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7

# Sequence Analysis of MHC Class II Genes in Cetaceans

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## 1. Introduction

Genes of the major histocompatibility complex (MHC) offer several assets that make them unique candidates for studies of adaptation in natural populations (Potts & Wakeland, 1990; Hedrick, 1994). The primary role of the MHC is to recognize foreign proteins, present them to specialist immune cells and initiate an immune response (Klein & Figueroa, 1986). The MHC gene family includes highly polymorphic genes encoding a set of transmembrane glycoproteins that are critical to the generation of immune responses (Kennedy et al., 2002). In general, foreign proteins enter cells either by infection or by phagocytosis into antigen-presenting cells such as macrophages. These foreign proteins are broken down into small peptides and loaded onto specific MHC molecules. The MHC molecule comprises an immunoglobulin stalk, which anchors the molecule to the cell surface, and a basket receptor called antigen-recognizing sites (ARS) located in peptide binding region (PBR). A subset of these protein/MHC complexes are then transported to the cell surface and presented for interrogation by the circulating T-cell population. A complex cascade of immune responses is triggered when the T cell binds to the presented peptide. Two major groups of MHC genes can be distinguished. MHC class I genes play an essential role in the immune defense against intracellular pathogens by binding peptides mainly derived from viral proteins and cancer-infected cells. They are expressed on the surface of all nucleated somatic cells. In contrast, MHC class II genes are predominantly involved in monitoring the extracellular environment by presenting peptides mainly derived from parasites (e.g. bacteria, nematodes, cestodes) to the T-cells. They are primarily expressed on antigen-presenting cells of the immune system, such as B cells and macrophages. Although ARS do show a degree of specificity, a single MHC molecule can bind multiple peptides that have common amino acids at particular anchor positions (Altuvia & Margalit, 2004). Genes within the MHC involved in antigen presentation constitute the most polymorphic loci known in vertebrates (Hedrick, 1994). The polymorphism of the MHC-molecules is associated with the diversity of the T-lymphocyte receptors that in turn determine the disease and parasite resistance of an organism and thus may affect the long-term survival rate of populations (Hedrick et al., 1999; Paterson et al., 1998). The ARS show high levels of polymorphism not only in the number of alleles but also in the sequence variation among alleles (Hughes & Yeager, 1998). The general view is that balancing selection is the determinant role in shaping patterns of nucleotide diversity in MHC genes (Bernatchez & Landry, 2003; Hughes & Nei, 1989).

Balancing selection refers to forms of natural selection in which no single allele is absolutely most fit (Hughes & Yeager, 1998, Meyer & Thomson, 2001). It is in contrast to directional selection that favors a few alleles. Balancing selection results not only in the maintenance of large numbers of alleles in populations, but also in greatly enhanced persistence of allelic diversity over extremely long time periods relative to neutral genetic variation (Paterson, 1998). It results in an observation termed 'trans-species evolution of polymorphism (Klein & Figueroa, 1986), which some alleles from a species are more similar to the alleles of different species than each other, rather than the species-specific pattern.

Genetic and antigenic diversity of the MHC could be important in a host's ability to accommodate rapidly evolving infectious agents that periodically afflict natural populations (Klein & Sato, 1998). Exactly how much MHC diversity is required to ensure long-term population viability remains a fundamental question in conservation genetics. A lack of variation at the MHC may increase the susceptibility of an isolated population to infectious disease epidemics, with potentially catastrophic consequences (Bowen et al., 2002). For example, a link between MHC diversity and an effective response to both pathogenic and toxicogenic challenges was proposed (Acevedo-Whitehouse et al., 2003). Therefore, understanding the polymorphism of these genes, and their products, is vital for studying infectious disease ecology at the population level. This is particularly important in marine species whose chemical and microbial environment is increasingly influenced by anthropogenic encroachment, which increases marine species' risk of exposure to novel pathogens (Harvell et al., 1999). However, not all MHC genes show high diversity. The most diverse and extensively studied MHC genes are the *DQB* and *DRB* genes. Diversity of *DQB* or *DRB* genes has been characterized in many mammalian species such as primates (Bontrop et al., 1999), bank vole (Axtner & Sommer, 2004), domestic mammals (Schook & Lamont, 1996, Yuhki & O'Brien, 1997, Mikko et al., 1999, Wagner et al., 1999), and marine mammals (Murray et al., 1999, Bowen et al., 2002, 2004, Baker et al., 2006, Hayashi et al., 2006, Yang et al., 2007, Xu et al., 2007). After these studies on non-model free-ranging species were carried out, intriguing questions were raised about whether and how selection operates on the MHC of natural populations characterized by distinct pathogens and demographic and environmental conditions (Bernatchez & Landry, 2003; Sommer, 2005).

