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The Major Histocompatibility Complex of Primates: Evolutionary Aspects and Comparative Histogenetics

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GENETIC CONSIDERATIONS

The major histocompatibility complex of primates: evolutionary aspects and comparative histogenetics

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All mammalian species investigated have a chromosomal region designated as the major histocompatibility complex or m.h.c. The biological significance of the m.h.c. goes far beyond controlling the most important histocompatibility or transplantation antigens; the capacity to respond immunologically, the susceptibility to disease (including cancer), the serum level of several complement factors and numerous other biological traits are regulated by genetic systems closely linked within that chromosomal region.

While the basic structure of the m.h.c. seems to be rather similar for all mammalian species, the similarities among the m.h.c. of human and non-human primates are particularly impressive. In this communication, m.h.c. gene products of rhesus monkey, chimpanzee and man are compared and reviewed. Evolutionary aspects of the persistence of the m.h.c. region or 'supergene' throughout the animal kingdom are discussed.

A symposium dealing with evolution is hardly the right forum for a discussion of primate tissue antigens, since only a very limited number of primate species have been investigated and studies on these were not really aimed at trying to solve evolutionary problems. Nevertheless, when serological methods were used to compare m.h.c.-controlled tissue antigens of man, the chimpanzee and the rhesus monkey (also with those of several other primate species), observations were made that permit certain cautious conclusions concerning the probable phylogenetic relations among those species.

In view of the multidisciplinary nature of this symposium, it might be appropriate to start with a brief introduction to the major histocompatibility complex (m.h.c.), its organization, biological significance and some of its evolutionary aspects.

The concept of an m.h.c. was first introduced by Snell in the early 1950s. Working with inbred strains of mice, he made the distinction between genes associated with acute and with chronic rejection of allografts (transplants exchanged among individuals of the same species). Acute rejections were assumed to be due to disparity for products of an m.h.c., slow rejection to disparities for products of multiple 'minor' histocompatibility genes (Snell *et al.* 1953). Today we know that, in nearly all species investigated, there is a cluster of closely linked highly polymorphic genes designated as the m.h.c. Broadly speaking, the m.h.c. is involved in cellular recognition and differentiation phenomena and in the regulation of immune responses (for details, see Götze (1977)).

For practical purposes, the m.h.c. can be divided into three parts that delineate regions related by their genetic origin and/or function (Klein 1977). Class I genes code for molecules that are target antigens in transplantation reactions and play a role in the recognition of virus-infected cells; class II genes are involved in cellular proliferation, cell to cell interactions and immune responsiveness; class III genes control complement components or receptors for complement.

The evolutionary aspects of the m.h.c. have been the subject of numerous investigations and speculations. Here we will address ourselves to three questions only. (1) Which classes of organisms have a demonstrable m.h.c.? (2) How can the absence or presence of an m.h.c. in different species be explained in terms of evolutionary development? (3) How similar are m.h.c. products of various species and what are the implications of such similarities in terms of evolution?

