Genetic variation in the MHC of the Collared peccary: A potential model for the effects of captive breeding on the MHC

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The Collared peccary (*Pecari tajacu*) is an environmentally and economically significant animal distributed across the southern United States to South America. There is a growing interest in the commercial farming of the Collared peccary to supply a growing demand for local meats. The Major Histocompatibility Complex (MHC) plays a significant role in the susceptibility and resistance of individuals and populations to novel parasite and pathogen challenges. Changing the environmental pressures on a population can alter the levels of diversity and the alleles present in such a population. While the importance of maintaining MHC diversity in limited populations is understood, there is little information about the effects of captivity and captive breeding on such populations, and the different selection pressures that captive populations may be exposed to. Further research is required into the different selection pressures exerted on captive populations, the effects these pressures may have on the genetic diversity in the MHC, and on the fitness of these populations. With the increased interest in the commercial breeding of the Collared peccary, this species offers a unique opportunity to study the effects of captivity and selection for commercial traits on immune function and provide an insight into the pressures placed on the MHC in wild and captive populations.

Keywords: *Pecari tajacu*, MHC, genetic diversity

1. Introduction

The Collared peccary (*Pecari tajacu*) is a small pig-like animal distributed across the southern United States, Central America, and much of South America. It is widely hunted across its range for meat and hides (Sowls, 1984). While this appears sustainable, there is also a growing interest in commercial production of peccaries to supply a growing demand for local meats (Nogueira-Filho et al., 2004). The Collared peccary plays an important role in maintaining local ecosystems across its distribution and may be an important indicator of the movements of large cat predators (Cullen et al., 2001, Motta et al., 2008, Novack et al., 2005). However, it can also act as a maintenance host and vector for a number of economically significant pathogens and parasites (Herrera et al., 2005, Mayor et al., 2006, Teran et al., 2004). A number of genetic studies have been conducted on the Collared peccary to establish the phylogenetic relationships between it and other members of the Tayassuidae family (Gongora and Moran, 2005, Gongora et al., 2006).

The Major Histocompatibility Complex (MHC) is a highly polymorphic region of the genome responsible for immune function and disease resistance. As a result, infectious diseases and parasites are thought to be the major drivers of MHC diversity. Compounds produced through the expression of MHC genes are also thought to influence individual odour and pheromone production, thereby facilitating an olfactory cue for kin recognition and mate choice. MHC diversity is thought to be maintained through two forms of balancing selection: heterozygote advantage and frequency dependent selection (Jeffery and Bangham, 2000, Kelley et al., 2005, Tregenza and Wedell, 2000).

Genetic diversity is a major factor affecting a population's ability to adapt to environmental changes. Inbreeding, habitat loss, and population bottlenecks can

drastically affect the diversity present within populations, especially in threatened and endangered species and isolated populations. Diversity in functional loci such as the MHC is thought to be the main driver of a population's ability to adapt to environmental changes (O'Brien et al., 1985, Vali et al., 2008).

This review presents the current state of knowledge about the structure and function of the MHC with regards to population genetic diversity and its importance to breeding and conservation programs. It also discusses the research to date on the genetics of the Collared peccary, an environmentally and potentially economically important species of the Americas.

2. The Collared peccary

2.1 Family Tayassuidae

The peccaries belong to family Tayassuidae, in the order Artiodactyla, also known as the even toed ungulates. Within Artiodactyla, there are a number of families including the commercially important Suidae (pigs and hogs) and Bovidae (sheep, cattle and goats) (Wilson and Reeder, 2005). Of these families, the Suids are the most closely related to the peccaries. Within Tayassuidae, there are three genera, each with a single species. These are the Collared peccary (*Pecari tajacu*), white-lipped peccary (*Tayassu pecari*), and the chacoan peccary (*Catagonous wagneri*) (Sowls, 1984). Recently a new species of peccary, the giant peccary (*Pecari maximus*) has been proposed based on findings in the Brazilian Amazon (van Roosmalen et al., 2007), however, in lieu of more detailed genetic and morphological studies, the validity of this has yet to be assessed (Gongora et al., 2007).

2.2 The Collared peccary

Figure 1: The Collared peccary, (*Pecari tajacu*). Photo by Jaime Gongora

2.2.1 Description

Peccaries and pigs share a number of superficial morphological characteristics, such as a snout, and general body shape (Sowls, 1984). However there are a number of fundamental differences which are summarised in Table 1.

The Collared peccary is generally smaller than the other peccary species, particularly the white lipped peccary (Donkin, 1985). Its most distinguishing feature is a narrow, white, semi circular collar of fur around the neck, from which this species gets its name (see Figure 1). The hair of the Collared peccary is black or dark brown in colour with a darker erectile mane running from the base of the skull to midway down the back. The fur may be darker in colour during winter periods and lighter over the warmer months (Sowls, 1984). There are no visible morphological differences between males and females except when scrotum is visible, although males tend to be heavier than females (Donkin, 1985). There may also be some size difference between populations across the range of the Collared peccary, but so far, research into this is inconclusive (Sowls, 1984). The diet of the Collared peccary consists mainly of fruits and underground roots and tubers although the predominant plant species consumed varies across its distribution (Sowls, 1984, Motta et al., 2008).

