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MHC Genotype and Ornamentation

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Abstract

Differences among males in immunocompetence can affect resistance to parasites and diseases, and sexual ornaments have been suggested to function as indicators of additive genetic variation in disease resistance, health and condition in the good gene models of sexual selection. In this paper the role of genetic variation in the immune system is discussed as an alternative route to explore whether or not immunological variation influences condition and sexual ornamentation. In vertebrates, the effect of the genes located in the major histocompatibility complex (MHC) in shaping immunodominance, lasting immunity, and the risk of developing pathological immune responses are suggested as the link between genetic variation at the MHC and male ornaments. It is also suggested that general immune responsiveness may be optimized at an individual basis depending on the MHC associated risk of autoimmune disorders.

The expression of ornaments is highly variable among males within a species and can also differ both between and within seasons for individual males. The variation in ornaments is often correlated with condition and survival (canine teeth in primates: Manning & Chamberlain 1993; carotenoid pigmentation in fish and birds: Milinski & Bakker 1990; Hill 1990, 1991; Niccoletto 1993; combs in red jungle fowl Gallus gallus: Zuk et al. 1990; see also a general review by Andersson 1994). Theoretical models have suggested that the intensity of male ornaments and displays are used by the females in many animal species through behaviours and other adaptations aimed at picking out high quality males to sire their young (Zahavi 1975, 1977; Andersson 1982, 1986, 1994; Hamilton & Zuk 1982; Kodric-Brown & Brown 1984). By basing mate choice on the information displayed by the males, a female can increase the quality, viability, and future reproductive success of her offspring even in the absence of non-genetic direct benefits (Pomiankowski & Møller 1995; see also Kirkpatrick & Ryan 1991). Studies of animals, from vertebrates to insects, in the lab and the wild support the concept of honest indicators of good genes by showing that females indeed can increase offspring fitness by mating with more ornamented males (Norris 1993; Møller 1994; von Schantz et al. 1994; Hasselquist et al. 1996; Welch et al. 1998; Hoikkala et al. 1998).

In search of the link between ornamentation and condition of males, controlled infection experiments have shown that ornaments are sensitive to diseases (Houde & Torio 1992) even more so than other morphological traits (Hillgarth 1990; Zuk et al. 1990). Several different methods have been used to evaluate an individual's capacity to control infections. Antibody response to novel or familiar antigens, levels of serum globulin, size of immune organs and lymphocyte counts have all been used to estimate variation in immunocompetence. From an immunological perspective it is not always evident that these assays accurately reflect individual variation in immunocompetence and how these estimates relates to variation in fitness (Sheldon & Verhulst 1996; Penn & Potts 1998). The emerging picture is less than clear: more ornamented males have been interpreted to show weaker responses to pathogens, as measured by counts of white blood cells (Zuk et al. 1995; Skarstein & Folstad 1996) but stronger immune reaction to novel antigens when assayed with delayed hypersensitivity tests (Zuk & Johnsen 1998) or total immunoglobulin response (Sanio & Møller 1996).

A major problem when exploring the connection between variation in disease resistance and ornamentation comes from the observation that immune function and disease resistance is itself dependent on condition. Individuals with a poor immune system will be in poor condition but it is equally true that individuals in poor condition will have a weakened immune system (Lord et al. 1998). Hence, the causality works in both directions and firm evidence that link disease resistance and ornamentation, independently of an underlying correlation to general condition, can be difficult to establish by exploring the relationship between quantitative variables of the immune system and ornamentation (Fig. 1).

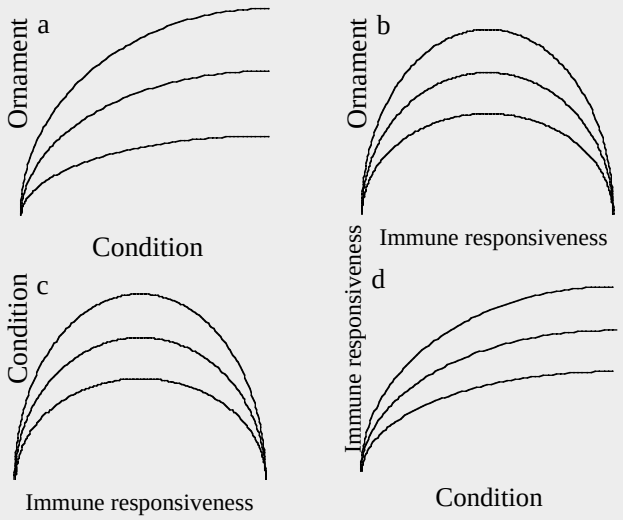

Figure 1. *Hypothetical relationships underlying an observed correlation between male ornamentation and condition (three lines shown for each relationship indicating individual variation in reaction norms). Ornaments are supposed to increase with condition, but only up to a given level above which increased condition will not lead to a further increase (a). Increased immune responsiveness gives bigger ornaments, but an overly aggressive immune system can lead to immunopathological diseases (b). Accordingly, condition will show a similar relationship with immune responsiveness (c). A correlation between immune responsiveness and ornamentation as in (b) may however be confounded by an underlying relationship between condition and immune function (d).*

Genetic variation in the immune system

An alternative approach to explore how differences between males in resistance to diseases may affect ornamentation, that circumvents much of the complexity of the immune system, is to directly study if genetic variation in disease resistance and susceptibility correlate with ornamentation. This approach depends on the straightforward assumption that differences in condition may depend on the genes in the immune system but not the other way around. Both acquired (adaptive) and preimmune (innate) host resistance shows extensive genetic variation in mice (Malo & Skamene 1994) and humans (Hill 1998). Disease resistance is in most cases a multigenic quantitative trait and most species are challenged with a multitude of different pathogens. Variation among males in genetic resistance to parasites and diseases will influence the likelihood of developing a disease when exposed to pathogens and thus also affect the expression of condition-dependent ornaments.