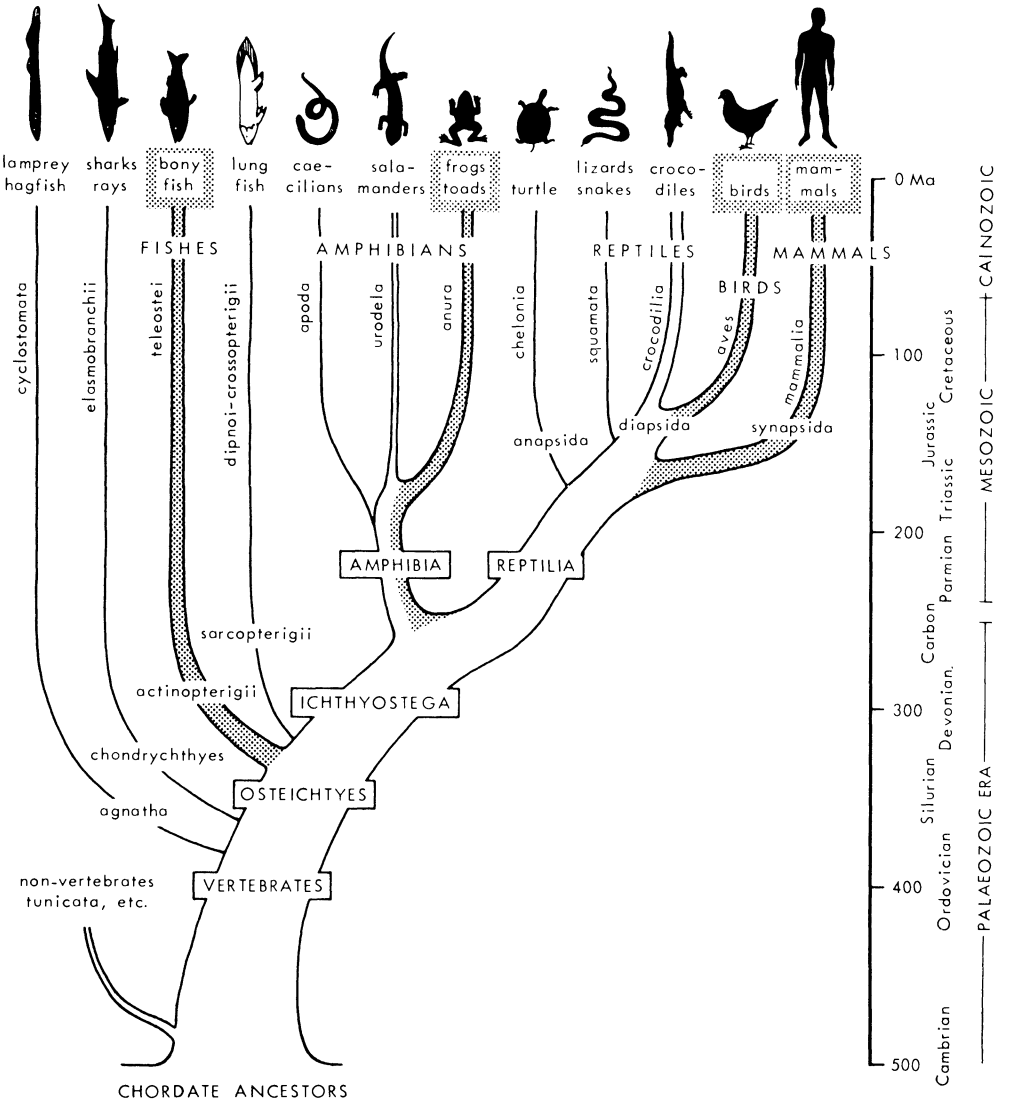

FIGURE 1. Convergent evolution of the major histocompatibility complex (m.h.c.) among vertebrates. The presence of a 'genuine' m.h.c. as defined by the capacity to mount an acute allograft reaction is indicated by a shaded branch of the evolutionary tree. Note that the emergence of this type of m.h.c. did not proceed in a straight evolutionary line. Solid black symbols at the top indicate that relevant data are available for at least some members of that class; no data are available for dipnoi (e.g. lung fish). The figure is modified after Klein (1977, fig. 10.2).

An answer to the first question obviously depends on the criteria applied. If the criterion is an organism's capacity to effect an acute allograft rejection, then such a 'true m.h.c.' cannot be demonstrated in invertebrates. Among the vertebrate species, a true m.h.c. is present in some bony fishes, some amphibia and all birds and mammals investigated so far. This is schematically

depicted in figure 1. If we accept this information, the emergence of the m.h.c. did not proceed in a straight evolutionary line, since some relatively young phyla such as reptiles lack a genuine m.h.c. while older ones (like bony fish) seem to have it. There are even differences among closely related phyla, since some amphibia (anura) have a typical m.h.c. while others do not. Likewise, birds and reptiles that are rather closely related phylogenetically do not show the same development with regard to an m.h.c.