Table 1: A summary of the differences between peccaries and suids. Adapted from Sowls (1984).

Character	Peccaries	Suids
Feet	Median metacarpals and metatarsals fused into cannon bones	Not fused
Legs	Ulna and radius co-ossified	Not fused
Teeth	38 teeth, different dental formula	34 or 44 teeth
	Upper canines relatively small, straight, grow vertically	Upper canine tusks curved upward and out
	Posterior grinding teeth not enlarged	Posterior grinding teeth greatly enlarged
	3 premolars on each side, above and below	2-3 premolars top and bottom – vary between species
Scent Gland	Present – located on mid dorsal line	Absent
Stomach	Complex	Simple
Gall Bladder	Absent	Present
Tail	Greatly reduced to non existent	Generally long
Liver, hepatic lobules and large hepatic arteries	Absent	Present
Chromosome number	2n = 20 – 30 (Gongora and Moran, 2005)	2n = 32 – 38 (O'Brien et al., 2006)

2.2.2 Origins and Distribution

Pigs and peccaries evolved from a common ancestral species during the Oligocene era (Sowls, 1984). Peccaries are thought to have diverged from pigs in South East Asia, and from there migrated to North America (Ducrocq, 1995). Subsequently, the peccary family diverged, spreading to Central America and South America during the late Cenozoic era with the formation of the land bridge between Central and South America (Sowls, 1984).

While the historical distribution of the Collared peccary has significantly contracted since the arrival of Europeans to the Americas, particularly in South America, it is the most widely distributed of the three peccary species (Sowls, 1984). Collared peccaries are habitat generalists and consequently are found in a diverse range of habitats from

dry hillside scrublands to semi tropical and tropical forests (Polisar et al. 2008; Sowls 1984). They inhabit various forest types as well as areas of human habitation and agricultural lands (Reyna-Hurtado and Tanner, 2005). It is an opportunistic feeder, and can exploit fruits and seeds from many different plant species. The Collared peccary also shows adaptations to large amounts of climatic variation (Polisar et al., 2008, Sowls, 1984).

2.2.3 Environmental significance

Collared peccaries are often regarded as 'ecosystem engineers' due to their wallowing and rooting behaviour which can promote the germination of litter gap dependent plant species (Motta et al., 2008). Peccaries and other ungulates play a large role in seed removal and dispersal within many ecosystems (Cullen et al., 2001, Motta et al., 2008). In particular, the Collared peccary is responsible for the dispersal of seeds from 212 plant species (Beck et al., 2005). Their long food retention time and roaming tendencies within their home ranges suggests that collared peccaries may help disperse small seeds long distances from the parent trees. Large or hard seeds tend to be discarded by peccaries during feeding, resulting in short distance dispersal of these seeds. Peccaries also play an important role through the seed predation of species with softer seeds (Motta et al., 2008). Consequently, peccary behaviour can affect flora diversity and the plant population dynamics of ecosystems, which in turn can affect the population dynamics of animals dependent on particular plant species. Thus, over-hunting can affect populations of other species inhabiting in these habitats, and cause large scale changes to the local environment as a result of changes to the fauna and dispersal of flora (Cullen et al., 2001).

Peccaries are also an integral part of the diets of higher order predators across their distribution, forming an integral part of the diet of pumas (*Puma concolour*), jaguars (*Panthera onca*), and ocelots (*Leopardus pardalis*). A number of studies have identified preferential prey choices in these species, particularly in the large cat predators, with the puma and the jaguar displaying selection for larger to mid-sized prey species (Novack et al., 2005, Moreno et al., 2006). Both species also exhibited a preference for the Collared peccary over other peccary species, despite a similar abundance of collared and white lipped peccaries, perhaps influenced by the smaller herd sizes and less aggressive nature of the former (Moreno et al., 2006, Novack et al., 2005, Weckel et al., 2006). Prey availability has a large influence on the population dynamics of these species, and can have a significant effect on the viability of populations due to availability and competition between individuals. Novack et al (2005) noted a strong correlation between the historical distributions of the jaguar and the Collared peccary, suggesting a degree of dependence on the availability of the Collared peccary as a prey species. Thus the intricate predator-prey relationship between the Collared peccary and its large cat predators make the Collared peccary a significant indicator of large cat movements (Mendes Pontes and Chivers, 2007, Novack et al., 2005).