It was suggested that the pathogen environment of marine mammals may provide a diminished selective pressure for maintaining MHC polymorphism (Murray et al., 1995; Murray & White, 1998; Slade, 1992), due to the relatively low prevalence of infectious disease in the marine environment. For example, Murray et al. (1995) found that the genetic variability at the MHC *DQB* loci of the beluga (*Delphinapterus leucas*) was much lower than those of primates. There are several other hypotheses that have been put forward to explain the reduction of MHC diversity in marine mammals, such as population bottlenecks and random drift acting in small populations (Murray & White, 1998; Slade, 1992). In order to discriminate among the hypotheses, it would be most informative to assess MHC variation in delphinids with large populations and no evidence of historic population bottlenecks.

Seventy to fifty five million year ago (Mya), in the warm shallow waters of the Tethy Sea, mammals related to ungulates are thought have begun one of the most successful recolonizations of the marine environment (Arnason & Gullberg, 1996; Bajpai & Gingerich, 1998; Thewissen & Williams, 2002). It is possible that earliest cetaceans were faced with a new range of pathogens associated with the marine environment. The study of the evolution

of the MHC in cetaceans presents an exciting opportunity to observe the response of the MHC to the new pressures of the marine environment. We reviewed the relationship between alleles in different cetacean species to evaluate whether certain allele sequences were shared by different cetaceans inhabiting similar or different environments. In addition, phylogenetic analyses revealed that the sequence divergence in several species might reflect different selective pressures between pathogens in oceanic and coastal waters. The information gained from sequence analysis is the essential foundation to analyze variation of MHC genes and study infectious disease ecology.

## 2. Sequence variation of MHC class II genes in cetaceans

The studies of MHC variation in cetaceans were directed at investigating variation of *DQB* gene exon 2 locus, which has been shown to be highly polymorphic in many terrestrial carnivores and domestic animals (Schook & Lamont, 1996; Wagner et al., 1999; Yuhki & O'Brien, 1997). MHC class II gene investigation in cetacean species presumed that immunogenetic diversity is generated by polymorphism at one or two specific loci (Murray et al., 1999), a reasonable assumption based on established knowledge in terrestrial species (Mikko et al., 1999; Wagner et al., 1999). In most studies, the sequence analysis of amplified 172 bp fragments showed that there are no more than two alleles revealed in each individuals. One single *DQB* locus has been reported in other toothed whales (Hayashi et al., 2003; Hayashi et al., 2006; Murray et al., 1995). However, duplicate *DQB* genes were described in the baleen whales (Baker et al., 2006), baiji (*Lipotes vexillifer*) (Yang et al., 2005), and finless porpoise (*Neophocaena phocaenoides*) (Xu et al., 2007, 2009). It was proposed that bearing multiple *DQB* genes is consistent with the retention of an ancestral condition shared with the ruminants, and it has been lost in the more derived cetaceans such as the true dolphins (Baker et al., 2006). However, this suggestion is not supported by the finless porpoise, which is also supposed to be a derived species.