At the level of populations, much of the genetic variation in the immune system of vertebrates is located in the major histocompatibility complex (MHC). The MHC region contains several linked genes of central importance to antigen processing and immune function (Malo & Skamene 1994; Hill 1998). The genomic organization and function of MHC has been revealed in both humans and other vertebrates (Trowsdale 1993, 1995). These genes are often inherited together on one chromosome as one haplotype and are critical for the function and control of the innate and acquired immune functions of vertebrates. In this

genetic region there are two kinds of slightly different MHC receptors, class I and class II, which present peptides from normal host metabolism and invading pathogens to the T-cells. In most organisms MHC class I and II genes exists in several duplicated loci with different but overlapping degrees of function and allelic polymorphism. Also situated in the MHC class II region are two genes for transporters associated with antigen processing, TAP1 and TAP2 that interact with the MHC class I antigen presentation. In the MHC class III region several complement component genes C2, C4 and factor B, the heat shock protein HSP70 and the tumour necrosis factor (TNF-A and -B) are located and code for proteins with critical functions in the immune response. Many, maybe most, of the genes in the MHC region seem not show an extensive polymorphism within populations and probably do not contribute much to the variation in condition and ornamentation in Nature. The remarkable exceptions are some of the loci encoding MHC class I and class II and possibly the TAP and TNF genes (Trowsdale 1993; Poland 1998), but extensive population data for other genes than MHC I and MHC II is still lacking even in humans and mice. However, by studying variation at MHC class I and II one can get a handle also on the linked immunogenetic variation in the MHC region.

Cellular function of the MHC class I and II genes

MHC class I receptors are expressed on all nucleated cells and presents intracellular peptides to cytotoxic T-cells (CTL). Hence, MHC class I is mainly involved in protection against viruses and intracellular parasites, and mark infected cells for destruction by the immune system. Class II MHC is expressed on specialized phagocytic white blood cells (e.g. macrophages), specialized antigen presenting cells (e.g. dendritic cells) but also on B-cells, and presents peptides of extracellular origin to regulatory T-helper (Th) cells. MHC class II is thus involved in the activation of the major regulatory cells in the immune system. Activated Th-cells (T-cells whose receptors have attached to an antigen-presenting MHC molecule) release immune regulating hormones (cytokines) that attract other immune cells to start an inflammatory response (Roitt et al. 1996). Th-cells also interact with B-cells (Clark & Ledbetter 1994) to induce the clonal selection and proliferation of those particular B-cells that produce antibodies with high affinity for the presented antigen (Rajewsky 1996). Unlike most of the variability of the T- and B-cell receptors, which is generated anew at the individual level by genetic rearrangements and other mutations during somatic development, the variation of MHC is inherited from the parents' gametes and are dependent on the variation in the local population (Roitt et al. 1996). The MHC class II receptor is a dimeric protein formed by two subunits, a and b. The antigen binding part of the b chain is coded by the second exon of the MHC class II b gene (Roitt et al. 1996). MHC class II b genes have been found to be highly polymorphic in the majority of species studied, with most of the variation located in the second exon. In mice up to 20 different alleles have been found in local populations in the wild (Potts & Wakeland 1990).

The MHC phenotype

A useful description of the phenotypic effect of MHC could be that the variable MHC class I and II genes to a large extent shapes the adaptive immune system and sets the boundary conditions for its' function. While the target antigens of innate immunity do not change qualitatively during the lifetime of the individual they can do so for adaptive immunity. Hence, the adaptive immune system can respond to, and somewhat keep track of, the rapid evolutionary change of many pathogens, both within a host and between hosts in a population. However, with this flexibility comes the associated risk of developing immunity to self, autoimmunity. Most host cells express several thousands of different genes. Peptide fragments from this pool creates blind spots in the immune defense and an opportunity for molecular mimicry and detection evasion strategies of pathogens. The main problem to be solved by the adaptive immune system is how to detect a set of peptides from invading pathogens against a much larger background set of self generated peptides (Fig. 2). In normal cases the adaptive immune response is blocked by self peptides presented by MHC by the selective destruction of self responsive T-cells in the thymus (Roitt et al. 1996). Hence, peptides from pathogens that readily bind to a MHC molecule can not elicit an immune response since there are no responding T-cells (Jones et al. 1993; Gelder et al. 1998). Each variant of the MHC receptor is able to bind only a limited