In the wild, the Collared peccary is frequently considered a pest species as many parts of its distribution overlap with areas of human habitation and agriculture (Sowls, 1984). Damage to agricultural crops such as maize and cassava is the primary problem. Peccaries are capable of toppling crop plants to access growing cobs, and can cause a large amount to damage to tuberous crops such as cassava as they root for the underground tubers (Motta et al., 2008, Donkin, 1985).

The Collared peccary can also act as a maintenance host for a variety of pests and pathogens, notably those of agricultural significance such as swine fever, leptospirosis, brucellosis, and the protozoan parasite, *Trypanosoma evansi*. Swine fever is a highly contagious viral disease, mainly affecting members of the Suidae family. Peccaries can act as hosts and vectors although they do not appear to contract the disease (Teran et al., 2004). Similarly, peccaries can act as reservoirs for leptospirosis and brucellosis, especially when animals are present in higher densities, such as in farmed situations (Mayor et al., 2006, Mayor et al., 2007). Collared peccaries have also been identified as a maintenance host and vector for *Trypanosoma evansi* in the Pantanal region of South America. This parasite can cause American Trypanosomiasis and the wasting disease, Surra in many species and can inhabit a wide variety of domestic and wild mammalian hosts. Interestingly, peccaries appear not to be severely affected by this parasite despite high rates of infection (Herrera et al., 2008, Herrera et al., 2005). However, despite the potential of the peccary as a source of disease transmission to commercial farming systems, there is little information about disease resistance or susceptibility in the peccary from an immunogenetic perspective.

2.2.4 Economic importance of the peccary

The Collared peccary is hunted for meat and hides across its range. It is an important source of meat for the indigenous peoples of Central and South America both historically and at present for many of the rural inhabitants. In many areas it is preferred over other wild game species and can constitute up to one third of the meat consumed by rural communities depending on the season and availability of other game species (Sowls, 1984, Naranjo and Bodmer, 2007, Altrichter, 2006). Ungulates as a whole can comprise up to 60% of the overall biomass harvested by subsistence hunters in the South-Eastern Amazon (Peres and Nascimento, 2006). Similarly, studies in Argentina found that ungulates comprised 40% of the wild meats consumed by rural communities, with peccaries making up 25% of the total wild meat consumption (Altrichter, 2006).

The hunting of animals in most regions of Central and South America is currently sustainable and does not pose a significant threat to the peccary populations in these areas. Collared peccary populations in particular, appear to be minimally affected by hunting (Peres, 1996). However, the hunting of wild meats increases during periods of economic uncertainty, potentially threatening local populations (Altrichter, 2006). Additionally, in some areas, peccary populations may be threatened by habitat fragmentation as a result of human settlement and land clearing for agriculture (Sowls, 1984). It is also unclear how an increase in hunting and removal of animals will impact on local peccary populations as village sizes and population density increase (Peres and Nascimento, 2006).

Commercialisation of wildlife products, primarily meat and skins, contributes to the incomes of many rural families. As a result, an increase in the illegal trade of these products has the potential to drastically alter population dynamics in these regions. Income from hunting of local game species in many areas of South America is as economically advantageous as logging for many rural communities, with a high demand for the skins in particular. The total wild meat consumption in Argentina in 2003 was valued at US$79,600 (Altrichter, 2006). Similarly, annual exports of peccary skins from Argentina have been valued at US$256,250 per annum (Roth and Merz, 1997).

There is a large interest in the Collared peccary as a game animal in southern states of USA and northern Mexico (Sowls, 1984). This combined with its demand as a native meat in Central and South America has led to the development of commercial peccary farming and game hunting reserves. The traditional practice of small scale breeding farms utilising a small number of animals has so far been unsuccessful due to low economic returns. A pilot investigation and evaluation of commercial peccary farming by Nogueira-Filho et al. (2004) found that large scale extensive farming can be economically viable. Reproduction in collared peccaries does not appear to be affected by captivity, although social dynamics within groups may be a restrictive factor in controlled breeding situations (Mayor et al., 2007). On the other hand, an increase in population density can affect the incidence of disease and parasites in the population, thereby altering the potential selection pressures imposed on these populations (Mayor et al., 2006).

2.2.5 Genetic studies in the Collared peccary

Mitochondrial DNA analysis of the three species in Tayassuidae found that Collared peccaries have higher levels of diversity within the mitochondrial control region than is present between the White lipped and Chacoan peccaries (Gongora and Moran, 2005). Subsequent studies by Gongora et al. (2006) suggests that there may be two species, or at least subspecies within the Collared peccary. Genetically, the Collared peccary appears to be divided into two major clades with North and Central American populations forming one clade, and the South American populations falling into the second. Recent karyotype analysis on animals from North, Central and South American populations support these findings (Souza et al., 2008). This apparent divergence may necessitate the re-evaluation of breeding management within captive populations to avoid cross breeding within the major clades.