What is the evolutionary explanation for such 'erratic' development (question (2))? Most investigators regard the occurrence of the m.h.c. as a typical example of convergent evolution. To quote Ohno (1970): 'divergent species maintain ancestral [m.h.c.] genes; natural selection independently favours similar types of tolerable mutations to cope with demands by similar environments'. Thus, while all vertebrates have the ancestral m.h.c. gene, it evolves into a functional m.h.c. only when there is a need for it and at different stages of evolution. Cohen (1979) agrees with the principle of convergent evolution. However, he also believes that an ancestral gene that did not develop into a genuine m.h.c. (in invertebrates and some vertebrates) may have evolved into that species' predominant minor histocompatibility locus.

The third and last question deals with similarities observed for m.h.c. products of different species. There are various methods of comparison. One of the more sophisticated ones is the determination of amino acid sequences of the m.h.c. products. When data for sequences of class I antigens of the murine H-2 complex became available, it appeared that the similarity among the allelic products of the *K* or the *D* locus was about 80%. When the products of those two linked loci were compared, the similarities were slightly less outstanding but still 60–80%. Similar studies of the *A*- and *B*-locus antigens of HLA revealed 90% similarity among the allelic antigens and 80–90% similarity between the products of the two loci. The observation that closely linked loci such as HLA-*A* and -*B* code for products that are biochemically nearly identical certainly suggests that an original single locus was duplicated, probably to maintain the advantage of heterozygosity even when in-breeding occurs (Ohno 1970). Finally, a striking similarity with regard to amino acid sequences of the N terminal of the class I molecules was also found when antigens of mouse and man were compared (Klein 1977). Such interspecies similarity between the products of homologous loci in phylogenetically rather distant mammalian species again favours the hypothesis that the modern mammalian m.h.c. developed from a common ancestral gene.

RhLA, THE MAJOR HISTOCOMPATIBILITY COMPLEX OF RHESUS MONKEYS

In the mid-1960s, the increasing activity in clinical organ transplantation led to a major interest in human tissue typing and a search for optimal animal models for preclinical transplantation research. For the latter purpose, the rhesus monkey was a particularly suitable candidate because of its phylogenetic closeness to man and the availability of much biological background information. Thus, around 1965, two teams of investigators (one in Holland, one in the U.S.A.) began studying the tissue antigens of rhesus monkeys. Domestic breeding was initiated and, by 1970, a number of pedigreed families was available to facilitate genetic studies of the m.h.c. and its products. In the context of this review, the RhLA story will be told in a very cursory fashion only. As before, we will subdivide the m.h.c. into three classes of genes.

The class I or SD antigens of RhLA were the first to be identified. The closely linked, highly polymorphic *A* and *B* loci were established in 1970 (Balner *et al.* 1971). SD antigens are

identifiable with alloantisera, i.e. sera raised by cross immunization of individuals of the same species, and by the use of a complement-dependent cytotoxicity test. About 25 *A*- and *B*-locus antigens are now identifiable; their characteristics and biological significance are fully described elsewhere (Vreeswijk *et al.* 1977). Three categories of class II products of RhLA have also been studied: the *D* or m.l.c. determinants, the Ia or B-cell specific antigens and the *Ir* genes. The *D* or major m.l.c. locus of rhesus was established in 1973 (Balner & Toth 1973). Products of the *D*

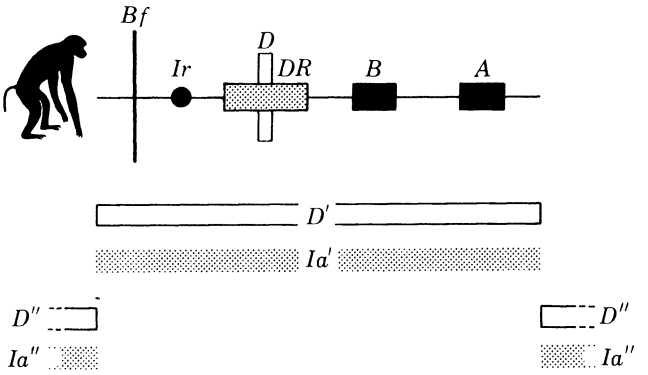

FIGURE 2. Tentative model of RhLA, the major histocompatibility complex of the rhesus monkey. An explanation for the symbols used and for the suggested mapping positions of the proposed genes and loci is given in Balner (1980*b*).