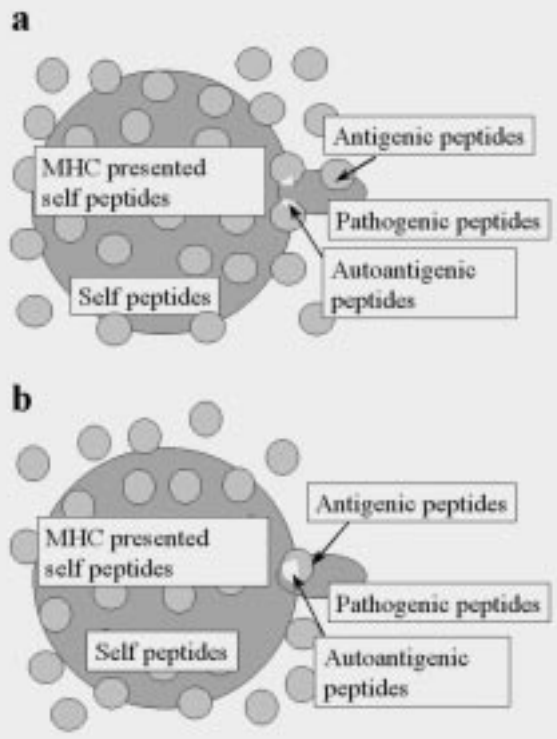

Figure 2. *The Swiss cheese model of the MHC effect on the adaptive immune system. Different MHC genotypes (a and b) will differ in their presentation of self peptides (small circles overlapping with the big circle), creating a specific pattern of 'blind spots' in the adaptive immune system. The MHC genotypes will also differ in their presentation of peptides derived from an invading pathogen (small circles overlapping the oval). Some of the peptides from the pathogen will be similar to self derived peptides and may be presented by the MHC (white sections). The area of this overlap will differ between MHC genotypes and this cross reactivity may elicit an autoimmune response with different probability depending on pathogen, host genetic background, and host MHC genotype.*

number of different peptides, and different MHC alleles thus allow the presentation of a different set of pathogenic antigens and self peptides, creating a different pattern of presentation and blind spots. (Fig. 2). From this simple model follows some important observations. Both MHC dependent resistance to infection and susceptibility to autoimmunity are codominant traits. Any particular MHC allele can provide protection or disease depending on the genetic background variation in the host or in the pathogen.

MHC and fitness

Several studies have found an association between specific MHC haplotypes and resistance to infectious diseases and autoimmune disorders in mammals and birds (Briles et al. 1983; Tiwari & Teraski 1985; Hill et al. 1991; Nepom & Erlich 1991; Han et al. 1992; McGuire et al. 1994; Apanius et al. 1997; Paterson et al. 1998). Therefore, it has been suggested that the high degree of within-population variability of MHC genes is the result of selection from pathogens. From the pathogens' point of view, different hosts are different "food patches," and even if a pathogen evolves the ability to avoid adverse immune responses in hosts of one specific MHC genotype it may still be less effective to infect other hosts in a population with high MHC variation (Zinkernagel 1996, see also Hamilton et al. 1990). In this system, uncommon MHC genotypes will be at an advantage compared to common ones, leading to frequency-dependent selection favoring rare and disfavoring common MHC alleles (Clarke & Kirby 1966; Hedrick 1994; Potts & Slev 1995; Apanius et al. 1997). Furthermore, it has been suggested that heterozygotes may be able to detect a larger set of antigens and therefore be more resistant to diseases (Doherty & Zinkernagel 1975; Black & Salzano 1981; Wakeland et al. 1989; Kroemer et al. 1990; Nevo & Beiles 1992). Studies of MHC polymorphism in some mammal and bird populations have found a high allelic variation and an excess of heterozygotes, compared to Hardy-Weinberg expectations (reviewed by Potts & Wakeland 1990, 1993; von Schantz et al. 1996; but see Edwards & Potts 1996; Ellegren et al. 1996).

In wild male pheasants (*Phasianus colchicus*), MHC genotype was found to correlate both with spur length, which is a condition-dependent ornament in this species (von Schantz et al. 1989; Grahn and von Schantz 1994), and survival (von Schantz et al. 1996, 1997). There was an excess of MHC heterozygous pheasants compared to the Hardy-Wienberg expectation but MHC heterozygosity was not associated with increased survival or ornamentation. Paterson et al. (1998) found that particular MHC alleles, rather than MHC heterozygosity, correlated with survivorship of young Soay sheep (*Ovis aries*). Both von Schantz et al. (1997) and Paterson (1998) found some evidence indicative of frequency dependent selection on the MHC. In the sheep, the two most common alleles were associated with decreased survival and in the pheasant the relationship between MHC genotype and spur length differed between years. Survival to very old age in humans are positively associated with specific MHC class II alleles but not with MHC heterozygosity (Ivanova et al. 1998).

MHC and immunocompetence

A basic definition of immunocompetence often given in medical literature is the strength of the response to a random antigen. Although this definition may be useful when studying immunology as a separate subject, immunocompetence needs a more detailed definition to be helpful in ecological and evolutionary models. The definition could be recast in more detailed immunological functions:

- Rapid detection of pathogens.
- Activation of relevant effector cells.
- Avoidance of immunopathology.
- Response to evolutionary constrained epitopes.

