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Review Article

Major Histocompatibility Complex (MHC) Diversity and its implications for human and wildlife health and Conservation – A review

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Abstract

It is clear that the global environment has changed and is still changing. The results of climate change, pollution, human use, and misuse of natural resources are tolling on humans and global biodiversity. The appropriate response(s) to these changes can be attributed to the efficacy of the immune system. The Major Histocompatibility Complex (MHC) has a key role in maintaining global biodiversity in the face of obvious threats. Genetic variation, especially those within MHC proteins has been known to influence the ability of individuals to cope with various pathogens. In this review, we reveal from empirical research, the diversities within the MHC in wildlife, highlight the importance of MHC to wildlife and human health, emphasize the need to conserve MHC diversity for adequate conservation, and open a discussion on whether the interplay between the MHC genes and disease resistance is a question of quantity or quality. For most jawed vertebrates, classical MHC genes are the most gene-dense and polymorphic. This polymorphism in the MHC genes can be explained by host-pathogen coevolution and provides an excellent tool for determining a population's or species' immunological fitness. Their variation is undoubtedly adaptively important, and there is strong evidence that pathogen-imposed balancing selection is the primary cause of its maintenance. Over the years, variants in the MHC have been reported as major risk factors for autoimmune and infectious diseases in humans and wildlife species of conservation concern. It has been observed that, though high diversity within the MHC proffers some protection for most natural populations, this seems not to be universal. The influence of this high diversity on the survival of natural populations should be further investigated. As the debate lingers, there is a dire need to protect the present diversity at the locus. This will definitely play a very important role in maintaining the health of both humans and animals and ensuring the conservation of biodiversity in response to the inevitable changes in our world.

Keywords: Biodiversity health, Conservation, Genetic variations, Immune genes

Introduction

Selective processes require genetic diversity as a starting point. Populations with high levels of diversity are better able to respond to threats like pathogens and predators, as well as long-term effects like environmental change (Wang, 2017). Low genetic diversity, on the other hand, may hinder a population's ability to respond to these threats over time (Hedrick, 2002). Genetic diversity measures are frequently based on neutral markers, e.g., microsatellites (Sommer, 2005), while adaptive markers, such as genes of the major histocompatibility complex (MHC), are better reflected by genetic diversity to capture information about population conservation (Holderegger *et al.*, 2006; De Bruyn, 2007; Piertney and Webster, 2010).

It is crystal clear that the global environment has changed and is still changing. The results of climate change, pollution, human use, and misuse of natural resources are tolling on humans and global biodiversity. The appropriate response(s) to these changes can be attributed to the immune system's efficacy. Diversity within the Major Histocompatibility Complex (MHC) has a key role in maintaining

global biodiversity in the face of the obvious threats they face. Genetic variation, especially those within MHC proteins has been known to influence the ability of individuals to cope with various pathogens (Castillo *et al*., 2010; de Groot *et al*., 2017).

Though previous studies of MHC diversity have primarily focused on the allelic level (Hedrick, 2003; Kalbe *et al.,* 2009; Thoss *et al.*, 2011), the distinguishing feature of classical MHC genes is their extreme polymorphism (Piertney and Oliver, 2006; Schwensow *et al.,* 2007). As revealed by the high relative nonsynonymous substitution rate inside the peptide-binding domain (PBD) (Hughes *et al.*, 1990), notably at peptide binding sites (PBS) (Reche and Reinhertz, 2003) as well as large short-term selection coefficients, polymorphism evolves adaptively (Schwensow *et al.,* 2007; Biedrzycka and Radwan, 2008). MHC genes are useful for investigating how selection might produce and sustain genetic variation in natural populations because of their high polymorphism and evidence of positive selection (Radwan *et al.,* 2020). Given MHC's key function in the immune system of vertebrates, pathogen-driven selection may be more viable to decipher the high MHC diversity (Ziegler *et al.,* 2005) seen in most vertebrates. Because of gene duplication, recombination, and conversion, alleles from different MHC loci, particularly in birds and reptiles, can be very similar and even identical to each other (Burri *et al.*, 2010; Gaigher *et al.*, 2016), and gene copy numbers can also vary between individuals (Gaigher *et al.,* 2016; Tsuji *et al.,* 2017). MHC genes are often duplicated in fish, reptiles, birds, and mammals, with 1–9 copies and 1–1,400 alleles per gene (Babik *et al.,* 2005; Huchard *et al.,* 2006; Castro-Prieto *et al.,* 2011). Apart from the challenges posed by duplications and allelic variation, genotyping adequate sample sizes in a population for MHC-related studies can be time-consuming and costly.