A number of studies have shown that the peccary genome still shares many characteristics with the Suidae family. There is evidence that porcine primers can be used to amplify regions of the peccary genome (Gongora et al., 2002). Both genomes share common microsatellite markers and short interspersed nucleotide elements as almost the same frequencies (Lowden et al., 2002, Sulandari et al., 1997). Chromosome painting between the domestic pig and the Collared peccary further supports this with 31 regions of homology identified (Adega et al., 2006, Bosma et al., 2004). The degree of similarity between these species suggests that porcine genetic resources may be a significant factor facilitating further research into the peccary genome.

3. The Major Histocompatibility Complex

The Major Histocompatibility Complex (MHC) is a region of the genome responsible for antigen presentation on the surfaces of cell membranes, parasite resistance and susceptibility, and susceptibility to autoimmune disease (Hughes, 1991, Kelley and Trowsdale, 2005, Piertney and Oliver, 2006, Tanaka et al., 2005, Tregenza and Wedell, 2000). The classical MHC genes encode the key receptor molecules responsible for binding and presenting foreign peptides for the initiation of the adaptive immune response (Piertney and Oliver, 2006). A high proportion of the immune genes are found within the MHC, along with a small number of non immune genes (Kelley et al., 2005, Tanaka et al., 2005). The MHC is also thought to be responsible for the genetic basis of mate choice (Sommer, 2005b), avoiding inbreeding via production of pheromones; and

may be associated with particular traits linked to behaviour and fitness of individuals and in the maintenance of pregnancy (Piertney and Oliver, 2006, Ryan and Altmann, 2001).

3.1 Role in immune function

The primary role of the MHC is to recognise foreign proteins and present these to specialised immune cells to initiate the adaptive immune response (Piertney and Oliver, 2006). As a result, pathogen driven disassortative mating is thought to influence MHC heterozygosity (Cooper et al., 2007, Benacerraf, 1981). There is an observed decrease in pathogen resistance in homozygotes and inbred animals in general, although in stable populations with few immune challenges, this is not necessarily the case (Sommer, 2005a). Additionally, populations with limited MHC diversity are more susceptible to lethal infections (see section 4.5) (Jeffery and Bangham, 2000, O'Brien et al., 1985).

The main functional region of the MHC immune molecules is the peptide binding region (PBR). This is the region responsible for the recognition and binding of antigenic peptides. It is the association between the PBR, antigenic peptides and the T cell receptors that triggers the adaptive immune response (Piertney and Oliver, 2006). Individual MHC molecules are capable of binding multiple peptides provided they share common amino acids at the crucial anchor positions (Altuvia and Margalit, 2004). Thus a single allele at an MHC locus can detect and induce in immune response to a number of pathogens. Although the number of MHC alleles may be reduced in some species, there is still usually a high degree of divergence between alleles. This broad range of alleles can still provide a considerable degree of resistance across a range of pathogens (Sommer, 2005a).

3.2 Non-immune functions of the MHC

The MHC genes are thought to influence individual odour through production of soluble proteins or proteins capable of binding volatile molecules and differences in the composition of bacterial gut flora, thereby providing the chemical cues allowing for individual and kin recognition (Tregenza and Wedell, 2000). MHC genes potentially alter concentrations of volatile fatty acids in urine and sweat giving an indication of health and, potentially, a cue as to the particular MHC haplotype of that individual (Piertney and Oliver, 2006, Kalbe et al., 2009). It is known that compounds produced by expression of MHC genes in humans can act as odour recognition cues. Cooper et al. (2007) found that MHC Class 1 molecules can also act as pheromones in rodents, which may be to prevent or reduce instances of inbreeding (Piertney and Oliver, 2006). These pheromones may also act as kin recognition markers.

It has been suggested that in a number of species, mate choice is dependent on physical or chemical cues linked to the genetic make-up of potential mates (Tregenza and Wedell, 2000). These are thought to be linked to peptides and protein complexes synthesised from MHC genes that are not expressed on cell surfaces, but are released into extracellular spaces. These compounds are excreted through urine and other body secretions and are detected through the vomeronasal organ (Sommer, 2005a). There is evidence of MHC dependent selection in many mammals (Tregenza and Wedell, 2000). This may be a mechanism for avoiding inbreeding and ensuring that offspring have the greatest possible chances of survival (Ryan and Altmann, 2001, Penn, 2002). Disassortative mating suggests that females will mate with genetically fitter males to

gain advantages for offspring (Tregenza and Wedell, 2000). As a result, MHC dissimilar matings may be prevalent to increase offspring heterozygosity (Penn, 2002).