Infection with complex pathogens elicits T-cell responses to only a small subset of all possible peptide antigens from any given pathogen (the so called epitopes), an effect called immunodominance. The major effect of MHC on immunocompetence is probably a function of how MHC affect immunodominance and the establishment of lasting immunity. In acute stages of viral infections more than 25% and up to 50% of all activated CTLs are specific to as few as three major epitopes (McMichael & O'Callaghan 1998). Immunodominance is a puzzling phenomena. Large numbers of different peptides ($>10^3$) can be presented by class I molecules on cells, largely derived from self-proteins. However, dominant epitopes do not always bind to MHC molecules with high affinity or come from the most abundant pathogenic proteins. Yet immunodominance is not a chance event, because most individuals with the same MHC molecules respond to the same epitope peptides, regardless of genetic background (McMichael & Phillips 1997; McMichael & O'Callaghan 1998). From studies of the specificity of the response after vaccination with whole pathogens or complex antigens it seems clear that different MHC class I (Goddeeris et al. 1990; Taracha et al. 1995) and MHC class II (Gelder et al. 1998; Hayney et al. 1996; Poland 1998) genotypes differ in their pattern of immunodominance and that this affect both the repertoire of CTLs, antibody response and establishment of immunological memory. Furthermore, T-helper cells can be categorized into two functional subsets, Th1 and Th2 cells, which produce different regulatory signals, lymphokines. In general, Th1 cells mediate cellular immune responses and Th2 cells mediate humoral immunity. MHC seems to influence the activation of different effector cells, via its effect on the balance between Th1/Th2 type of immune response (Milich et al. 1995; Schountz et al. 1996; Murray 1998). In humans, the pattern of Th1 or Th2 activation may affect the risk for immunopathology after infection of pathogens (De Carli et al. 1994). These and other findings have led to an increasing recognition that genetic factors, such as the genes in the MHC, and their interaction with host and parasite genetic variation, and environmental factors have a significant role in disease susceptibility, resistance and progression (Poland 1998).

The presentation by MHC of evolutionary conserved epitopes to CTLs and Th-cells may be an adaptation in hosts to constrain the adaptation of the pathogens by lowering the fitness of escape mutants (McMichael & Phillips 1997; da Silva & Hughes 1998; Gelder et al. 1998). Similarly, the preferential presentation by MHC of evolutionary constrained

self epitopes (Hughes & Hughes 1995) can lower the risk for autoimmunity while maintaining the tolerance for evolutionary change in host background genes. Studies of heat shock proteins (HSP) provide a clear example of the interaction between host background genes, pathogens and the MHC (Lamb et al. 1989; Jones et al. 1993). Immune responses to microbial HSP could lead to autoimmune responses because of cross-reactivity with host HSP. The risk of cross-reactivity may depend on an individual's MHC class II genotype (Lamb et al. 1989; Jones et al. 1993). As infection or stress is liable to increase the risk of autoimmune responses, individuals with low-risk MHC genotypes could maintain a higher immune responsiveness at a given point than those carrying a high-risk genotype (see also Råberg et al. 1998; Westneat & Birkhead 1998). Thus, there is a trade-off between the benefit of resistance to parasites and the cost of immunopathology that will differ between MHC genotypes. Immune responsiveness may be optimized at an individual basis with respect to this trade-off. A simple graphical cost-benefit model (Råberg et al. 1998; Behnke et al. 1992) can illustrate this trade off (Fig. 3).

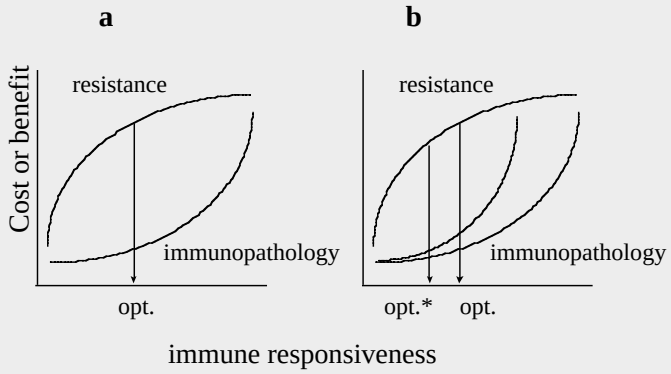

Figure 3. *Hypothetical cost (immunopathology) and benefit (resistance to parasites) curves as a function of immune responsiveness, and the optimal solution to this trade-off (opt., a). The cost function (immunopathology) varies depending on the MHC genotype of the organism (b). During infection there is a change in antigen repertoire that stimulates the immune system and could cause immunopathological responses. Consequently, the cost curve will be steeper and optimal immune responsiveness (opt*) will be reduced. High risk genotype and low risk genotype refer to difference in factors predisposing individuals to developing autoimmunity (redrawn from Råberg et al. 1998).*

MHC variation, disease resistance and ornaments

It is likely that differences in nutritional status, exposure to pathogens and other environmental factors directly affect males investments in ornaments and immune system in a condition dependent manner. Low nutritional status caused by, for instance inferior competitive ability, may leave some males less to allocate to either immune function or reproductive effort, or both (eg. Sheldon & Verhulst 1996; Westneat & Brikhead 1998). Males may even have the ability to grow larger ornaments by transferring resources, such as calories, proteins or carotenoids, from investment in the immune system to investment in ornaments (Folstad & Karter 1992; Lozano 1994). The influence of MHC genes on male

ornamentation, suggested here, is not an alternative explanation to the condition dependence of male ornaments. It is an attempt to explain how genetic variation in the immune system can translate into condition dependent information revealed in male ornaments.

