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HYPOTHESIS

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Evolution of the *Mhc* class I region: the framework hypothesis

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Abstract A comparison of the major histocompatibility complex (*Mhc*) region between human and mouse highlights both stability and differences. The class II and class III regions are orthologous; they probably existed in the ancestor in a similar organization and were not subjected to major rearrangement. The class I genes, by contrast, are definitely paralogous, having been reorganized several times. As long as only class I genes were identified, the class I regions of human and mouse were difficult to compare directly. The identification of non-class I genes has allowed a comparative map to be drawn, which shows that the class I region is orthologous between human and mouse as well. The lack of orthology specifically applies to the class I sequences. However, the comparative map shows that the non-orthologous class I sequences occupy homologous locations with regard to the conserved genes. I propose a model to explain this paradox. The conserved genes may represent samples of a dense "framework" of genes whose alterations are deleterious. The homologous positions occupied by class I genes would thus represent the few permissive places allowing major perturbations. The evolution of the class I sequences, by duplication and deletion, independently in the two species, has taken place within the scope defined by the framework: insertion at the permissive places, and expansion by creation of class I-related DNA by duplication, thus pushing back the boundaries of the framework.

Key words Major histocompatibility complex · Class I region · Evolution · Orthology · Olfactory receptor genes

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Introduction

Ongoing studies to elucidate the evolution of the major histocompatibility complex (*Mhc*) have divided it into two subregions: on the one hand, the class II and class III regions appear highly stable, on the other hand, the class I region was thought to be more plastic. Between human and mouse, numerous genes of the class II and class III regions exhibit orthologous relationships and the gene order is conserved (Beck et al. 1996; Trowsdale 1995) [Orthologous and paralogous relationships are used as defined by the Comparative Genome Organization (1996). Paralogous genes are genes within the same species descended from the same ancestral gene by duplication and divergence in the course of evolution. Orthologous genes are homologous genes in different species that are descended from the same gene in the nearest common ancestor.] This chromosomal segment is likely to have existed in the ancestor with a similar organization, and it has not been subjected to major rearrangement. Within this highly conserved structure, the class II genes are not directly homologous, but paralogous, because they have undergone subsequent duplications in both species after rodent radiation (Klein et al. 1993). However, the class II subfamilies, *DR*, *DQ*, *DP*, *DM,* and *DN*/*DO*, are orthologous between human and mouse; they were established prior to the divergence of the marsupial and eutherian mammal lineages (Klein et al. 1993; Slade and Mayer 1995).

Concerning the class I region, direct comparison has been difficult as long as the only genes identified were class I. Phylogenetic analyses showed that classical and non-classical class I genes are more closely related within one species than they are to any gene from the other species (Hughes and Nei 1989). Class I sequences have undergone several reorganization steps and are definitely paralogous (Hughes 1991; Klein and O'hUigin 1994; Klein et al. 1993). Since the publication of the compiled map of the human *Mhc* by Trowsdale and coauthors in 1991, which presented only class I sequences

in the class I region, non-class I genes have been identified and mapped in both species, showing that the class I region is orthologous, just as are the class II and class III regions (Amadou et al. 1995). One general scheme thus appears concerning *Mhc* evolution: plasticity of the *Mhc* genes within a highly conserved structure.

This clear picture is, however, only a partial answer, and reveals a paradox: class I genes are located in homologous positions with regard to the orthologous genes, although they are not derived directly from ancestors similarly located.

The purpose of this study is to propose a model to solve the paradox.

An updated comparative map

From the proximal to the distal part of the class I region, conserved genes mapped in both species are:

- *POU5F1* (EMBL Z11900), encoding the transcription factor Oct-3/4, is located 100 kilobases (kb) telomeric to *HLA-B* in human (*OTF3*; Crouau-Roy et al. 1994; Krishnan et al. 1995) and between *H2-Q10* and *H2-T24* in mouse (*Oct-3*; Uehara 1991, *Oct-4*; Yeom et al. 1991 and K. Fischer Lindahl, personal communication).
- *TCF19* (GB U25826), a cell cycle-regulated gene, is located closely telomeric to *POU5F1* in human (Krishnan et al. 1995). Its mouse equivalent has been identified close to *Pou5f1* by cosmid end sequencing (M. Yoshino and K. Fischer Lindahl, personal communication);
- *S* (GB L20815), expressed in keratinocytes, is located 60 kb telomeric to *POU5F1* in human (Zhou and Chaplin 1993) and between *H2-Q* and *H2-T* in mouse (K. Fischer Lindahl, personal communication). It is physically linked (on the same P1 clone) to *Pou5f1* (D. Chaplin, personal communication);
- *GNL1* (GB L25665), potentially encoding a GTP-binding protein, is located close and centromeric to *HLA-E* (*HSR1*; Vernet et al. 1994) and in the proximal mouse *H2-T* region, on the same cosmid as *H2-T24* (*Gna-rs1*; Yoshino et al. 1997);
- *ZNF173* (GB U09825), potentially encoding a nucleic acid binding protein, is located 200 kb centromeric to HLA-A in human (Chu et al. 1995) and in the mouse *H2-M* region, between the clusters *H2-M8*,*-M7*,*-M1* and *H2-M6*,*-M4*,*-M5* (Jones and coworkers, in press);
- *RFB30*, encoding a ring-finger protein, is located 200 kb centromeric to *HLA-A* in human (*B30.2*; El Kahloun et al. 1992) and in the mouse *H2-M* region, between the clusters *H2-M8*,*-M7*,*-M1* and *H2-M6*,*-M4*,*-M5* (*B30*; Jones et al. 1995, 1998);
- *TCTEX-5* (EMBL X81003), testis expressed sequence, is located between *HLA-E* and *HLA-A*, 150 kb centromeric to *HLA-A*, in human (Amadou et al. 1995; *HCGV*, Giffon et al. 1996) and between *B30* and *Mog* in mouse (Jones et al. 1998);
- *MOG* (GB U18798; U64572), myelin oligodendrocyte glycoprotein, is located 60 kb telomeric to *HLA-F* in human (Amadou et al. 1995) and 25 kb telomeric to *H2-M5* in mouse (Pham-Dinh et al. 1995);
- two mouse probes were found conserved in human (Amadou et al. 1995): the *D17Tu42* locus is located between *Mog* and *H2-M3*. At least two copies of the *Tu42* probe, duplicated in tandem, were identified (Jones et al. 1995; Yoshino et al. 1998); the human equivalent is located 70 kb telomeric to *MOG*, and two copies have also been identified (Amadou 1996). The *D17Leh89* probe is located telomeric to the *H2-M* class I genes (Yoshino et al. 1997), and the human equivalent is located distal to the class I genes, 600 to 800 kb telomeric to *HLA-F* (Amadou et al. 1995). Sequencing and fine mapping have shown that these genes belong to a cluster of olfactory receptor (*OR*) genes (Amadou 1996). The genes themselves could be paralogous sequences, having undergone subsequent duplications after speciation. Nevertheless, the *OR* cluster can be considered orthologous between the two species.

Figure 1 illustrates the features of the comparative data. The class I region is orthologous between human and mouse, and it is not an exception in the large conserved synteny unit that includes the *Mhc*. Comparative mapping can be used to identify and localize genes, so long as class I sequences are not considered. The case of *Tctex-5* is illustrative. The three clustered genes *Tctex-4*, *-5,* and *-6* were mapped distal to the mouse *H2-Q* region (Ha et al. 1991). The human equivalent, *TCTEX-5*, was localized between *RFB30* and *HLA-A*. *Tctex-5* has now been physically mapped in the mouse and is located between *B30* and *H2-M6,-M4,-M5* (Jones et al. 1998). The order of the conserved genes is thus strictly respected.

It is to class I sequences that a lack of orthology applies specifically, because of their evolution by successive waves of duplication and deletion. However, class I sequences are located at homologous positions with regard to the conserved genes, but they are not derived from ancestors similarly located.

The framework hypothesis

The conservation of genes between human and mouse, divergent by 100 million years, reflects the conservative selection pressure exerted on the gene through the function of the protein. The conserved genes already identified in the class I region can be hypothesized to be a representative sample of dense regions of genes with essential functions, thus defining a "framework" of genes whose alterations are deleterious. Class I genes have evolved by duplication independently in the two species. From the ancestral class I sequence, wherever it was located, new duplicates have been inserted among the functionally important genes that constitute