MHC variation has been examined in some species of cetaceans and revealed different results. Earlier studies demonstrated low level of MHC genetic diversity in fin whales (*Balaenoptera physalus*) and sei whales (*Balaenoptera borealis*) (Trowsdale et al., 1989). However, Nigenda-Morales et al. (2007) reported the PBR of the *DQB* locus in fin whales from Gulf of California has experienced strong positive selection. Sequence analysis of beluga whales MHC-II loci (including *DQB* and *DRB*) revealed low but measurable polymorphism (Murray et al., 1995; Murray & White, 1998). Recent sequencing analysis of cetacean populations revealed considerable sequence variation in some species of the baleen whales and toothed whales (Baker et al., 2006; Hayashi et al., 2003; Xu et al., 2007, 2008, 2009; Vassilakos et al., 2009; Yang et al., 2005; Yang et al., 2007, 2008, 2010; Heimeier et al., 2009). These studies also found evidence of positive selection, as showed by high levels of nonsynonymous substitutions at ARS. For example, the amount of variation of *DQB* in common bottlenose dolphins (*Tursiops truncatus*) (Yang et al., 2008) is significantly higher (6 alleles and 21 nucleotide substitutions in 172 bp found in 42 dolphins) than that in beluga (only 5 alleles and 11 nucleotide substitutions in 172 bp found in 233 beluga) (Murray et al., 1995). Xu et al. (2007) reported that finless porpoises seem to retain considerable MHC genetic variation (14 *DQB* alleles in 195 porpoises) despite population decline in recent years. Moreover, the finding in humpback whales (23 *DQB* alleles from 30 individuals) (Baker et al., 2006) provided a counter example to the expectations of a slow mutation rate

for animals with large body size and long generation time. These findings not only suggest a positive selection pressure on the cetacean *DQB* locus but also argue against a reduction in the marine environment selection pressure. Similar arguments were made in the studies on beluga *DRB*1 locus (Murray & White, 1998), North Atlantic right whale (*Eubalaena glacialis*) *DQB* locus (Murray, 1997), Baiji *DQB* locus (Yang et al., 2005), and finless porpoise *DQB* locus (Hayashi et al., 2006). Besides, no deviation from Hardy-Weinberg expectations (i.e. no excess of heterozygotes) was observed in beluga and common bottlenose dolphins, suggesting that the effect of balancing selection for short time periods might be weak and masked by other microevolutionary forces (e.g. gene flow, mutation, drift, and non-random mating). Similar conclusions were reached by Boyce et al. (1997) from bighorn sheep (*Ovis canadensis*), Huang and Yu (2003) from the Southeast Asian house mouse (*Mus musculus castaneus*) in Taiwan, and Miller et al. (2004) from New Zealand robins (*Petroica australis*). Nonetheless, there are other possible explanations, such as spatiotemporal variation of selection and demographic processes acting on small populations (reviewed by Piertney & Oliver, 2006). Hayashi et al. (2006) also found evidence for both balancing selection overall, and genetic drift in small, local populations for the *DQB* locus in the finless porpoise.

The sequence information raises important questions regarding immunologic diversity in cetaceans. While those studies present valuable information, variation at 1 part of a gene, or 1 gene, is not an appropriate measure of variation for the entire MHC (Murray & White, 1998). It is possible that low diversity at the MHC has been observed only because short fragments (usually less than 200 bp) were amplified and the functionality of the alleles was not taken into account (e.g., Sommer, 2003, Amills et al., 2004), which might lead to a misinterpretation of the results (Axtner & Sommer, 2007), with the possible consequence that a severe population bottleneck is inferred (Baker et al., 2006). Besides, the MHC variation in one locus cannot definitely represent the ability of pathogen defense of a species because MHC polymorphism in marine mammals arises from several loci. For example, a moderate to high degree of polymorphism is only found in *DRB* genes, not in *DQB* gene, in beluga and California sea lion (*Zalophus californianus*) (Bowen et al., 2004; Murray and White, 1998), and the situation reverses in humpback whale (*Megaptera novaeangliae*) (Baker et al., 2006). Therefore, characterization of full-length expressed sequences of MHC genes is very important for making valid evolutionary inferences on non-model species like cetaceans. To date, there is only one published article characterizing the full-length *DQB* and *DRB* gene sequences in cetaceans (Yang et al., 2007), which were from the RACE cDNA products of *T. truncatus* and *T. aduncus*. The nucleotide and deduced amino acid sequences of the 780- (*DQB*-primer derived) and 801-bp (*DRB*-primer derived) products were typical of transcripts from mammalian class II genes. The result revealed the presence of 1 *DQB* locus and 2 *DRB* loci in *Tursiops*. The high proportions of non-synonymous nucleotide substitutions in the putative peptide-binding regions of *Tutr-DQB*, *Tuad-DRB*, and *Tutr-DRB* suggest positive selection pressure on these gene loci (Hughes & Yeager, 1998) and imply functional roles for these molecules in pathogen-specific immune responses. In *DRB* of *T. aduncus*, for example, the majority of 44 variable sites were in exon 2 (38/44), with the remainder being distributed in exons 1 (1/44), 3 (4/44), and 4 (1/44). The deduced amino acid sequences indicated that the substitutions clearly tended to be clustered around the ARS. The divergence of non-synonymous substitutions was significant at the codons of the ARS ($p < 0.005$). The polymorphic *Tuad*-DR$\beta$ amino acid residues ($n = 25$) were located in the leader peptide (1/25), the $\beta$1 domain (21/25), the $\beta$2 domain (2/25), and the transmembrane domain (1/25).