locus have an overriding influence on reactivity in mixed lymphocyte culture (m.l.c.). Disparity for D antigens evokes a proliferative response, which is measurable *in vitro*, by means of the incorporation of radiolabelled thymidine. The *D*-locus antigens can be identified by a cellular method with 'homozygous typing cells'. Evidence has been recently obtained that loci other than *D* can also exert an influence on m.l.c. reactivity (for details, see Es & Balner (1979)). The Ia or B-cell specific antigens of rhesus have been known since 1974 (Balner & Vreeswijk 1975). They are the homologues of the murine Ia antigens, and like SD antigens, are identifiable with alloantisera. However, tissue distribution, chemical characteristics and biological properties of Ia antigens are different from those of SD antigens. Initially, there was evidence for only one major locus controlling the Ia antigens of primates, the *DR* locus, which defines Ia antigens highly associated (possibly identical) with the D antigens mentioned earlier. More recently, non-DR Ia antigens of rhesus monkeys have been identified, some being controlled by RhLA, others not (for details, see Es & Balner (1979)). Finally, there are m.h.c.-controlled *Ir* genes. In mice and in rhesus monkeys, *Ir* genes have been identified by determining the capacity to respond immunologically to certain synthetic antigens. The nature of the *Ir* gene product is not known; it may be a 'T-cell receptor', a structure by which T lymphocytes recognize foreign antigens and subsequently help other cells to mount an effective immune response (for details regarding *Ir* genes of rhesus, see Dorf *et al.* (1975)). Some class III gene products of rhesus monkeys have also been investigated. Thus, Bf, the proactivator of complement factor C3, was found to be controlled by the m.h.c. (Ziegler *et al.* 1975), as it is in man and the chimpanzee.

Figure 2 schematically illustrates the current knowledge of the approximate mapping positions of some of the loci of RhLA. Details, also with regard to the biological function of the depicted loci, are presented elsewhere (Balner 1980*a*, *b*). It should also be mentioned that cell hybridization studies by Garver *et al.* (1980) have revealed that the m.h.c. of the rhesus monkey is located

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on that species' homologue of the human chromosome no. 6, which carries the HLA complex. Garver's studies also showed that some of the enzyme systems syntenic with HLA in man are syntenic with the m.h.c. also in rhesus monkeys and in chimpanzees (see below).

ChLA, THE MAJOR HISTOCOMPATIBILITY COMPLEX OF CHIMPANZEES

Tissue antigens of chimpanzees have been investigated less extensively than those of man or the rhesus monkey. Yet the availability of a chimpanzee breeding colony at the Primate Center T.N.O. made it attractive also to study the tissue antigens of a primate species very closely related to man phylogenetically. In this section we will briefly summarize the current knowledge of the m.h.c. of chimpanzees. Again, the ChLA region will be subdivided into the three classes of genes proposed by Klein (1977).

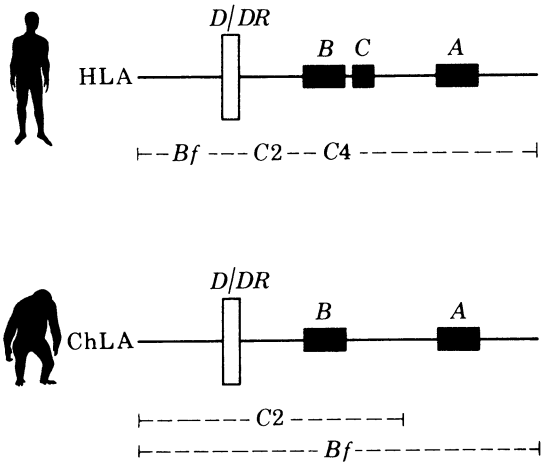

FIGURE 3. Current state of genetic mapping of the ChLA system and comparison with the human HLA system. An explanation for the symbols used and for the suggested mapping positions of the proposed genes and loci, is given in the text and in Balner (1980*a*) and Jonker & Balner (1980*a*, *b*).