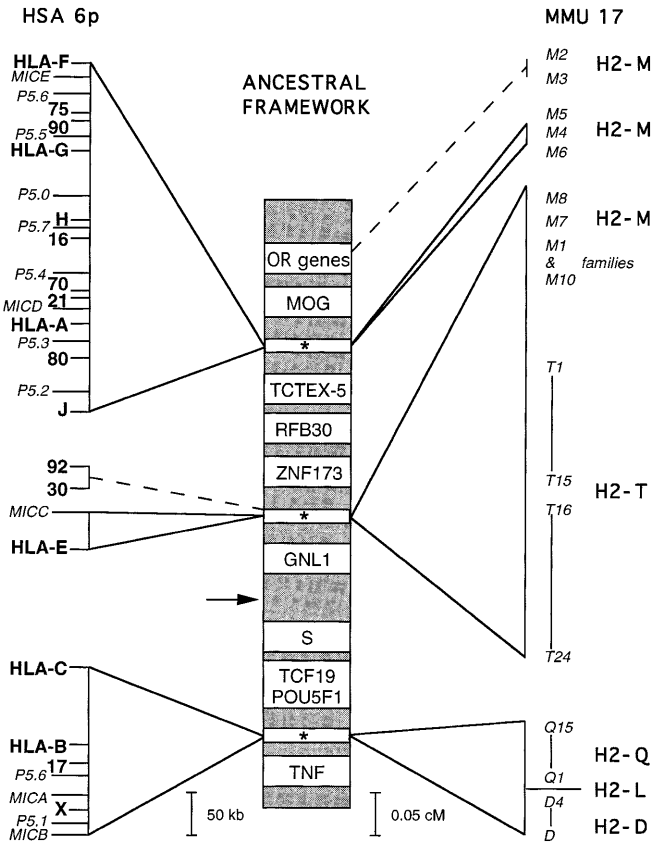

Fig. 1 The "crazy butterfly" model illustrates the independent expansion of class I sequences within the scope of a framework of highly conserved genes. *Asterisks* identify the permissive places in the framework. The arrow is explained in the text. Not all the multicopy sequences duplicated with the class I sequences are drawn (see text). "*OR* genes" stands for "a cluster of olfactory receptor genes". The map has been drawn according to Yoshino and co-workers (1997), Campbell and Trowsdale (1997), Fischer Lindahl and co-workers (1997), the 1997 report on mouse Chr 17 (http://www.informatics.jax.org), and unpublished results from K. Fischer Lindahl's laboratory

the framework. The "homologous positions" today occupied by the class I sequences thus represent the few places that permit the major perturbations produced by class I insertions and/or duplications.

This model, opposing the framework to the class I expansion, presents the class I region at two levels:

1. The framework, so defined, represents the ancestral structure. It is a "conserved ordered segment" according to the Comparative Genome Organization (1996), as the synteny and order of the genes are conserved.
2. The insertions and duplications of class I sequences have to take place within the scope defined by the framework.

The discrepancies in the size of the class I region in human and mouse should not be seen as expansions or contractions in one species with regard to the other, but as expansions of the class I genes with regard to an ancestral framework, separately in the two species.

More arguments and consequences

Class I-devoted zones

The zones where the class I sequences are located should be class I-devoted, created by the class I duplications and reorganization. This view is supported by the *en bloc* duplication evidenced in human (Avoustin et al. 1994; Leelayuwat et al. 1995; Pichon et al. 1996a). In a review of the genes or pseudogenes located close to the class I sequences, many multi-copy sequences have been reported (Campbell and Trowsdale 1997). With the exception of the *PERB11*/*MIC* genes, these sequences are not conserved outside the primate order. It appears that a 30 kb fragment has been amplified, multiplying the class I sequence with *P5* (Vernet et al. 1993), *PERB11*/*MIC* (Bahram and Spies 1996a; Bahram et al. 1994; Leelayuwat et al. 1994), *HCG-II*,*-IV* (El Kahloun et al. 1993), *HCG-VIII*,*-IX* (Pichon et al. 1996b), *3.8*, and *10.0* (Venditti et al. 1994). Partial duplications or subsequent deletions can explain why the entire duplicated segment has not been preserved in all locations. For example, *HLA-E* lacks a *P5* copy. From *HLA-J* to *HLA-F*, the high number of gene fragments supports the view that successive duplications occurred at the same place, resulting in fragmented segments. In this way, the *MIC-C*, *-D* and *-E* copies, respectively located close to *HLA-E*, *-A* and *-F*, are gene fragments (Bahram and Spies 1996b). Moreover, large-scale comparative mapping between *HLA* haplotypes has shown that the region around *HLA-A* is subject to great variability, involving large deletions and insertions (Chimini et al. 1988; Venditti and Chorney 1992; Watanabe et al. 1997). The class I expansion around *HLA-A* was not smooth. In such a chaotic context, it is difficult to imagine an essential gene escaping destruction and, therefore, negative selection.