The correlations between MHC alleles and disease resistance (e.g. malaria, hepatitis B, leprosy, tuberculosis) and disease-susceptibility (cancer, parasite infestation) have been reported (reviewed by Sommer, 2005). Human pathologies have also been correlated to specific amino acid replacement and motif changes in ARS among different populations (reviewed by Vassilakos et al., 2009). There are striking differences in the prevalences of some disease-resistance alleles in different human population. MHC associations also show some geographic variation. It seems likely that the same evolutionary selection pressures that have given rise to polymorphisms in genes involved in resisting infectious pathogens have contributed to marked allele frequency differences at the same loci. Gene-environment interactions are likely to introduce another layer of complexity. In marine mammals, for example, MHC genotypes of California sea lions were associated with urogenital cancer (Bowen et al., 2005). One of the *DQB* allele in *T. truncatus* was found being assocaited with strandings although only marginally significant (Yang et al., 2008). In addition, only five individuals carried this allele were fresh enough for pathological examination in that study so that the subsequent statistical analysis of lesions could not be done. Therefore, further studies are needed to identify genes of major to moderate effect in a single population with large sample size and then determine whether a similar effect is found elsewhere, and we may elucidate the potential mechanisms underlying the association between MHC alleles and cetacean strandings.

## 3. Phylogenetic analyses of MHC class II genes in cetaceans

Recent molecular and morphological studies have suggested that the order Cetacea may be more closely related to even-toed ungulates than to other orders of ungulates (Arnason et al., 2000; Boisserie et al., 2005; Kumar & Hedges, 1998; Murphy et al., 2001). In addition, cetaceans and hippopotamuses (*Hippopotamus amphibius*) form a monophyletic group deeply nested within Cetartiodactyla while camels and pigs are basal to this order (Boisserie et al., 2005; Gatesy 1997; Gatesy et al., 1996; Nikaido et al., 1999). The molecular clock estimate for the divergence of the artiodactyls and cetaceans is about 60 Mya (Arnason and Gullberg 1996). It is believed that early cetaceans initially lived in freshwater habitats as terrestrial quadrupeds and were partly dependent on freshwater at some stages of their life before they gradually adapted to the marine environment and became fully aquatic marine mammals in the end (Thewissen & Williams, 2002). The adaptation of immune response in cetaceans is supposed to be critical to cetaceans in their move from land to water, which is an enormous shift in habitat environment. Since major qualitative differences in microorganisms and infectious diseases are believed to exist between marine and terrestrial environments (McCallum et al., 2004), the immune genes of primitive cetaceans are supposed to be adapted for defending against distinct pathogens in aquatic environment. Several empirical studies showed that heterogeneity in selection pressure directly correlates with MHC gene diversity (Bernatchez & Landry, 2003; Charbonnel & Pemberton, 2005; Wegner et al., 2003).

Both class I and class II MHC gene families have been shown to evolve according to the birth-and-death process (Nei et al., 1997). The MHC class II loci of mammals have homologous relationships and slower rate of birth-and-death evolution than that of class I loci (Takahashi et al., 2000). Takahashi et al. (2000) used long nucleotide sequences (573 bp) including PBR and other regions from vertebrate MHC class II α and β-chain loci to study