Class I or SD antigens of the chimpanzee were first reported in 1967 (reviewed in Götze (1977)). Because of the paucity of available typing reagents and related animals for segregation studies, the progress in tissue typing of chimpanzees lagged behind that for man and the rhesus monkey. It was not until 1973 that two linked series of class I antigens were established and shown to be markers of the chimpanzee's m.h.c., designated as ChLA (Balner *et al.* 1974). The *A*- and *B*-locus products of chimpanzees were clearly the homologous of the products of the *A* and *B* loci of man and rhesus monkeys (see following section). (For details regarding serological techniques, genetic analysis etc., see Balner *et al.* (1978).) The class II determinants of ChLA were more difficult to identify than their counterparts in class I. A major m.l.c. or *D* locus was tentatively reported in 1973 (Seigler *et al.* 1974). But it was not until recently that the ChLA-linked *D* locus was firmly established and some of its determinants were defined (Jonker & Balner 1980*b*). Only little information is available on Ia or DR antigens of chimpanzees. The close phylogenetic relation with man permitted the use of human anti-DR typing reagents in attempts to demonstrate DR antigens in chimpanzees. Such 'cross-species typing' (see below) revealed that chimpanzees probably carry DR antigens similar to those of man (Balner 1980*a*). Immune response genes have not yet been demonstrated in chimpanzees. With regard to class

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III determinants, two complement factors, C2 and Bf, were shown to be ChLA-linked also in chimpanzees (Raum *et al.* 1980); the genetic control of factor C4, which is also m.h.c.-linked in man, is the subject of current investigations. Finally, Garver, Pearson and their coworkers were able to prove synteny of ChLA with the enzyme systems SOD2, GLO-1, ME-1 and PGM3, all on chimpanzee chromosome 5, the homologue of human chromosome 6 (Garver *et al.* 1980).

Figure 3 schematically depicts the current state of provisional genetic mapping of the identifiable loci of the ChLA system and a comparison with some of the known loci of the human HLA system. The position of the chimp's *A* and *B* loci is unquestionably identical to that of the *A* and *B* loci of HLA. Linkage of the *D* locus with ChLA is now firmly established.† There is also evidence that C2 and Bf are linked to ChLA (see above). When the segregation of C2 in chimp families, was studied, an aberrant segregation pattern was observed in a single offspring, suggesting a recombinational event. Since that particular offspring appeared to be a recombinant also for the *D* locus product (Jonker & Balner 1980*a*), *C2* as well as *D* can be provisionally mapped 'to the left' of the ChLA-*A* locus.‡ Thus, if *D* is placed outside the *A*–*B* region (which is reasonable in view of the firm data for the homologous loci of man and rhesus monkey), the most reasonable mapping positions are those depicted in the figure 3.

Similarities among m.h.c.-controlled tissue antigens of different primate species

In this last section, we will briefly review what has been done so far to compare m.h.c.-controlled antigens among several primate species by serological means and the conclusions that can be cautiously drawn.

Comparing primate characteristics by cross-species typing is certainly not as accurate as comparing chromosomal banding patterns (Dutrillaux *et al.* 1973; Mitchell & Gosden 1978), gene mapping by various kinds of hybridization (Finaz *et al.* 1975; Pardue & Gall 1970), biochemical analysis (Jeffreys & Barrie, this symposium; King & Wilson 1975) and data obtained with monoclonal antibodies (Brodsky *et al.* 1979). Nevertheless, cross-species typing as described here can also reveal similarities and dissimilarities that may be revelant to phylogeny and evolution.

Let us now discuss briefly the principle of cross-species typing. Let us first take chimpanzee and man; as indicated, *A*- and *B*-locus antigens of chimpanzees are most readily identified with antisera raised by alloimmunization of chimpanzees. Likewise, selected human alloantisera will identify *A*- and *B*-locus antigens of humans. To compare the SD antigens of the two species, a simple approach would be: (*a*) to test chimp cells with human typing reagents; (*b*) to test human cells with chimp typing reagents; and (*c*) to absorb the antisera of both species with cells of either species and subsequently retest the absorbed reagents with cells of both species (there are of course refinements of cross-species typing which have been described elsewhere (Balner 1980*a*)). However, when performing these kinds of serological tests, one is often

† Although the data for the chimp's *DR* or *D*-related Ia antigens are scanty and based on cross-species typing only, it is fair to predict that the position of *DR* in relation to *D* will be similar to that in man and rhesus monkey (for details Jonker & Balner (1980*a*)).