Genetic variation in the immune system may affect male sexual signals if development of ornaments compete with pathogens or the immune system for shared resources, for instance energy or nutrients and these resources are in short supply. Specifically, MHC genes may affect the strength and effectiveness of the immune response and establishment of lasting immunity that may influence how often a male contract a disease and how well he will recover.

The supply of energy and nutrients need not be the only connection between MHC and ornaments. The effect of oxidative stress induced by free radicals on ornamentation has recently been suggested to provide a reliable measure of the genotype-environment interactions of the immune system (Grahn et al. 1998; von Schantz et al. 1999). The cytotoxic effects of free radicals are used by phagocytes and other cells in innate immunity when killing pathogens in the inflammatory response (Klebanoff & Clark 1978). The MHC-mediated recognition is essential for the adaptive immune system to mount a specific and more effective response (shorter time lag, higher antibody titre, and higher antibody affinity) on subsequent infections. Some of the activated B-cells develop into long-lived memory B-cells which, upon a secondary infection of the same pathogen, present antigen very efficiently to T-cells (Rajewsky 1996). Hence, individuals whose battery of MHC molecules fail to bind efficiently to the peptide fragments from the pathogen will produce a less efficient, low-affinity, antibody-mediated response (Roitt et al. 1996). A less specific defense, or a misdirected immune response leading to an autoimmune disease, may be costly in that it generates prolonged periods of sickness and extensive oxidative stress.

Genetic resistance may not always result in ”parasite-free” individuals, but can be manifested as a greater tolerance to common parasites (Zinkernagel 1996), and mate choice based on condition-dependent ornaments may promote matings with parasite tolerant partners (Skarstein & Folstad 1996). The double edged nature of the immune system have prompted a broader analysis considering both benefits and costs associated with the immune system and the relation to fitness traits discussing, not only the energetic and nutritional constraints on the immune system, but also the balance between immunresponsiveness and immunopathology (Westneat & Birkhead 1998; Råberg, et al. 1998). A strong immune response does not always imply higher fitness. For instance, several diseases are immunopathological where a misdirected immune response causes more harm than good to the organism (Westneat & Brikhead 1998; Råberg et al. 1998; Penn & Potts 1998). It is conceivable that phenotypic condition-dependent adjustments in male ornamentation are made at a lower cost to the male if his immune system is operating smoothly and at a lower risk for misfired immune responses (Fig. 3). This provides a direct link between mate choice based on condition-dependent ornaments and the populations ability to track co-evolving diseases (Grahn et al. 1998).

In conclusion, it is likely that MHC genotype can affect male ornaments through its effects on the immune system. Beside phenotypic condition-dependent adjustments, part of the variation among males in immunity may depend on the effects of the MHC on immunodominance, the balance between Th1/Th2 type response, and on the risk of developing autoimmune disorders or pathological responses to otherwise harmless pathogens. The MHC genes may constitute an important justification for the good genes implied in the Hamilton & Zuk (1982) model for the evolution of female choice and male condition-dependent ornamentation. The operation of female choice can, via mating preferences for males possessing large ornaments, select for MHC alleles that are both less sensitive to autoimmune disorders and more protective against common pathogens.

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References

Andersson, M. 1982. Sexual selection, natural selection, and quality advertisement. *Biological Journal of the Linnean Society*, **17**, 375-393.

Andersson, M. 1986. Evolution of condition-dependent sex ornaments and mating preferences: sexual selection based on viability differences. *Evolution*, **40**, 804-816.

Andersson, M. 1994. *Sexual selection*. New Jersey: Princeton University Press.

Apanius, V., Penn, D., Slev, P. R., Ruff, L. R. & Potts, W. K. 1997. The nature of selection on the major histocompatibility complex. *Critical Reviews in Immunology*, **17**, 179-224.

Behnke, J. M., Barnard, C. J. & Wakelin, D. 1992. Understanding chronic nematode infections: evolutionary considerations, current hypotheses and the way forward. *International Journal for Parasitology*, **22**, 861-907.

Black, F. L. & Salzano, F. M. 1981. Evidence for heterosis in the HLA system. *American Journal of Human Genetics*, **33**, 894-899.

Briles, W. E., Briles, R. W., Taffs, R. E. & Stone, H. A. 1983. Resistance to a malignant lymphoma in chickens is mapped to subregion of major histocompatibility (B) complex. *Science*, **219**, 977-979.

Clarke, B. & Kirby, D. R. S. 1966. Maintenance of histocompatibility polymorphisms. *Nature*, **211**, 999-1000.