3.3 Genomic regions of the MHC in mammals

The MHC is normally divided into regions containing genes with similar functions, dubbed Class I, Class II and Class III (Klein, 1977, Kelley et al., 2005). In eutherians (placental mammals), the MHC is located on a single autosomal chromosome, with Class I and Class II separated by the Class II genes (Hughes and Yeager, 1998). This structure is not consistent across all mammal groups, with recent studies in the tammar wallaby (*Macropus* eugenii), platypus (*Ornithorhynchus anatinus*) and the short-beaked echidna (*Tachyglossus aculeatus*) suggesting that marsupial and monotreme MHC genes are dispersed throughout the genome rather then in a discrete cluster (Deakin et al., 2006, Deakin et al., 2007, Dohm et al., 2007). Additionally, the Class I genes of the gray short-tailed opossum (*Monodelphis domestica*) are interspersed with the genes of the Class II region forming a unique Class I/II region. This suggests that the Class I and Class II regions may have been adjacent in an ancestral form and the Class I-Class III-Class II organisation of the eutherian MHC evolved relatively recently (Belov et al., 2006).

3.3.1 MHC Class I

Class I genes encode the regions responsible for the recognition of intracellularly derived antigens (Piertney and Oliver, 2006). These proteins process and present endogenous peptides derived from nuclear and cytosolic proteins (Yeager and Hughes, 1999). It is also thought that some of these genes may bind some surface and secreted proteins through cross presentation. This mechanism is not yet well understood, and has been found only on CD8+ T dendritic cells (Villadangos and Schnorrer, 2007). Class I proteins are present on surface of all nucleated cells (Piertney and Oliver, 2006)

The MHC Class I genes encode a protein heterodimer consisting of three extracellular domains (α1,2, and 3), transmembrane domains, and cytoplasmic domains (Yeager and Hughes, 1999). These domains are encoded by exons of the same gene (Piertney and Oliver, 2006). The residues from the α1 and α2 domains make up the peptide binding regions of these structures (Hughes and Yeager, 1998)

The Class I region is one of the most dynamic regions of the MHC (Renard et al., 2006). It can be further divided into the classical (Class Ia) and non classical (Class Ib) genes (Kelley et al., 2005). Class I classical molecules present antigens to cytotoxic T cells, while the non classical genes encode a diverse range of functions (Kelley et al., 2005, Yeager and Hughes, 1999). The non classical genes tend to have a narrower range of tissue expression and lower polymorphism than the classical Class I genes (Yeager and Hughes, 1999).

3.3.2 MHC Class II

MHC Class II genes encode regions responsible for the recognition and defence against extracellular parasites and pathogens through the binding of both endogenous and exogenous peptides (Piertney and Oliver, 2006, Villadangos and Schnorrer, 2007). These molecules present antigens to CD4+ T helper cells (Kelley et al., 2005, Yeager and Hughes, 1999). Unlike Class I proteins, Class II proteins are found only on antigen

presenting cells, such as macrophages, lymphocytes (predominantly B lymphocytes) and dendritic cells (Piertney and Oliver, 2006).

The MHC Class II protein is a heterodimer consisting of an α (A) and a β (B) chain. Each of these chains consists of two extracellular domains, transmembrane, and cytoplasmic domains (Yeager and Hughes, 1999). Unlike Class I proteins, each chain is encoded by a separate gene (Piertney and Oliver, 2006). Residues for the α1 and β1 regions make up the peptide binding region. The MHC Class II region is divided up into a number of sub regions, for example the DR, DQ and DP regions in humans, each made up of complementary sets of Class II genes (Hughes and Yeager, 1998).

Class II loci are more constrained in their evolution than class I loci as a functional heterodimer requires compatible α and β chains. Since the genes encoding each of these chains are linked, both α and β chains need to be duplicated in tandem to create a new subregion (Hughes and Nei, 1990). Different subregions within the Class II region also have different modes of evolution. For example, within the DR subregion, the DRA gene appears to be monomorphic within mammals, and as a result, the DRB genes evolve in a manner similar to Class I genes. Multiple independent duplications have occurred through evolution, some of which have been silenced to pseudogenes (Yeager and Hughes, 1999). On the other hand, within the DQ locus, both DQA and DQB genes may contain polymorphisms, such that DQ genes evolve differently as each chain needs to associate with a compatible DQ chain to form a functional heterodimer (Yeager and Hughes, 1999).

3.3.3 MHC Class III

The MHC Class III region is a dense coding region made up of genes with both immune and non immune functions, and appears to be highly conserved between mammalian species (Kelley et al., 2005, Peelman et al., 1996). Tumour necrosis factor (TNF) genes and genes related to inflammatory responses and components of the complement cascade have been identified in this region (Deakin et al., 2006, Lunney et al., 2009). Studies suggest that it also contains genes related to scent production for kin recognition and mate choice as well as genes linked to economically important traits (Peelman et al., 1996, Tregenza and Wedell, 2000).