the time of origin and evolutionary relationships of these loci. Their result showed the definite grouping of sequences from different genes. However, only three species from Cetartiodactyla (pig, cattle, and sheep) were studied while the evolutionary relationships of MHC genes among Cetartiodactyla remain unresolved. We may know how and when the habitat shift, accompanied by the change of foreign antigens, affected the history of co-evolution between MHC genes and pathogens when cetaceans moved from land to water by interpreting the phylogenetic relationship and divergence time estimates of MHC class II genes in cetaceans and their close-related terrestrial species. Yang et al. (2010) constructed phylogenetic trees and estimate the divergence times of clades using cDNA sequences (616 bp) of *DQB* and *DRB* genes that encode the extracellular domain (including PBR), connecting peptide, transmembrane, and part of the cytoplasmic tail from cetaceans (bottlenose dolphins; *T. truncatus* and *T. aduncus*), hippo and other ungulates, together with other MHC class II β-chain genes from fish, frog, chicken, and other mammals. It showed that the phylogenetic relationships in the respective cetartiodactyl group in *DQB* and *DRB* clades in this study do not correspond to that in the previously accepted species tree. It is striking to observe that cetaceans (bottlenose dolphins) and artiodactyls (pig, hippo, and ruminants) form two distinct clades in both *DQB* and *DRB* phylogenies, rather than being of the same clade with hippo and dolphin as the closest relatives. The authors presumed that the sequences of cetaceans and artiodactyls are paralogous in *DQB* and *DRB* genes, respectively. Paralogous genes separated by gene duplication events, which has been proposed to be a major force in MHC evolution, while the orthologous genes separated by speciation events. (Klein et al., 1998). The gene duplication has been observed in the genetic organization of MHC genes in many mammals. In bovine MHC class II genes, for example, two *DQB* genes and nine *DRB* genes were detected, with eight of the *DRB* genes being likely pseudogenes (Ellis & Ballingall, 1999). Since natural selective pressures of infectious diseases between terrestrial and aquatic (especially marine) environments are different (McCallum et al., 2004), the pathogen-driven evolution (Meyer & Thomson, 2001) was supposed to be very likely the driving force of birth-and-death process in the MHC genes for the cetaceans and their terrestrial relatives leading to the paralogy (Yang et al., 2010). Besides, if the MHC genes of cetaceans did evolve in a different direction from their terrestrial relatives, it is important to know when cetaceans entered into the water and how their MHC genes evolved. For estimating the divergence time of MHC genes of cetartiodactyls, Bayesian inference (BI) tree with birth-death clock model provided better estimates of divergence time of MHC genes than neighbor-joining (NJ) tree using Kimura 2-parameter model with linearized tree method (Yang et al., 2010). The result suggested that cetaceans (*T. truncatus* and *T. aduncus*) diverged from artiodactyls (pig, hippo, and ruminants) about 60 Mya or slightly earlier, which is comparable with the first appearances of fossil cetaceans around 53.5 Mya, artiodactyls at 55 Mya, and other molecular estimate of divergence time of cetacean/artiodactyl at 60 Mya (Arnason & Gullberg, 1996; Arnason et al., 2000, 2004; Theodor, 2004). However, only two close-related species of true dolphins were included in this study, and therefore the full-length sequences from other early divergence of cetaceans (such as baleen whales and river dolphins) are needed for confirming the hypothesis. Furthermore, several other mammal groups have also made the evolutionary transition from land to sea, such as pinnipeds, sea otters, polar bears and sirenians. Studying MHC genes of these marine mammals and their terrestrial relatives will provide us further insight into the evolution of MHC genes.