Clark, E. A. & Ledbetter, J. A. 1994. How B and T cells talk to each other. *Nature*, **367**, 425-428.

De Carli, M., D'Elios, M. M., Zancuoghi, G., Romagnani, S. & Del Prete, G. 1994. Human Th1 and Th2 cells: functional properties, regulation of development and role in autoimmunity. *Autoimmunity*, **18**, 301-308.

Doherty, P. C. & Zinkernagel, R. M. 1975. Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex. *Nature*, **256**, 50-52.

Edwards, S. V. & Potts, W. K. 1996. Polymorphism of genes in the major histocompatibility complex: implications for conservation genetics of vertebrates. In: *Molecular Genetic Approaches in Conservation*. (Ed. by TB Smith & R K Wayne). pp 214-237. Oxford: Oxford University Press.

Ellegren, H., Mikko, S., Wallin, K. & Andersson, L. 1996. Limited polymorphism at major histocompatibility complex (MHC) loci in the Swedish moose. *A. alces. Molecular Ecology*, **5**:3-9.

Folstad, I. & Karter, A. J. 1992. Parasites, bright males and the immunocompetence handicap. *The American Naturalist*, **139**, 603-622.

Gelder, C., Davenport, M., Barnardo, M., Bourne, T., Lamb, J., Askonas, B., Hill, A. & Welsh, K. 1998. Six unrelated HLA-DR-matched adults recognize identical CD4+ T cell epitopes from influenza A haemagglutanin that are not simply peptides with high HLA-DR binding affinities. *International Immunology*, **10**, 211-222.

Goddeeris, B. M., Morrison, W. I., Toye, P. G. & Bishop, R. 1990. Strain specificity of bovine Theileria parva-specific cytotoxic T cells is determined by the phenotype of the restricting class I MHC. *Immunology*, **69**, 39-44.

Grahn, M., Langefors, Å. & von Schantz, T. 1998. The importance of mate choice in improving viability in captive populations. In: *Behavioral ecology and Conservation Biology* (Ed. by T. Caro), pp. 341-363. Oxford: Oxford University Press.

Grahn, M. & von Schantz, T. 1994. Fashion and age in pheasants: age differences in mate choice. *Proceedings of the Royal Society of London, Series B*, **255**, 237-241.

Hamilton, W. D. Axelrod, R. & Tanese, R. 1990. Sexual reproduction as an adaptation to resist parasites: a review. *Proceedings of the National Academy of Sciences, United States of America*, **87**, 3566-3573.

Hamilton, W. D. & Zuk, M. 1982. Heritable true fitness and bright birds: a role for parasites? *Science*, **218**, 384-387.

Hayney, M. S., Poland, G. A., Jacobson, R. M., Schaid, D. J. & Lipsky, J. J. 1996. The influence of the HLA-DRB1*13 allele on measles vaccine response. *Journal of Investigative Medicine*, **44**, 261-263.

Han, R., Breitburd, F., Marche, P. N. & Orth, G. 1992. Linkage regression and malignant conversion of rabbit viral papillomas to MHC class II genes. *Nature*, **356**, 66-68.

Hasselquist, D., Bensch, S. & von Schantz, T. 1996. Correlation between male song repertoire, extra-pair paternity and offspring survival in the great reed warbler. *Nature*, **381**, 229-232.

Hedrick, P. W. 1994. Evolutionary genetics of the major histocompatibility complex. *The American Naturalist*, **143**, 945-964.

Hill, A. V. S. 1998. The Immunogenetics of Human Infectious Disease. *Annual Review of Immunology*, **16**, 593-617.

Hill, A. V. S., Allsopp, C. E. M., Kwiatkowski, D., Anstey, N. M., Twumasi, P., Rowe, P. A., Bennett, S., Brewster, D., McMichael, A. J. & Greenwood, B. M. 1991. Common West African HLA antigens are associated with protection from severe malaria. *Nature*, **352**, 595-600.

Hill, G. E. 1990. Female house finches prefer colorful males: sexual selection for a condition-dependent trait. *Animal Behaviour*, **40**, 563-572.

Hill, G. E. 1991. Plumage coloration is a sexually selected indicator of male quality. *Nature*, **350**, 337-339.

Hillgarth, N. 1990. Parasites and female choice in the ring-necked pheasant. *American Zoologist*, **30**, 227-233.

Hoikkala, A., Aspi, J. & Suvanto, L. 1998. Male courtship song frequency as an indicator of male genetic quality in an insect species, *Drosophila montana. Proceedings of the Royal Society of London, Series B*, **265**, 503-508.

Houde, A. E. & Torio, A. J. 1992. Effect of parasitic infection on male color pattern and female choice in guppies. *Behavioral Ecology*, **3**, 346-351.

Hughes, A. L. & Hughes, M. K. 1995. Self peptides bound by HLA class I molecules are derived from highly conserved regions of a set of evolutionary conserved proteins. *Immunogenetics*, **41**, 257-262.

Ivanova, R., Henon, N., Lepage, V., Charron, D., Vicaut, E. & Schachter, F. 1998. HLA-DR alleles display sex-dependent effects on survival and discriminate between individual and familial longevity. *Human Molecular Genetics*, **7**, 187-194.