In addition, human MHC differs significantly from other animals in terms of the quantity and organization of genes and are thought to have experienced large-scale duplication events, leaving paralogous sets of genes on chromosomes 1, 9, and 19. MHC class I is found in all mammals, however, a lack of orthology suggests several rounds of gene duplication and loss during evolution (Yamaguchi and Dijkstra, 2019).

Furthermore, balancing selection on MHC genes has revealed a pattern of trans-species polymorphism, which has resulted in the maintenance of MHC allelic lineages among related species for prolonged periods. Some vertebrate species have been found to have low MHC variation in wild populations that have experienced population reduction in the past (Castillo *et al.,* 2010; Castro-Prieto *et al.,* 2011; Niskanen *et al.*, 2014; Kohyama *et al.,* 2015), making them vulnerable to pathogens and increasing the risk of extinction (Niskanen *et al.,* 2014). However, inbred populations have minimal MHC variation, leading to reduced parasite resistance (Radwan *et al.,* 2010). Characterization of MHC genes is important in measuring the health of natural populations, which in no small way contributes to biodiversity conservation (Ujvari and Belov, 2011; de Groot *et al*., 2017). This review, therefore, explores the diversities within the MHC in wildlife, highlights the importance of MHC to wildlife and human health, emphasizes the need to protect/conserve MHC diversity in wildlife for adequate conservation, and opened a discussion on whether the diversity within the MHC genes and disease resistance is a question of quantity or quality.

Genetics of MHC

The MHC is a large gene cluster in the vertebrate genome that codes for cell surface proteins, which are utilized by the immune system. In vertebrates, MHC is vital for reacting to antigens and initiating an immune response. The bulk of the research that has addressed immune genes in wild populations has concentrated mainly on the MHC genes as a single family, which is a crucial component of adaptive immunity (Morris *et al*., 2015). MHC diversity has been related to a range of fitness features, including parasite resistance, survival, and reproductive success, which all have implications for population viability (Sommer, 2005; Ujvari and Belov 2011; Manlik *et al.,* 2019).

The MHC is a multi-gene family in birds and mammals that consists of two tightly linked subclasses that play a key role in the initiation of the immune response (Yamaguchi and Dijkstra,

2019). It spans 4 million base pairs and is traditionally divided into three regions: class I, class II, and class III, or the inflammatory region (Sommer, 2005). MHC, also known as human leukocyte antigen (HLA), is the most polymorphic gene cluster in the human genome, with more than 200 genes encoding various aspects of the immunological response mechanism. It is located on the short arm of chromosome 6 and consists of about 4,000 kilobases of DNA covering about 2.5 map units (Ujvari and Belov, 2011).

The MHC complex is one of the most diverse in the vertebrate genome. Most of its diversity is concentrated in the functionally essential peptide binding region (PBR), which binds peptides and exposes them to T-cells, triggering the required immunological response (Piertney and Oliver, 2006). MHC genes code for proteins that identify "self" peptides from "non-self" peptides (Piertney and Oliver, 2006). Individuals express only a small number of distinct MHC molecules, in contrast to the huge population diversity of MHC molecules. This is thought to be a trade-off between enhancing the detection of foreign antigens and limiting the loss of T cell clones during thymus self-tolerance induction. Immune recognition, vulnerability to viral and autoimmune disorders, kin recognition, individual odors, mating preferences, and pregnancy outcome are all influenced by MHC variations (Sommer, 2005).

For most jawed vertebrates, classical MHC genes are the most diverse genes (Hughes and Hughes, 1995), and are scattered throughout a large genomic region with varying levels of recombination with other genes (Radwan *et al.,* 2020).