Some MHC alleles from a species are more similar to the alleles of different species than each other, rather than the species-specific pattern. This scenario has been referred to as trans-species evolution (Klein, 1987), which is one of the characteristics of the MHC genes and has been identified in a wide range of taxa including primates, salmonids, ungulates, pinnipeds, rodents, geckos, and warblers (reviewed by Piertney & Oliver, 2006). In cetaceans, most of the phylogenetic analyses of PBR sequences of *DQB* and *DRB* loci also show trans-specific pattern (Baker et al., 2006; Hayashi et al., 2003; Xu et al., 2009; Yang et al., 2008; Heimeier et al., 2009). Involving in 28 species of cetaceans, Xu et al. (2009) shows no or weak support for clades of same family or species in the phylogenetic relationship among *DQB* alleles. For example, no monophyletic groups for two cetacean suborders (Mysticeti and Odontoceti) were found. In addition, some alleles were more closely related with those from other species even from other families rather than with intraspecific alleles. It raised question about whether such pattern of apparent transspecific sharing of alleles is due to common lineages or convergence of independent lineages (Yeager & Hughes, 1999). Coalescent and neutral theories predict that two species will share a proportion of alleles at any given locus immediately following divergence from their ancestral form. Over time, from a phylogenetic perspective one should see a gradual progression from polyphyly, through paraphyly, to monophyly. However, balancing selection, which acts on MHC genes, retains alleles among species for considerably longer periods of time and increases the time over which there is incomplete lineage sorting and delaying the time to monophyly (Piertney and Oliver, 2006). If the trans-species evolutionary pattern in cetaceans described in previous studies is due to common lineage, the sharing of similar alleles by a common ancestry between cetacean families would require their preservation for a considerably long time, such as Delphinidae (dolphins) / Monodontidae (beluga) separating at least 15 Mya (Arnason et al., 2004), or Delphinidae/Lipotidae (baiji) 25 Mya (Nikaido et al., 2001). The result in Yang et al. (2010) supported this assumption. The authors estimated the divergence time of two close-related dolphin species (*Tursiops truncatus* and *T. aduncus*) in *DQB* and *DRB* genes (>20 Mya) is much earlier than the separation date of these two species. The earliest fossils identifiable as *Tursiops* dated to only 4-7 Mya (Barnes 1990), as well as the emergence of oldest delphinid which is possible 11 Mya of latest Miocene (Barnes 1977). The authors postulated these allelic lineages of *Tursiops* MHC genes may emerge by gene duplication during the period of early radiation of small toothed whales (from late Oligocene to early Miocene, 22 Mya (Arnason et al., 2004). Since MHC alleles could be persisted over extremely long time period by balancing selection (Bernatchez and Landry 2003), these lineages were maintained for a long evolutionary period through speciation events of cetaceans and cause the observed scenario of trans-species evolutionary pattern.

Apart from trans-species evolution, several studies on phylogenetic analyses of PBR sequences of *DQB* and *DRB* loci showed other interesting evolutaionay patterns. The first is the homoplasy of PBR in *DQB* and *DRB* genes (Baker et al., 2006; Yang et al., 2010). The *DQB* and *DRB* genes are thought to have arisen early in the placental mammals and evolved independently such that sequences of each gene can be recognized as orthologous across lineages (e.g., Ellis 1999; Groenen et al., 1990). Thus, sequences from either gene of different mammals should group together with their orthologs in phylogenetic reconstruction, exclusive of sequences from paralogous loci. Although this pattern was observed when the longer or full length of the fragment was used (Baker et al., 2006; Yang et al., 2010), it was not the case when only PBR sequences (~170 bp) were for comparison: the *DQB* and *DRB*

sequences of *Tursiops* are sistergroups within the clade containing all other *DRB* sequences of mammals (Yang et al., 2010), and cetacean *DQB* sequences grouped with some cetacean *DRB* sequences and appeared most closely related to the primate and ungulate *DQB* (Baker et al., 2006). A similar pattern of *DQB*/*DRB* convergence is reported in the canids (Seddon & Ellegren, 2002). The best explanation is convergent evolution (Yeager & Hughes, 1999), and small-scale conversion of the *DRB* by *DQB* alleles seems most consistent with the available evidence and is the most potentially responsible for convergence (Baker et al., 2006).

Second, Xu et al. (2008) reported that the *DQB* exon 2 of the baiji revealed striking similarity with those of the finless porpoise. Especially, some identical alleles were shared by both species at the DQB locus. The scenario of total identity amongst MHC alleles from different species have been reported, but most of which are restricted to congeneric species and rarely from above genus level (reviewed by Xu et al., 2008). The two species are highly divergent with each other, with the baiji included in Lipotidae of the superfamily Lipotoidea and the finless porpoise in Phocoenidae of the superfamily Delphinoidea, respectively. It is difficult to explain the identity and high similarity between distantly related species using trans-species evolution. Unlike trans-species evolution, the identity and similarity that are shared in the case of convergent evolution are not the result of evolution from a common ancestor, but typically explained as the result of common adaptive solutions to similarly environmental pressures. It is known that baiji and finless porpoise are sympatric in the Yangtze River and facing similar selection pressure from the similar freshwater environment, shaping the same motifs or alleles in both species in order to adapt to the similar pressures (Xu et al., 2008). Further studies are needed to clarify the convergent evolution with more MHC loci or other molecular data.