Jones, D. B., Coulson, A. F. & Duff, G. W. 1993. Sequence homologies between hsp60 and autoantigens. *Immunology Today*, **14**, 115-118.

Kirkpatrick, M. & Ryan, M. J. 1991. The evolution of mating preferences and the paradox of the lek. *Nature*, **350**, 33-38.

Klebanoff, S .J. & Clark, R.A. 1978 *The neutrophil: function and clinical disorders*. Amsterdam: North-Holland.

Kodric-Brown, A. & Brown, J. H. 1984. Truth in advertising: the kinds of traits favored by sexual selection. *The American Naturalist*, **124**, 309-323.

Kroemer, G., Bernot, A., Béhar, G., Chaussé, A-M., Gastinel, L-N., Guillemot, F., Park, I., Thoraval, P., Zoorob, R. & Auffray, C. 1990. Molecular genetics of the chicken MHC: current status and evolutionary aspects. *Immunological Reviews*, **113**, 119-145.

Lamb, J.R., Bal, V., Rothbard, J.B., Mehlert, A., Mendez-Samperio, P. & Young, D. B. 1989. The mycobacterial stress protein : a common target of T-cell recognition in infection and autoimmunity. *Journal of Autoimmunology*, **2** (Supplement), 93-100.

Lord, G. M., Matarese, G., Howard, J. K., Baker, R. J., Bloom, S. R. & Lechler, R. I. 1998. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature*, **394**, 897-901.

Lozano, G. A. 1994. Carotenoids, parasites, and sexual selection. *Oikos*, **70**, 309-311.

Malo, D. & Skamene, E. 1994. Genetic control of host resistance to infection. *Trends in Genetics*, **10**, 365-371.

Manning, J. T. & Chamberlain, A. T. 1993. Fluctuating asymmetry, sexual selection and canine teeth in primates. *Proceedings of the Royal Society of London, Series B*, **251**, 83-87.

McGuire, W., Hill, A. V. S., Allsopp, C. E. M., Greenwood, B. M. & Kwiatkowski, D. 1994. Variation in the TNF-a promoter region associated with susceptibility to cerebral malaria. *Nature*, **371**, 508-511.

McMichael, A. J. & O'Callaghan, C. A. 1998. A new look a T cells. *Journal of Experimental Medicine*, **187**, 1367-1381.

McMichael, A. J. & Phillips, R. E. 1997. Escape of human immunodeficiency virus from immune control. *Annual Review of Immunology*, **15**, 271-296

Milich, D. R., Peterson, D. L., Schodel, F., Jones, J. E. & Hughes, J. L. 1995. Preferential recognition of hepatitis B nucleocapsid antigens by Th1 or Th2 cells is epitope and major histocompatibility complex dependent. *Journal of Virology*, **69**, 2776-2785.

Milinski, M. & Bakker, T. C. M. 1990. Female sticklebacks use male coloration in mate choice and hence avoid parasitized males. *Nature*, **344**, 330-333.

Møller, A. P. 1994. *Sexual selection and the barn swallow*. New York: Oxford University Press.

Murray, J. S. 1998. How the MHC selects Th1/Th2 immunity. *Immunology Today*, **19**, 157-163.

Nepom, G. T. & Erlich, H. 1991. MHC class-II molecules and autoimmunity. *Annual Review of Immunology*, **9**, 493-525.

Nevo, E. & Beiles, A. 1992. Selection for class II MHC heterozygosity by parasites in subterranean mole rats. *Experimentia*, **48**, 512-515.

Norris, K. 1993. Heritable variation in a plumage indicator of viability in male great tits *Parus major*. *Nature*, **362**, 537-539.

Nicoletto, P. F. 1993. Female sexual response to condition-dependent ornaments in the guppy, *Poecilia reticulata*. *Animal Behaviour*, **46**, 441-450.

Paterson, S., Wilson K. & Pemberton, J. M. 1998. Major histocompatibility complex variation associated with juvenile survival and parasite resistance in a large unmanaged ungulate population *(Ovis aries L.). Proceedings of the National Academy of Sciences, United States of America*, **95**, 3714-3719.**Error! Bookmark not defined.**

Penn, D. & Potts, W. K. 1998. Chemical signals and parasite-mediated sexual selection. *Trends in Ecology and Evolution*, **13**, 391-396.

Poland, G. A. 1998. Variability in immune response to pathogens: using measles vaccine to probe immunogenetic determinants of response. *American Journal of Human Genetics*, **62**, 215-20.

Pomiankowski, A. & Møller, A. P. 1995. A resolution of the lek paradox. *Proceedings of the Royal Society of London, Series B*, **260**, 21-29.

Potts, W. K. & Slev, P. R. 1995. Pathogen-based models favoring MHC genetic diversity. *Immunological Reviews*, **143**, 181-197.

Potts, W. K. & Wakeland, E. K. 1990. Evolution of diversity at the major histocompatibility complex. *Trends in Ecology and Evolution*, **5**, 181-187.

Potts, W. K. & Wakeland, E. K. 1993. Evolution of MHC genetic diversity: a tale of incest, pestilence, and sexual preference. *Trends in Genetics*, **9**, 408-412.