MHC and human health

The MHC-encoded glycoproteins in humans are known as human leukocyte antigen (HLA) and the best-characterized function of MHC-encoded molecules is the presentation of antigenic peptides to T cell receptors (TCR) on cognate T-cells (Tsai and Santamaria, 2013). The MHC genes are the most variable in the human genome, and the function of HLA molecules is to present peptides from invasive organisms (Robinson *et al.,* 2015). The HLA molecules are slightly different from each other in their amino acid sequences leading to different structures in the peptide-binding cleft (Mosaad, 2015). In an immune response, T cells become activated upon interacting with the foreign antigen/HLA complex (Bose *et al.,* 2013). Upon activation, the immune response is elicited as a result of the interaction between the cytokines release and the T cells, and this will lead to the recognition and destruction of cells with the same foreign antigen/HLA complex when next encountered (Mosaad, 2015). HLA Class I and HLA Class II antigens behave differently in this process in terms of their precise mechanism of action. By their existence on all nucleated cells, HLA Class I molecules present antigens that are peptides generated by invading viruses. These are delivered to CD8 T lymphocytes (Tsai and Santamaria, 2013), which will then kill the infected cell immediately.

Over time, the largest number of connections between human disease and the MHC region of the genome have been documented. However, the significance of MHC genes extends beyond immunological disorders as it also affects other infectious diseases (Howell, 2013). The MHC shows associations with most autoimmune diseases as well as many inflammatory and infectious diseases [such as Hodgkin's lymphoma (Amiel, 1967), Acute lymphocytic leukaemia (Walford *et al.,* 1970), Ankylosing spondylitis (Brewerton *et al.*, 1973), Psoriasis (Zhou and Zhang, 2018), Myasthenia gravis (Hjelmström and Sanjeevi, 2000), Malaria (Riley *et al.,* 1992), Dengue shock syndrome (Khor *et al.,* 2011), Sialidosis (Milner *et al.,* 1997), Complement deficiencies (Truedsson *et al.,* 1993), Congenital adrenal hyperplasia (Fleischnick *et al.,* 1983), Sarcoidosis (Judson, 2018), Type 1 diabetes (Morran *et al.,* 2015), Rheumatoid arthritis (Newton *et al.,* 2004), Systemic lupus erythematosus (Fernando *et al.,* 2007; Fernando *et al.,* 2012), Multiple sclerosis (Ramagopalan *et al.,* 2009), Pemphigus vulgaris (Delgado *et al.,* 1996), Leprosy (Gorodezky *et al.,* 2004), Narcolepsy (De la Herrán-Arita and García-García, 2014), Ulcerative colitis (Zhang *et al.,* 2019), Graves' disease (Chu *et al.,* 2018), Celiac disease (Gutierrez-Achury *et al.,* 2015), Selective IgA deficiency (Wang

et al., 2011), Bare lymphocyte syndrome (Reith and Mach, 2001), and Juvenile myoclonic epilepsy (Wong *et al.,* 2001)].

Importance of MHC on animals

A good number of natural populations are threatened by a sharp decline in the total amount of habitat that is available, and also by an increase in habitat fragmentation and degradation. These cause populations to shrink in size and restrict gene flow among subpopulations. (Peacock and Smith, 1997). Understanding the mechanisms that influence genetic variation and differentiation in endangered species is critical for evolutionary processes and conservation efforts (Sommer, 2005; Piertney and Oliver, 2006). The MHC genes, because of their characteristic polymorphism and their association with fitness, have become a valuable adaptive marker (Lan *et al.,* 2019). MHC is a genetic system that can be used to examine disease dynamics in animals (Janeway *et al.,* 2001). MHC research has focused on wildlife species that have witnessed population reduction due to diseases and human activities e.g., common frog (*Rana temporaria*) (Zeisset and Beebee, 2009), Eurasian beaver (*Castor fiber*) (Babik *et al.,* 2005), lemur (*Microcebus murinus*) (Averdam *et al.,* 2011), chacma baboon (*Papio ursinus*) (Huchard *et al.,* 2006), sea lion (*Zalophus californianus*) (Bowen *et al.,* 2004), giant panda (*Ailuropoda melanoleuca*) (Zeng *et al.,* 2007), raccoon (*Procyon lotor*) (Castillo *et al.,* 2010), cheetah (*Acinonyx jubatus*) (Castro-Prieto, 2011), European mink (*Mustela lutreola*) (Becker *et al.,* 2009), and red-crowed crane (*Grus japonensis)* (Akiyama *et al.,* 2017). Studying MHC variation in these species has widened our understanding of the immune response of host species to pathogens. On endangered species, MHC markers have been utilized (Miller *et al.,* 2010; Mason *et al.,* 2011). Individual variation in parasite load (Madsen and Ujvari, 2006; Schwensow *et al.,* 2007), local adaptations (Evans *et al.,* 2009), maternal-fetal interactions (Hedrick and Thomson, 1988), and lifetime reproductive success (Kalbe *et al.,* 2009) are associated with MHC genes, making them useful molecular markers for assessing the status of endangered wildlife populations when conducting conservation programs.