‡ Since the relevant parent of the recombinant offspring in question was homozygous for a *B*-locus antigen, *C2* and *D*/*DR* can be mapped to the left of the *A* locus and their mapping position with regard to the ChLA *B* locus are not yet known (although *D*/*DR* is very likely located outside the *A*–*B* region (Jonker & Balner 1980*a*).

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faced with problems and uncertainties. Therefore, it was necessary to establish rules according to which the degree of similarity between cell membrane antigens of related species can be assumed. The criteria that we have used are shown in table 1. Thus, when cross-species typing between the chimpanzee and man was done in both directions (chimp to man and man to chimp), 'meaningful' serological patterns were obtained, i.e. some human HLA antigens are probably very similar to corresponding ChLA antigens. Moreover, *A*-locus antigens of the one species

TABLE 1. CRITERIA FOR ASSUMING THE PRESENCE OF HLA-LIKE ANTIGENS ON CHIMPANZEE CELLS

serological conditions that apply		likelihood that HLA-like antigen is present on chimp cells
1. a single HLA serum shows polymorphism, by one technique		unlikely
2. several HLA sera show concordant typing results	with one technique	unlikely
	with several techniques	possible
3. HLA reactivity removed by absorption with chimp cells (retesting on human cells)		probable
4. 'meaningful' results obtained in absorption and elution studies on cells and sera of both species (see text for explanation)		very likely
5. alloimmunization of chimpanzees yields antibody of same HLA specificity in man		very likely

corresponded only to *A*-locus antigens of the other and the same so for the *B* locus products of both species. This is schematically shown in figure 4. Some of the similarities indicated in the figure could be shown to be 'near-identities' when detailed studies were performed along the lines of points 4 and 5 of table 1 (e.g. ChLA-A108 and HLA-A11 (Balner 1980*a*)).

This 'game' of cross-species typing can of course also be played to compare D and DR antigens (class II) of the two species. Thus, highly concordant results were obtained when human sera defining certain human DR antigens were tested with suspensions of chimpanzee B lymphocytes (Balner 1980*a*). Therefore, according to the rules of table 1, we can cautiously predict that chimpanzees carry DR antigens similar to those of man. However, absorption studies and the reverse typing (i.e. using chimpanzee anti-DR sera for the typing of human B cells) have not yet been done. Likewise, conventional cellular methods for identifying *D*-locus antigens were employed to compare the D or m.l.c. antigens of the chimp and man. Provisional data reveal that it is indeed possible to type chimpanzees with human typing cells†; likewise, typing cells of chimpanzees have shown some meaningful reactions when tested with human cells (Jonker & Balner 1980*a*). Thus, it can be cautiously concluded that *D*- and *DR*-locus products of chimpanzees resemble the homologous m.h.c. products of man.

Cross-species typing has also been performed with the panel of antisera that define the RhLA-*A* and -*B* locus antigens of rhesus monkeys. The sera were first tested with cells from two cercopithecoid species, the Asian stumptail (*M. arctoides*) and an African baboon species

† 'Typing cells' homozygous for *D*-locus antigens are traditionally used to determine D antigens in man, the chimpanzee, the rhesus monkey and dogs (for details see Jonker & Balner (1980*a*)).

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(*P. cynocephalus*). The methods were the same as those used for chimp–human typing and the criteria used for assuming similarities were again those shown in table 1. The results revealed that, of the 15 RhLA antigens identifiable at that time (1972), stumptails and baboons seemed to carry six or seven antigens presumably similar to those of rhesus monkeys (RhLA 1, 6, 9, 19, 11 and 14 for stumptails; RhLA 1, 5, 6, 19, 2, 11 and 13 for baboons). Here, the evidence for