3.4 The Swine Leukocyte Antigen

The MHC of domestic pigs, also known as the SLA complex, is approximately 2.0 Mbp in size, and is situated around the centromere of chromosome 7. The genes within the SLA complex are designated with numbers, to avoid confusion with human MHC genes and their functions (Chardon et al., 1999). The SLA is characteristic of most MHC regions, being one of the most gene dense regions of the swine genome. Interestingly, it is also one of the smallest MHC regions found in the mammalian genomes that have been studied (Lunney et al., 2009). Due to the continued interest in porcine organs as candidate organs for xenotransplantation, a great deal of research has been directed at characterising the genes of the SLA. SLA Class I and Class II regions have largely been characterised, however, to date relatively few studies have looked into the SLA Class III region.

3.4.1 SLA Class I

The SLA class I regions contains 7 classical (SLA-1, 2, 3, 4, 5, 9 and 11), 3 non classical genes (SLA-6, 7 and 8) (Lunney et al., 2009). Of the classical genes, only

SLA-1, 2 and 3 are functional, while the rest of the classical genes are pseudogenes. SLA-5 has an intact coding region but the promoter region may harbour mutations resulting in altered or inactivated expression (Renard et al., 2001). All three of the non classical genes appear to be fully functional (Lunney et al., 2009). The SLA Class I region also contains MHC Class I related chain genes – MIC-1 and 2, of which MIC-2 is thought to be functional while MIC-1 is a pseudogene (Renard et al., 2001).

SLA Class I classical genes consist of 8 coding regions, with exon 1 making up the leading sequence, exons 2, 3 and 4 making up the extracellular domain, exon 5 coding for the transmembrane domain, and exons 6, 7 and 8 making up the cytoplasmic domain. Non classical Class I genes have a similar structure although the length of the coding and non coding regions differ, and the cytoplasmic domain is made up of exons 6 and 7 (Lunney et al., 2009).

3.4.2 SLA Class II

Several groups of genes are present within the SLA Class II region. These groups are primarily the α and β chains for SLA DR, DQ, DM and DO proteins as well as a number of pseudogenes related to the β chains of each of these regions. Currently only the DR and DQ regions have been characterised (Lunney et al., 2009).

The α chain genes contain four exons, with exon 1 encoding the leader region, exons 2 and 3 encoding the α1 and α2 regions of the extracellular domain, while exon 4 appears to encode components of both the transmembrane and cytoplasmic domains. The leader and extracellular domains of the β chain genes have a similar composition to those of the α chain with the leader and extracellular domains encoded by exons 1, 2 and 3. Unlike the α chain genes, exon 4 encodes the transmembrane domain, while exon 5 encodes the entire cytoplasmic domain of DQB genes and exons 5 and 6 encode the cytoplasmic domain of the DRB genes (Lunney 2009).

3.4.3 SLA Class III

Around 60 loci have been characterised in this region of the SLA (Lunney et al., 2009). Many of these genes are related to the immune response, such as genes belonging to the TNF superfamily and complement cascade (Renard et al., 2006). A number of genes associated with physiological traits have also been identified in this region, particularly those associated with economically important traits such as back-fat thickness, growth rate and carcase composition (Peelman et al., 1996).

4. Evolutionary Dynamics of the MHC

4.1 Importance of genetic diversity

Genetic diversity is a major factor affecting a population's ability to adapt to changes in environment. These changes may be novel diseases, changing resources as a result of fluctuating ecosystem and population dynamics, or indirectly, climatic changes (Vali et al., 2008). Low levels of genetic diversity can lead to an increased incidence of recessive lethal alleles being expressed, resulting in inbreeding depression and a lower genetic fitness of individuals in the population (O'Connell et al., 2005). Loss of variation can initially lead to a short-term reduction in population fitness, which may manifest as decreased survival of offspring, lower reproductive and growth rates, and a decreased ability to adapt to long term changes in environment. Loss of genetic diversity can result from natural processes such as genetic drift and selection, or

anthropogenic factors such as habitat fragmentation, degradation of existing habitats, urbanisation, and isolation of previously connected subpopulations (Sommer, 2005a).

To properly maintain genetic diversity in a population, it is important to look at diversity in functional loci such as coding genes or regulatory sequences (Vali et al., 2008). These regions are the ones that drive a population's ability to adapt to changes (Vali et al., 2008). The MHC is an ideal candidate region due to its high levels of polymorphism and its functionality as the main immune coding region of the mammalian genome. Loss of variation within the MHC has been suggested as the reason behind the increased susceptibility to diseases frequently found in severely bottlenecked species such as the cheetah (*Acinonyx jubatus*), the European bison (*Bison bonasus*) and the Tasmanian devil (*Sarcophilus harrisii*) (Radwan et al., 2007, O'Brien et al., 1985, Siddle et al., 2007).

Many animal species, particularly mammals, are frequently under threat due to habitat destruction and human activities. Much of this is due to human hunting, and the killing of animals thought to be preying on livestock (Vali et al., 2008). South African cheetahs have significantly lower levels of genetic variation than other mammalian species. Captive breeding in these populations is extremely difficult due to high neonate and juvenile mortality from both inbred and non-inbred matings. Genetic analysis has revealed a total absence of polymorphism at most allelic loci and very low degree of polymorphism in protein coding genes. Within populations, cheetahs also have very limited immune adaptability (O'Brien et al., 1985).