Comparison between Wildlife and human MHC as it relates to their health

Nonhuman primate MHCs are identical to human MHCs, even though they contain a distinct number of MHC class I chain-related (MIC) genes (Dadi *et al.,* 2015). The MIC has a structure that is comparable to that of classical MHC class I molecules. MIC proteins are made up of six exons that code for one transmembrane, one cytoplasmic, and three external (α1–3) domains (Jinushi *et al.,* 2008).

The MIC in humans is expressed in a variety of immune cells as well as most epithelial tissues. Only freshly isolated endothelium cells, fibroblasts, and gastric epithelium were found to express MIC on the cell surface. When triggered with cellular stress inducers, however, reports showed up-regulation of MIC transcripts and cell surface protein expression in various cell lines (Molinero *et al.,* 2002). Unlike humans, chimpanzees contain a single fused MICA/MICB gene, and MIC genes in less closely related primates may not be orthologous and are duplicated. Only MICA and MICB, both centromeric to HLA-B, are functioning MIC genes in humans (Al Hadra *et al.,* 2022).

The MIC genes' relevance has been highlighted by their role in a variety of human diseases. Several researchers have found plausible links between MHC genes and diseases. For instance, Cohen *et al.* (2002) found a substantial link between particular MICA alleles and autoimmune illnesses like Behçet's disease. The MICA alleles have also been linked to resistance and susceptibility to human brucellosis (Bravo *et al.,* 2007). Therefore, understanding the links among genetic diversities, immune resistance and susceptibility to pathogenic diseases, requires research into the diversity and evolution of MHC genes (Dadi *et al.,* 2015).

Diversity within the MHC genes and disease resistance: A question of quantity or quality?

As intellectually appealing as the principles explaining MHC polymorphism and disease resistance is, the majority of the empirical data came from investigations involving humans or in animal experiments

(Froeschke and Sommer, 2005) and very few cases of associations between particular MHC alleles and parasite resistance have been reported in natural populations (Kelly and Trowsdale, 2017). However, the primary use of MHC genes in conservation has been to quantify the genetic diversity of natural populations, with no specific conservation implications (Ujvari and Belov, 2011). MHC diversity is substantial in most natural populations, in terms of number of the alleles, sequence variation, and heterozygosity (Hedrick, 2003). Characterization of polymorphic and polygenic MHC genes is thus a great indicator of genetic health and has applications in conservation biology, such as managing captive breeding programs for endangered species (De Groot *et al.,* 2017).

Natural populations usually reveal high diversity within their MHC. Allelic variations leading to high levels of heterozygosity are usually observed in the MHC of most natural populations (Hedrick, 2003), which tend to proffer protection against pathogens and diseases. But this seems not to be universal. For example, bottlenecked populations of, Scandinavian beavers (*Castor fiber*), fallow deer (*Cervus dama*), and Northern elephant seals (*Mirounga angustirostris*) show no indication of increased susceptibility to infectious diseases despite their low polymorphisms in MHC genes (Weber *et al*., 2004). Also, Castro-Prieto *et al*. (2011) concluded that the low level of MHC diversity in free-ranging cheetahs (*Acinonyx jubatus*), in Namibia does not influence their immune-competence. Whereas, bottlenecked populations of desert bighorn sheep (*Ovis aries*), which show high levels of MHC diversity are also highly susceptible to many infectious diseases (Gutierrez-Espeleta *et al*., 2001). Apparently, the influence of the diversity within the MHC on the survival of natural populations, especially on disease resistance, requires a deeper look (Radwan *et al*., 2010). Is it a question of quality or quantity?