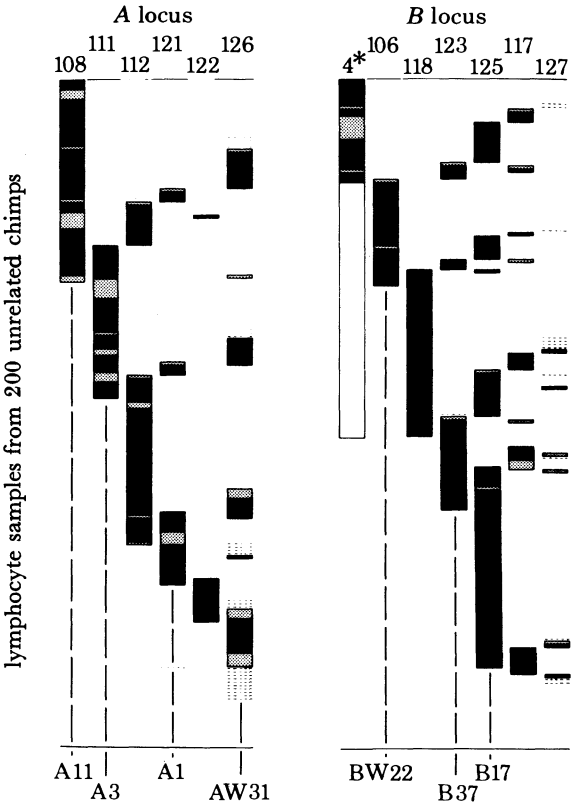

FIGURE 4. ChLA antigens of chimpanzees. Distribution of antigens controlled by the *A* and *B* loci of ChLA in 200 unrelated chimpanzees. The vertical columns indicate lymphocytotoxicity patterns of groups of antisera (group numbers at the top). An antigen was assigned if the majority or all sera of a group reacted strongly positive (black horizontal bars); shaded horizontal bars indicate variable, mostly weak serological reactions and uncertainty about the presence of an antigen; blanks are negative reactions and interrupted horizontal lines indicate that an animal was not typed for a particular antigen. The cell samples depicted in the left part of the figure were arranged for an optimal display of *A*-locus antigens, those in the right part for *B*-locus antigens. Symbols at the bottom of the figure stand for human HLA antigens 'associated' with certain ChLA antigens of chimpanzees; associations are based on results of typing part of the chimp population with human HLA sera (from Balner *et al.* 1978).

similarity was somewhat weaker than in the chimp–human comparison, since the reverse pattern of testing could not be performed (reliable alloantisera defining class I antigens of stumptails or baboons are not available).

From the standpoint of phylogeny, an important question is whether meaningful serological results can be obtained when cross-species typing is performed among less closely related primate species, e.g. when comparing hominids with simians. This kind of work has been carried out and the results are depicted in figure 5 in a highly schematic fashion. In the course of these studies, it appeared, that groups of sera defining RhLA antigens never showed meaningful

concordant results when tested against panels of human and chimpanzee cells, although many individual sera displayed polymorphic patterns (i.e. positive and negative lymphocytotoxic reactions). Such results were difficult to interpret, also because absorption or elution studies had not been performed. Nevertheless, it was interesting that RhLA sera, which showed a particular reactivity pattern against chimpanzee cells (only negative, only positive or clearly polymorphic reactions), usually displayed a similar reactivity pattern when tested against human cells. But

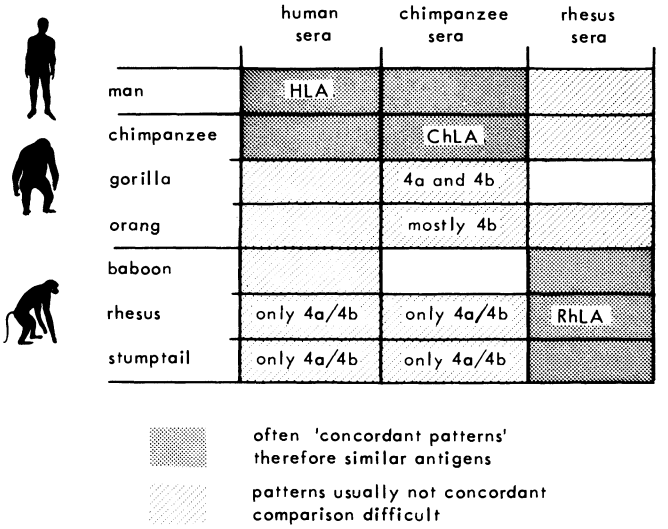

FIGURE 5. Sharing of tissue antigens between several primate species. Schematic presentation of conclusions drawn from results obtained in direct cross-species typing. Human, chimpanzee and rhesus alloantisera that define m.h.c.-controlled antigens were screened for cytotoxic reactivity against lymphocytes from the other species shown in the figure. For details and a further explanation of symbols and abbreviations, see text and Balner (1980*a*).