In the context of this model, it is interesting to follow the transcription studies (Gruen et al. 1996). Among the transcripts identified from the class I region, many correspond to the duplicated sequences cited above. No data have yet been presented to support their functional relevance. On the contrary, *P5-1* has been shown to be an irrelevant sequence dragged in by a class I promoter (Avoustin et al. 1994). Some other transcripts meet stronger criteria, such as sequence similarity in other species or with known protein domains. They have been mapped around *HLA-E* (e.g., *CAT54*), or between *HLA-92* and *HLA-J* (e.g., *ZNF178*), which are defined as framework zones. Others have not yet been mapped, and are arbitrarily drawn on the maps across the region covered by the YAC to which they belong (Campbell and Trowsdale 1997; Gruen et al. 1996). Taking the example of YAC 225B1, which spans from *HLA-E* to *HLA-A*, I predict that all the biologically relevant transcripts map to the areas belonging to the framework, exemplified by *GNL1* and *RFB30*.

In the mouse, the *H2-Q* and the *H2-T* genes are grouped into families by sequence comparison. They are thought to have expanded by tandem duplication and unequal crossing-overs. Strain differences reflect these recombinational events that resulted in direct duplications, deletions and gene fusions, such as the *Q8/Q9* fusion in the BALB/c mouse (Fischer Lindahl 1997; reviewed by Flaherty et al. 1990). The same scheme applies to the *H2-M1* and *H2-M10* gene families located in the proximal part of the *H2-M* region (Arepalli et al. 1998; Jones et al. 1995; Singer et al. 1988;). Up to now, no non-class I gene has been identified between the class I sequences within the *H2-Q* and *H2-T* regions. Strain variations have been used as an argument to infer that these class I genes, deleted in some strains, cannot be essential for survival, even if functional (Klein and Figueroa 1986). The same argument can apply in the context of the framework hypothesis: more than likely, the *H2-Q* and *H2-T* regions are class I-devoted. They have been created by class I-related sequence amplification and no conserved gene will be found in these regions.

The setting-up of the class I genes would thus have occurred by insertion at the permissive places defined by the framework, followed by expansion by creation of class I-related DNA, pushing back the boundaries of the framework.

High gene density and essential functions

The framework must contain a high density of genes with important or essential functions to justify a strong conservative selection pressure over the framework zones. Good candidates, whose alterations are drastically selected against, are genes playing a role in gametogenesis or development. At this point, it must be mentioned that the *Mhc* class I region is located at the distal end of the mouse *t*-complex inversion. This complex genotype is associated with multiple lethal mutations and abnormalities in fertility, embryogenesis and development (reviewed by Frischauf 1985). Up to now, most of the identified mutations associated with the *t*-complex map proximal to the *Mhc*. However, the *t*-complex is still far from having been fully elucidated, and this must be kept in mind in studies regarding the regions it spans. For example, the *Tctex* (*t*-complex testis expressed) genes were originally described as being differentially expressed in testis of wild-type and *t*-mutant mice (Ha et al. 1991).

As the high sequence similarity between human and mouse reflects conservative selection pressure, this conservation must be traceable far away in phylogeny. As an example, Giffon and co-workers (1996) report that the *TCTEX-5* gene contains a peptide motif highly conserved in *C. elegans*. A search for similarity with the BLAST program (Altschul et al. 1990) also identifies the same motif on yeast Chr VI. Another example of evolutionary conservation is given by *GNL1*, shown to contain a core ATP/GTP-binding motif shared with prokaryotes (Vernet et al. 1994). Search for similarity in the databases identifies extended similarities, far more extensive than the G boxes identified in *GNL1*, with sequences from *Drosophila*, *C. elegans*, and yeast (Fig. 2). For these three organisms, the sequences aligned by BLAST are collinear, and the identities and similarities are respectively 51% and 68% with *Drosophila*, 45% and 68% with *C. elegans* and 48% and 65% with *S. cerevisiae.* Such a high conservation, no doubt, reflects essential function.