Need to protect MHC diversity

The major histocompatibility complex (MHC) is a molecule that allows the immune system to recognize and eradicate pathogenic infections. Infectious pathogens are now regarded to be the primary selective mechanism driving and maintaining the MHC's incredible diversity. To combat emerging pathogenic threats and ensure biological systems' long-term survival, high levels of MHC polymorphism must be maintained (Sommer, 2005; Piertney and Oliver, 2006; Alcaide *et al.,* 2010). The facts that

(1) selection impacts allele frequencies in small populations

(2) frequency-dependence and heterozygote advantage are losing their ability in protecting polymorphism, is likely to contribute to the rate of decrease of MHC polymorphism.

The loss of rare alleles owing to drift would be facilitated by an increase in the allele frequency providing resistance to contemporary parasites in small populations (Sanjuán and Domingo-Calap, 2019). These unusual alleles would have been preserved in big populations, and many of them can be momentarily unfavorable (given the existing parasite genotype composition), lowering average population fitness (Loewe and Hill, 2010). As a result, population fitness should improve when such rare unfavorable alleles are lost due to drift. Additionally, if highly diverse alleles are preserved, a population's ability to resist pathogens may be significantly enhanced. However, as MHC alleles are lost and parasites evolve, host fitness falls below that of pre-bottleneck levels, as host mutations are ineffective in restoring the most resistant alleles (Ejsmond and Radwan, 2011), raising the need to maintain the MHC's diversity.

Reduced MHC variation may render endangered populations more susceptible to disease and negatively impact their capability to elicit immune responses to emerging diseases (Siddle *et al.,* 2007). If highly divergent alleles are retained, a population's ability to respond to pathogens may be significantly improved. However, simulations indicate that the maintenance of functional diversity in endangered species is not reliable (Ejsmond and Radwan, 2011).

How to protect MHC diversity

The MHC diversity just like any other polymorphism can be substantially reduced by incidental bottlenecks, but as the population grows larger, selection and mutation restore variance to pre-bottleneck levels. MHC

diversity has been recovered via mutation in American moose (*Alces alces*), which experienced a population bottleneck during the Pleistocene glaciations (Mikko and Andersson, 1995). Selection does not tend to maintain a significant increase in MHC allele diversity, making it unlikely that endangered populations will be able to respond to emergent disease attacks. However, a swift recovery in population size may allow selection to retain or restore MHC variation provided suitable conservation measures are applied quickly enough (Ejsmond and Radwan, 2011).

Conclusion

As the debate lingers on whether it is the type (quality) of MHC or its quantity of diversity that confers protection on individuals and/or populations, there is a dire need to protect the present diversity at the locus. This will definitely play a very important role in maintaining the health of both humans and animals and ensure the conservation of biodiversity in response to the inevitable changes in our world.

Captive breeding programs as a strategy for wildlife conservation need to consider MHC polymorphism. The success of this program depends largely on the adaptive fitness of the reared populations, therefore there is a need to increase the MHC polymorphism of individuals for such programs. The same is true for ex-situ conservation strategies (in zoos and other wildlife sanctuaries) and livestock industries since the goal is a healthy environment altogether.

It is recommended that more quality research be directed towards the diversity of MHC in human and wildlife populations (especially at the community level rather than isolated studies of species) as it holds the key to their survival in the long run. Also, the influence of the diversity within the MHC on the survival of natural populations, especially on disease resistance begs for further studies.

Author Contributions

OMC conceptualized the title, sub-titles and contributed to the literature search and review. OHO contributed to the literature search and formatting while AOF contributed to the literature search, review and formatting.

Conflict of Interest

There is no conflict of interest that may influence or be perceived to influence this work.

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