Råberg, L., Grahn, M., Hasselquist, D. & Svensson, S. 1998. On the Adaptive Significance of Stress-Induced Immunosuppression. *Proceedings of the Royal Society of London, Series B*, **265**, 1637-1641.

Rajewsky, K. 1996. Clonal selection and learning in the antibody system. *Nature*, **381**, 751-758.

Roitt, I., Brostoff, J. & Male, D. 1996. *Immunology*. 4th ed. London: Mosby.

Saino, N. & Møller, A. P. 1996. Sexual ornamentation and immunocompetence in the barn swallow. *Behavioral Ecology*, **7**, 227-232.

von Schantz, T., Bensch, S., Grahn, M., Hasselquist, D. & Wittzell, H. 1999. Good genes, oxidative stress and condition-dependent sexual signals. *Proceedings of the Royal Society of London, Series B*, **266**, 1-12.

von Schantz, T., Göransson, G., Andersson, G., Fröberg, I., Grahn, M., Helgée, A. & Wittzell, H. 1989. Female choice selects for a viability-based male trait in pheasants. *Nature*, **337**, 166-169.

von Schantz, T., Grahn, M. & Göransson, G. 1994. Intersexual selection and reproductive success in the pheasant *Phasianus colchicus. The American Naturalist*, **144**, 510-527.

von Schantz, T., Wittzell, H., Göransson, G., Grahn, M. & Persson, K. 1996. MHC genotype and male ornamentation: genetic evidence for the Hamilton-Zuk model. *Proceedings of the Royal Society of London, Series B*, **263,** 265-271.

von Schantz, T., Wittzell, H., Göransson, G. & Grahn, M. 1997. Mate choice, male condition-dependent ornamentation and MHC in the pheasant. *Hereditas*, **127**, 133-140.

Schountz, T., Kasselman, J. P., Martinson, F. A., Brown, L. & Murray, J. S. 1996. MHC genotype controls the capacity of ligand density to switch T helper (Th)-1/Th-2 priming in vivo. *Journal of Immunology*, **157**, 3893-3901.

Sheldon, B. C. & Verhulst, S. 1996. Ecological immunology: costly parasite defenses and trade-offs in evolutionary ecology, *Trends in Ecology and Evolution*, **11**, 317-321.

da Silva, J. & Hughes, A. L. 1998. Conservation of cytotoxic T Lymphocyte (CTL) epitopes as a host strategy to constrain parasite adaptation: evidence from the *nef* gene of Human Immunodeficency Virus 1 (HIV-1). *Molecular Biology and Evolution*, **15**, 1259-1268.

Skarstein, F. & Folstad, I. 1996. Sexual dichromatism and the immunocompetence handicap: an observational approach using Arctic charr. *Oikos*, **76,** 359-367.

Taracha, E. L., Goddeeris, B. M., Teale, A. J., Kemp, S. J. & Morrison, W. I. 1995. Parasite strain specificity of bovine cytotoxic T cell responses to *Theileria parva* is determined primarily by immunodominance. *Journal of Immunology*, **155**, 4854-4860.

Tiwari, J. L. & Teraski, P. I. 1985. *HLA and disease associations*. New York: Springer-Verlag.

Trowsdale, J. 1993. Genomic structure and function in the MHC, *Trends In Genetics*, **9**, 117-122.

Trowsdale, J. 1995. Both man & bird & beast: comparative organization of MHC genes. *Immunogenetics*, **41**, 1-17.

Wakeland, E. K., Boehme, S., She, J. X., Lu, C. C., McIndoe, R. A., Cheng, I., Ye, Y. & Potts, W. K. 1989. Ancestral polymorphisms of MHC class II genes: divergent allele advantage. *Immunology Research*, **9**, 123.

Welch, A. M., Semlitsch, R, D. & Gerhardt, H. C. 1998. Call duration as an indicator of genetic quality in male gray tree frogs. *Science*, **280**, 1928-1930.

Westneat, D.F. & Birkhead, T.R. 1998. Alternative hypotheses linking the immune system and mate choice for good genes. *Proceedings of the Royal Society of London, Series B*, **265**, 1065-1073.

Zahavi, A. 1975. Mate selection - a selection for a handicap. *Journal of Theoretical Biology*, **53**, 205-214.

Zahavi, A. 1977. The cost of honesty (further remarks on the handicap principle). *Journal of Theoretical Biology*, **67**, 603-605.

Zinkernagel, R. M. 1996. Immunology taught by viruses. *Science*, **271**, 173-178.

Zuk, M., Johnsen, T. S. & Maclarty, T. 1995. Endocrine-immune interactions, ornaments and mate choice in red jungle fowl. *Proceedings of the Royal Society of London, Series B*, **260**, 205-210.

Zuk, M. & Johnsen, T.S. 1998. Seasonal changes in the relationship between ornamentation and the immune response in red jungle fowl. *Proceedings of the Royal Society of London, Series B*, **265**, 1631-1635.

Zuk, M., Thornhill, R., Ligon, J. D., Johnson, K. 1990. Parasites and mate choice in red jungle fowl. *American Zoologist*, **30**, 235-244.