The third is adaptive differentiation. Yang et al. (2007) reported that the phylogenetic analyses of the full-length region and exon 2 of *DQB* and *DRB* showed no mixture but a clear division between *T. truncatus* (from Taiwan and Japan) and *T. aduncus* (from Taiwan and Indonesia). This is an intriguing result compared to the general trans-specific pattern of evolution observed for cetacean MHC loci. The species-specific clustering of *DQB* or *DRB* loci has been described in a few species (South African antelope by van der Walt et al. 2001, cotton rats by Pfau et al. 1999). Compared with *T. truncatus* which generally appears in deep, offshore waters, *T. aduncus* inhabits shallow, tropical, coastal waters and its body size is smaller than *T. truncatus* (Zhou & Qian, 1985). Because shallow waters along the coast are influenced by terrestrial runoff, the diversity and abundance of pathogens in the coastal waters likely differ from those in oceanic areas (Hayashi et al., 2006). Moreover, Wang et al. (1994) showed the parasites, Phyllobothrium, Monorhygma, and Crassicauda, are found only in the offshore form of *T. truncatus*, whereas Braunina is found in the coastal population in the western North Atlantic. Since *T. truncatus* and *T. aduncus* have different diets, microflora, and distributions (Wang et al., 1999, Wang 2003), thus it is reasonable to assume that different selective pressures from pathogens exist in oceanic (*T. truncatus*) and coastal (*T. aduncus*) waters. The most likely explanation is that species-specific alleles may have adaptive value for certain species and can be discriminately selected. When the selective advantage of MHC alleles differs among environments that vary in the diversity and abundance of pathogens, pathogen-driven directional selection could act differentially among individuals from distinct populations (Bernatchez and Landry 2003). This would have resulted in sequence divergence of exon 2 in bottlenose dolphins as observed in the study (Yang et al., 2007). The findings in Vassilakos et al. (2009) provided further support of

this hypothesis. They showed coastal and offshore samples of *Tursiops* from various sources exhibited significantly different profiles of PBR (Coastal: Western North Atlantic coastal *T. truncatus* and *T. aduncus* off South Africa; offshore: *T. truncatus* from the Mediterranean Sea, Eastern North Atlantic, Western North Atlantic pelagic, and the eastern North Pacific off southern California). Similar functional analysis has been used in human studies (reviewed by Vassilakos et al., 2009). We do not know how similar the pathogen environments are for coastal *T. truncatus* and *T. aduncus*. Although the possible pathogen-specific interactions are not known, it suggested the directional selection in local, differentiated populations because the pattern of differences and similarities is consistent with this interpretation (Vassilakos et al., 2009). Since extant cetacean fauna consists of more than 80 species and live in varied habitats, such as ocean, estuary, polar regions, and river, it is interesting to elucidate the evolution of cetacean MHC genes by obtaining more sequences and loci from a variety of cetacean species.

## 4. Conclusion

Over the past two decades cetacean MHC immunogenetics has developed from a genetic diversity study to a diverse field exploiting new methodologies to identify the evidence of pathogen-host coevolution. The previous studeis set out to achieve two major goals: (1) to assess levels of MHC variation in cetaceans to elucidate the role of selection in the evolution of cetacean MHC loci; (2) to characterize PBR and full-length MHC class II *DQB* and *DRB* genes in cetaceans and shed light on the evolution of cetacean MHC genes by performing the phylogenetic analyses. Although the information provides aspects for discussing the relationship between emergence of cetaceans and evolutionary pattern of MHC genes, the key questions remain the same. What MHC polymorphisms affect differential susceptibility to infectious diseases in cetaceans? What extent has selection by particular pathogens or enviroment given rise to observed polymorphism in MHC genes? Can the identification of certain allele related to specific environment or population identify loci that are targets for conservation interventions? For these highly mobile marine species, the expectation would be for random-mating across broad geographic ranges, but various studies have shown restricted gene flow over a range of hundreds or even tens of kilometers (Natoli et al. 2005). We could expect, and cannot excluded, the differentiation by drift at MHC loci. However, the stronger indications from previous studies reflect both the long-term unifying effects of balancing selection, and local, differentiated populations that suggest directional selection.

