer (hepatocellular and other tumors)	Diethylnitrosamine (Melhem et al. 1993); *rcc*

rats are highly susceptible to myelin basic protein (MBP)-induced EAE and resistant to MOG-induced EAE, whereas BN rats show the reciprocal pattern. MOG can induce a T- and B-cell response eliciting demyelination in contrast to MBP. Therefore, MOG-induced EAE presents a model more closely related to multiple sclerosis than MBP-induced EAE. The *Mog* gene maps to the *RT1-M* region at the telomeric end of the MHC (Fig. 3) and belongs to the butyrophilin-like gene family (Henry et al. 1999).

Class I and class II genes and the genes controlling antigen processing and loading are primary candidates for controlling susceptibility, because their gene products play a central role in autoantigen presentation to T lymphocytes in the thymus and in the peripheral immune system. By relating class II sequence differences with susceptibility to autoimmune diseases like EAE and arthritis, association of susceptibility to either *RT1-B* or *RT1-D* could be deduced (Vestberg et al. 1998). Distinct peptide sequences have been identified in the autoantigenic proteins that are capable of inducing the disease in an *RT1*-haplotype dependent manner as shown for MBP (de Graaf et al. 1999; Issazadeh et al. 1997; Mustafa et al. 1994) and MOG (Weissert et al. 2001). The relationship between peptide affinity to RT1-B and RT1-D class II molecules of various haplotypes, immunogenicity, T-cell reactivity, and disease-inducing potential has been studied in detail for MBP (de Graaf et al. 1999) and MOG (Weissert et al. 2001).

In MOG-induced encephalomyelitis (Stefferl et al. 1999; Weissert et al. 1998) and collagen-induced arthritis (Mattsson et al. 1999), susceptibility factors have also been assigned to MHC regions other than *RT1-B/D* like the *RT1-C/E/M* region. For most of the complex diseases listed in Table 3, an effect of the genetic background in addition to the *RT1* complex has been found, and non-MHC-linked QTLs have also been identified.

Analysis of various rat strains has revealed that BN rats are primarily susceptible to Th2-mediated autoimmune diseases like $HgCl_2$-induced nephritis, whereas LEW rats are mostly found susceptible to Th1-mediated diseases like MBP-induced EAE. Genetic evidence has been provided for the involvement of the *RT1* complex in controlling these different phenotypes of overall immunological responsiveness. BN rats have less $CD8^+$ T lymphocytes than LEW rats, so that a higher CD4/CD8 ratio is found in BN rats. This parameter is *RT1* controlled according to segregation analysis (Damoiseaux et al. 1999). Furthermore, in LEW rats interleukin (IL)-2- and interferon-γ-producing $CD45RC^{high}$ cells prevail among $CD4^+$ T lymphocytes compared to BN rats, in which IL-4-producing $CD45RC^{low}$ cells predominate among $CD4^+$ T cells. This distinct behavior is controlled by several QTLs detected by genome scanning, one being suggestively linked to the *RT1* region (Subra et al. 2001). In another study, however, no effect of the *RT1* complex on the Th1/Th2 ratio was found in the LEW/BN strain combination (Damoiseaux et al. 1998).

It is noteworthy that a QTL controlling stress-induced increase of blood pressure has been mapped to the *RT1*-encompassing chromosomal region, and the stress-inducible *Hsp70* genes in the class III region have been suggested to be responsible for this effect (Hamet et al. 1992; Rapp 2000).

A group of genes has been described in the rat MHC that control body size (*dw3*), fertility (*ft*), and resistance to chemical carcinogenesis (*rcc*) (Melhem et al. 1993). The genes are part of the *Grc* ("growth and reproduction complex") that has been mapped to the *RT1-C/E* region (Fig. 3a) and analyzed by overlapping cosmid clones (Salgar et al. 1997) (Fig. 3b). The $RT1^{r16}$ haplotype that is associated with the mutant phenotype dwarfism, male infertility, reduced female fertility, and susceptibility to diethylnitrosamine-induced hepatocellular cancer (Melhem et al. 1993) carries a deletion of about 50 kb including *RT1-N*, *RT1-O*, and *RT1-S* class I genes (Yuan et al. 1996). The genes responsible for the Grc^- phenotype have not yet been identified at the molecular level.

The large number of framework MHC genes that have been detected in the course of sequencing the *HLA* complex and that are found in the rat MHC as well provide a rich source of candidates for further disease susceptibility genes, so that MHC control might turn out to be also effective in controlling nonimmune-mediated diseases.

Concluding remarks

The complete nucleotide sequence of the rat MHC is expected to be available in the near future. This will be the final major step in the structural analysis of the rat MHC. Being based on the PAC and BAC libraries of BN strain ($RT1^n$) origin, the MHC sequence will be derived from a single haplotype of a widely used inbred rat strain. Molecular analysis of other *RT1* haplotypes will reveal the degree of variability in sequence, gene content, and genomic organization. The complete *RT1* nucleotide sequence will also provide a molecular basis for studying the function of the MHC much more extensively than is possible at present. As a by-product of the *RT1* sequence, a standardized nomenclature for the rat class I and class II genes can be established.

The comparison between the MHC of species like rat, mouse, and human shows a large degree of genomic conservation, the major exception being the diversity of class I genes. Extensive analysis of the MHC of many more species and the attempts to reconstruct MHC-paralogous regions and a primordial MHC (Flajnik et al. 1999; Kasahara 1999) will further contribute to our understanding of this gene complex.

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Note added in proof. A copy of the *C4* and *Stk19* genes could be detected in the *Btnl4/Notch4* interval of the BN rat. Updated information about the RT1 map will be available at http://www.immungenetik.uni-goettingen.de.

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