when the same sera were tested against orang-utan lymphocytes, reactivity patterns were erratic, with no resemblance whatsoever to the patterns observed in chimp and man.† Likewise, when testing human and chimpanzee alloantisera with cells from rhesus monkeys or other cercopithecoids, uninterpretable reactivity patterns were obtained. Only sera with anti-4a or anti-4b reactivity‡ showed interesting patterns. If we accept the results summarized in figure 5, also for combinations for which no absorption and elution experiments had been done, then the following, very tentative conclusions can be drawn. (*a*) Man and the chimpanzee 'share' a fairly large number of m.h.c.-controlled class I antigens, possibly also some of the class II antigens. However, no such similarities were found between man and the chimp on the one hand and gorilla and orang-utan on the other. A tentative conclusion would be that chimpanzees are closest to man phylogenetically, an opinion also held by a number of investigators who base their conclusions on cytogenetic, biochemical or other experimental approaches (Bodmer & Bodmer 1978). (*b*) Rhesus monkeys share class I m.h.c.-controlled antigens with other cerco-

† When testing RhLA sera against dog cells and cells from numerous mouse strains, the results were also erratic and uninterpretable. In those combinations, however, pre-existent heteroantibodies may interfere more strongly than in interprimate tissue typing.

‡ Antigens 4a and 4b are so-called supertypic HLA antigens first reported by Rood & Leeuwen (1963). They are present on chimpanzee and rhesus monkey cells and are considered to be a 'basic substance' of certain m.h.c. products of primates, and possibly of all mammalian species (Balner *et al.* 1974).

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pithecoid simians. Surprisingly, the 'degree of sharing' was rather similar for rhesus and the Asian stumptail macaque, as for rhesus and an African baboon species. However, by means of this serological approach, RhLA-like antigens could not be detected on cells of man or apes. The genetic distance between hominoids and cercopithecoids is likely to be the reason for this difference. (*c*) The so-called supertypic tissue antigens 4a and 4b (Rood & Leeuwen 1963) seem to be shared by all primate species so far investigated. This observation would be in accord with data obtained recently by Bodmer's group using monoclonal antibodies directed against some of the 'basic molecular structures' of m.h.c.-controlled antigens; those supertypic specificities were also widely distributed among primate species. Both sets of data (Bodmer's data obtained with monoclonal antibodies and ours with regard to 4a and 4b) support the concept of a common ancestral gene as the origin of the modern m.h.c. antigens.

Summary

The m.h.c. is a cluster of closely linked polymorphic genes with a major impact on cell to cell recognition, morphogenesis, cell differentiation and immunological defences. Its presence in many, but not all, vertebrate species suggests a convergent evolution from a common ancestral gene. In all mammalian species so far investigated, a 'genuine' m.h.c. has been found. The very similar organization of the m.h.c. and the biochemical near-identity of certain m.h.c. products, even among remotely related species such as mouse and man, also suggests a common ancestral gene as the origin of the modern m.h.c.

The m.h.cs of three primate species (man, the rhesus monkey and the chimpanzee) have been studied and compared. As expected, the organization of the m.h.c. in the three species is virtually identical. Results of so-called serological cross-species typing among those three and a few other primate species suggest a rather high degree of sharing of antigens between chimpanzee and man and also among the cercopithecoid simians investigated. However, there was little sharing of m.h.c. antigens between the hominoids on the one hand and the cercopithecoids on the other. The only exceptions were the supertypic antigens 4a and 4b, which may represent a 'basic molecular structure' shared by so-called private m.h.c. antigens of each species. Further, it appeared that the genetic distance among the hominoid species investigated is smallest between man and chimpanzee.

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