As emerging infectious diseases in the marine environment are becoming more widely recognized (Harvell et al., 1999), investigations into the genetics of host susceptibility are becoming increasingly important. It appears that most new diseases are not caused by new microorganisms, but rather by known agents infecting new or previously unrecognized hosts. Disease outbreaks are favored by the undermining of host resistance (Harvell et al., 1999), by a shift in balance in the microevolution between pathogens and host, or by the introduction of a novel pathogen into an immunogenetically naive host (Paterson 1998). The rise of catastrophic disease epidemics in marine organisms brings into question the balance between pathogen virulence and host resistance in these systems (Harvell et al., 1999). In fact, recent study in marine mammals proposes a link between MHC polymorphism and an effective response to both pathogentic and toxicogenic challenge (Acevedo-Whitehouse et al., 2003). While marine environment is increasingly influenced by anthropogenic

encroachment, the risk of exposure to novel pathogens of marine species is increased (Harvell et al., 1999), especially for coastal species such as *T. aduncus.* Yang et al. (2010) clearly show that MHC gene sequences of *T. aduncus* and *T. truncatus* diverged at least 20 Mya that may enable them to bear different assignment for pathogen defense, indicating that *T. aduncus* might be able to survive under the pathogen pressure in coastal waters. The species' near-shore distribution makes it vulnerable to environmental degradation, direct exploitation, and fishery conflicts (Hammond et al., 2008). Still of concern is the potential transmission of novel pathogens into populations of *T. aduncus* not equipped with the specific immunogenetic repertoire necessary for an effective immune response. Dolphin health and population status reflect the effects of natural and anthropogenic stressors on the species (Wells et al., 2004). Monitoring the health of *T. aduncus* could serve as not only sentinels of the health and status of lower trophic levels in the marine system, but also indicators and warning of impacts on human as more humans inhabit coastal regions. Furthermore, previous studies indicate that cetacean MHC genes have been adapted to different marine environments. Their ability to defend against terrestrial pathogens needs investigation and close monitor, especially in these times there are potential risks of epidemics for cetaceans when they have more occasions for encountering terrestrial pathogens through human exploitation of marine environments or, directly, keeping cetaceans in captivity.

## 5. Acknowledgment

We are grateful to Dr. Terry Harville for inviting us to publish this review, as well as to two anonymous reviewers for their constructive comments. The authors' research is supported by the grant from the Council of Agriculture of Taiwan to L. S. Chou (94AS-9.1.7-FB-e1(8); 95AS-11.1.3-FB-e1(10)).

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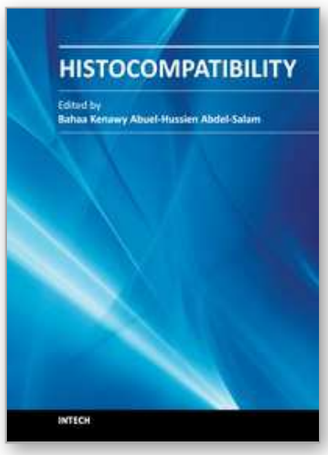


**Histocompatibility**

Edited by Dr. Bahaa Abdel-Salam

ISBN 978-953-51-0589-3
Hard cover, 188 pages
**Publisher** InTech
**Published online** 02, May, 2012
**Published in print edition** May, 2012

This book presents some recent researches related to histocompatibility for scientists interested in this field. It includes 10 chapters, in different topics, prepared by Sundararajulu Panneerchelvam and Mohd Nor Norazmi; Giada Amodio and Silvia Gregori; Adema Ribic; Bahaa K. A. Abdel-Salam; Kai-Fu Tang; Roberto Biassoni, Irene Vanni and Elisabetta Ugolotti; Wei-Cheng Yang, Lien-Siang Chou and Jer-Ming Hu; Shatrah Othman and Rohana Yusof; Masahiro Hirayama, Eiichi Azuma and Yoshihiro Komada; Gustav Roder, Linda Geironson, Elna Follin, Camilla Thuring and Kajsa Paulsson.

**How to reference**

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Wei-Cheng Yang, Lien-Siang Chou and Jer-Ming Hu (2012). Sequence Analysis of MHC Class II Genes in Cetaceans, Histocompatibility, Dr. Bahaa Abdel-Salam (Ed.), ISBN: 978-953-51-0589-3, InTech, Available from: http://www.intechopen.com/books/histocompatibility/sequence-analysis-of-mhc-class-ii-genes-in-cetaceans

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