Within breeding programs, whether they are for the purposes of commercial farming or conservation, it is important to know the degree of relatedness between individuals to minimise the effects of inbreeding depression and allele fixation (Hughes, 1991). This is important in both free ranging populations and within closely monitored captive breeding programs. Linkage analysis can be used on data to map genetic traits (Alford and Caskey, 1994). This is useful when breeding endangered species as well as livestock. Genetic analysis based on marker diversity usually use neutral markers such as mitochondrial markers, microsatellites or single nucleotide polymorphisms (Sommer, 2005a). These markers are useful for analysing population histories and dispersal patterns, but are not as effective for assessing capacity to adapt to future challenges. For these, the MHC and other functional loci may be more appropriate.

4.1.1 Effects of genetic diversity on the immune function

Genetic diversity plays a large role in maintaining immune function in populations, particularly through the MHC. It is generally accepted that in most cases, populations with low MHC diversity or inbred animals will have a compromised ability to adapt to environmental changes, particularly the advent of new diseases (O'Connell et al., 2005, Kuo and Janzen, 2004). There is evidence of disassortative mating patterns in many species, and is has been suggested that pathogen driven disassortative mating favours MHC heterozygosity (Cooper et al., 2007).

Given that the MHC is responsible for antigen recognition, increased variety in the MHC molecules expressed will increase the antigenic peptides an individual can express to initiate an immune response (Hughes and Yeager, 1998). From this, it follows that populations with a greater number of MHC alleles may be better equipped to deal with novel pathogens or parasites (Piertney and Oliver, 2006). However, this

does not necessarily mean that populations with the greatest number of alleles will necessarily by the most genetically fit. Studies on Three-spined Sticklebacks (*Gasterosteus aculeatus aculeatus*) suggest that the need for multiple parasite resistance will select for an optimal (in this case intermediate) number of alleles rather than maximal diversity of alleles (Wegner et al., 2003a, 2003b, Kalbe et al., 2009)

4.1.2 Effects on reproduction

Low genetic diversity also affects the reproductive capacity of individuals in a population. Decreased fecundity, and smaller litter sizes have been observed a in number of species, particularly in animals bearing many young at a time. It has been suggested that in a number of species, mate choice is dependent on physical or chemical cues linked to the genetic make-up of potential mates. These are thought to be linked to peptides and protein complexes synthesised from MHC genes (Tregenza and Wedell, 2000).

Indirectly, diversity in the MHC, and therefore resistance to a range of pathogens can also affect the reproductive capacity of individuals. In free ranging populations of the Rhesus Macaque (*Macaca mulatta*) males heterozygous at MHC Class II loci sired significantly more offspring than homozygous males, despite no evidence of disassortative mating in the populations. It was concluded that diversity in the MHC Class II alleles conferred an increased resistance to the effects of injury related infections, thereby increasing the reproductive success of heterozygote males (Sauermann et al., 2001).

4.2 Measuring genetic diversity

Genetic diversity is characterised using the frequency of alleles, and the distribution of mutations between and within populations. These may be visualised using a number of different genetic markers from different regions of the genome (Piertney and Oliver, 2006). Common measures of diversity include the observed number of alleles, effective number of alleles, observed heterozygosity, expected heterozygosity and the proportions of polymorphic loci. Observed heterozygosity refers to the number of alleles found in the population when compared to what is expected under neutral selection (Kuo and Janzen, 2004). In such a population, the number of alleles can be determined by the number of non-synonymous (amino acid altering) versus synonymous substitutions present (Hughes and Nei, 1989).

4.3 Evolutionary genetics of the MHC

The MHC region contains a high degree of polymorphism and heterozygosity (Kelley et al., 2005, Tanaka et al., 2005, Benacerraf, 1981, Tregenza and Wedell, 2000). At some MHC loci over 500 alleles have been identified. The Class I region displays high levels of duplications and gene turnover. For example, human MHC Class I genes show significantly higher levels of polymorphism than the immune genome as a whole. (Kelley and Trowsdale, 2005). It is believed that this polymorphism has evolved in response to selection pressures such as diseases and parasites (Kelley et al., 2005). Polymorphisms within the MHC region are not only limited to variations within sequences. Often a number of different genes are present within a population, creating different haplotypes (Kelley and Trowsdale, 2005). Individuals with limited variability at the MHC or with certain haplotypes are generally more susceptible to disease (O'Brien et al., 1985).