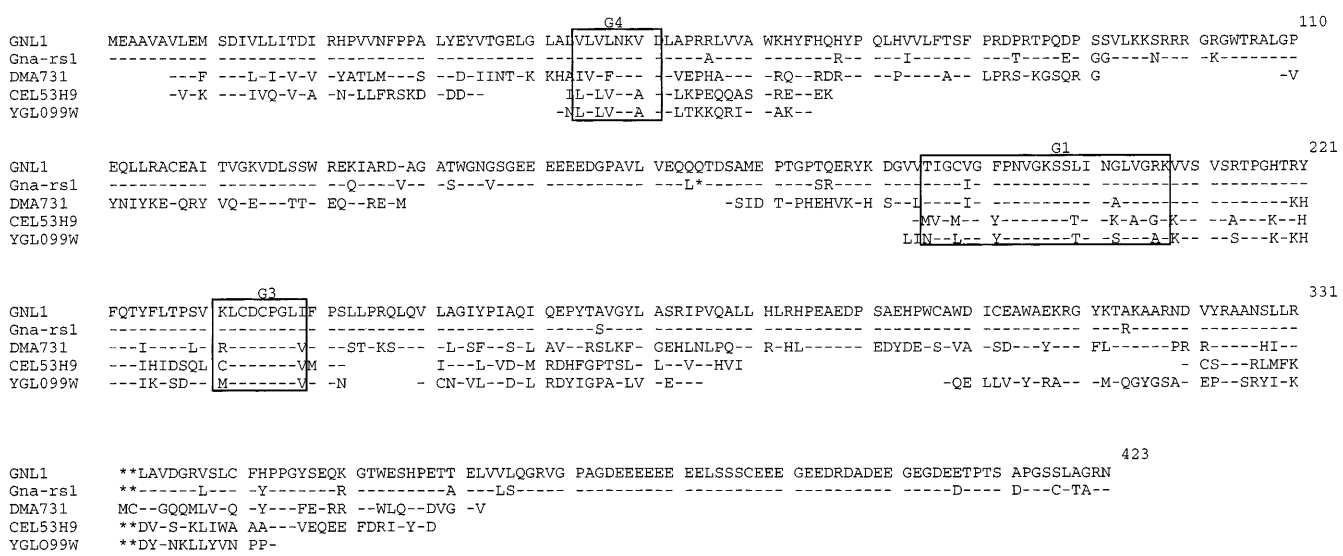

Fig. 2 *GNL1* is highly conserved in phylogeny. The figure presents the alignment of *GNL1* with putative translations identified by TBLASTN in the Databases Search Service at: http//www.sanger.ac.uk. *GNL1* (human, GB L25665); *Gna-rs1* (mouse, EMBL X65026); DMA731= sequence DMAC000731 from *D.melanogaster* (GB AC000731); CEL53H9= cosmid C53H9 from *C.elegans* (GB AF003143); YGL099W= ORF YGL099w from *S.cerevisiae* Chr VII (EMBL Z72621). A *dash* indicates identity, an *asterisk* indicates a gap. The GTP-box motifs identified by Vernet and co-workers (1994) are *boxed*

Specific locations

Three locations are specified in Fig. 1:

1. The arrow indicates the position previously attributed to *HLA-X/P5–1*. This location was first questioned by Venditti and co-workers (1994), who mapped it centromeric to *HLA-B*. Large scale sequencing analysis definitively relocated it between *MICB* and *MICA* (Shiina et al. 1998). This obliteration supports the framework hypothesis, as the equivalent region in the mouse, between *S* and *Gna-rs1*, is devoid of class I-exon 4 sequence (A. Kumánovics and K. Fischer Lindahl, personal communication).
2. The dashed lines mark species-specific locations. In human, *HLA-E/MICC* and *HLA-30/-92* could belong to the same "class I expansion" unit, or identify different permissive places in the framework. Progress in studies of the transcripts isolated from this region and the ongoing human MHC sequencing projects will answer the question.
3. In the mouse, *H2-M3* and *-M2* mark the distal limit of the *Mhc*. They are located between the *Tu42* and *Leh89* olfactory receptor genes (Yoshino et al. 1997). Phylogenetic relationships among the *H2-M* genes, and with other class I genes, have not been established; however, BLAST alignment and hybridization experiments clearly show that *M3* and *M2* are not more related to the other *H2-M* genes, divided in *M1* and *M10* subfamilies, than to other class I genes, classical or non-classical (Arepalli et al. 1998). *H2-M3* and *-M2* have an evolutionary history different from their neighboring *-M* genes, and this should be reflected by a change in nomenclature. With regard to the framework, they are located among *OR* genes. As the evolution of *OR* genes is similar to that of class I genes, by duplications from pre-existing genes, the regions where they expand are plastic. This cluster of *OR* genes could thus mark the end of the framework, as it also corresponds to the end of the conserved synteny with human (Amadou et al. 1995).

Conclusion

The definition of the class I framework applies to all mammals. Further mapping in other mammalian species will help to define precisely the permissive places within the class I framework. In the recent expansion of class I genes, the relative degree of expansion may differ from species to species, but, with regard to the framework, insertion points should be the same. The class I framework could also help define the ancestral *Mhc*, by tracing the highly conserved genes earlier in the phylogeny, and their linkage with *Mhc* genes.

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