4.4 Drivers of MHC diversity

Most MHC polymorphism is the result of point mutations and recombination events between loci. The MHC region also displays a large degree of diversity through the loss and gain of many loci between species. Additionally, different MHC haplotypes may contain different complements of loci or may lack some genes (Kelley and Trowsdale, 2005). Given its role in immune function, infectious diseases are likely to be the main driving force behind selection within the MHC (Jeffery and Bangham, 2000).

4.4.1 Heterozygote advantage in the MHC

MHC diversity is generally thought to be driven by two forms of selection – heterozygote advantage, and frequency dependent selection. Heterozygote advantage, also referred to as over-dominance, operates on the principle that heterozygotes will have higher fitness than homozygotes. This may be especially true when there are multiple strains of pathogens present in the environment, or a large number of different pathogens. Heterozygotes have a greater variety of MHC genes (Sommer, 2005a). Individuals heterozygous at functional MHC loci will be able to detect and present a greater variety of antigenic peptides, enhancing immune capabilities. There is evidence that females will often actively select males with different MHC complex, giving increased heterozygosity to their offspring (Tregenza and Wedell, 2000). However, this alone is unlikely to maintain the high levels of MHC polymorphism found in most populations (Penn, 2002).

4.4.2 Frequency dependent selection

Frequency dependent selection relies on one allele or genotype being more favourable at one frequency but at a disadvantage at others. This method of selection is dependent on the host-parasite interactions. Often a rare allele advantage is suggested, where pathogens adapt to overcome the majority of the population, leaving animals with less common alleles resistant (Sommer, 2005a). However, this model does not explain the long lasting polymorphism seen in MHC genes. Rather, it describes a system whereby a constant turnover of alleles occurs once a pathogen or parasite has adapted to overcome the immune response triggered by a common allele (Hughes and Yeager, 1998).

4.4.3 The Associative Balancing Complex

Recently, a new theory of MHC evolution has been proposed, modelled by Van Oosterhout (2009) that incorporates the potential effects of gene linkage and epistasis between genes within and surrounding the MHC region. The Associative Balancing Complex has been developed to explain the additional selective forces that may operate on the MHC helping to maintain the high levels of polymorphism found within this region. The regions surrounding the MHC are rich with linked single nucleotide polymorphisms that have resulted in recessive deleterious mutations. The model proposes that these regions create a ‘sheltered load’ that may accumulate and therefore contribute to the balancing selection seen in MHC regions by increasing epistatic selection against recombinant individuals (van Oosterhout, 2009).

4.5 MHC in limited populations

Active management plans are required to prevent the extinction of many species that are under threat or endangered. This may include the establishment of captive insurance populations to propagate a species and provide a source from which individuals may be

released into the wild. The main goal of these breeding programs is to maintain a representative sample of the genetic diversity present in a population, especially in endangered species where the majority of individuals exist in captive situations (Hughes, 1991). In order to implement an effective management plan, it is important to know the genetic diversity present in current populations. It is also important to note that remnant populations of long lived species can appear genetically healthy for much longer than short lived species (Kuo and Janzen, 2004). Despite this, the potential effects of captive breeding on the prevalence of disease and parasites, and thus the additional selection pressures imposed on the MHC, are not understood

In order to maintain a healthy breeding population, it is necessary to maintain a large effective population size. Hughes (1991) estimated that an effective population size of 200 will maintain 90% of heterozygosity over at least 40 generations in a captive breeding situation. However, this cannot predict effects of selection on specific loci unless we breed specifically to maintain these loci. Therefore, to properly maintain genetic diversity in a population, we need also to look at diversity in functional loci such as the MHC (Vali et al., 2008).

However, recent evidence of parasite mediated selection in non MHC genes suggests that MHC diversity cannot be used as the sole measure of immunological health in populations (Acevedo-Whitehouse and Cunningham, 2006). Studies on a population of the severely bottlenecked European bison suggest that the degree of divergence between MHC alleles may also be important for the maintenance of a healthy population. Only four alleles at the DRB-3 locus were identified in this population, less than what would be expected even under neutral selection, but all alleles were found to be highly divergent (Radwan et al., 2007). From this we can infer that the amount of diversity between MHC alleles may not be the most significant factor regulating the extent of immunity conferred, but the degree of divergence between groups of alleles.

5. Conclusions

The MHC is a highly diverse region of the genome which has critical importance to the maintenance of immune function and the ability of populations and species to adapt to new challenges. While the importance of maintaining MHC diversity in limited populations is understood, there is little information about the effects of captivity and captive breeding on such populations, and the different selection pressures that captive populations may be exposed to. Further research is required into the different selection pressures exerted on captive populations both in conservation and commercial breeding programs, and the effects these pressures may have on the genetic diversity in the MHC, and therefore the fitness of these populations as a whole. With an increased interest in the commercial breeding of native species to supplement or replace introduced species for production, the Collared peccary offers a unique opportunity to study the effects of captivity and selection for commercial traits on immune function and provide an insight into the different selection pressures placed on the MHC in wild and captive populations.

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