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International Journal of Molecular Zoology, 2024, Vol.14, No.6, 297-304
http://animalscipublisher.com/index.php/ijmz

Review Article Open Access

A Review of Canid Immunogenomics: How Domestication Shaped the Canine Immune System

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International Journal of Molecular Zoology, 2024, Vol.14, No.6 doi: 10.5376/ijmz.2024.14.0026
Received: 03 Nov., 2024
Accepted: 05 Dec., 2024
Published: 16 Dec., 2024

Preferred citation for this article:
Li J.Y., He J., and Chen M.Y., 2024, A review of canid immunogenomics: how domestication shaped the canine immune system, International Journal of Molecular Zoology, 14(6): 297-304 (doi: 10.5376/ijmz.2024.14.0026)

Abstract This study reviews the genetic basis of immune function in dogs, with a focus on key immune genes such as major histocompatibility complexes (MHC) and toll like receptors (TLRs). The evolutionary changes of immune genes during domestication were examined, and the comparative analysis between domestic dogs and their wild relatives (such as wolves and coyotes) highlighted significant immune genomic variations caused by differences in pathogen exposure and selection pressure. Taking sled dogs as an example, the unique immune adaptation to extreme environments was demonstrated, revealing how selection pressure affects immune gene diversity and pathogen resistance. The development direction of canine immune genomics was reviewed, including emerging technologies, personalized health management, and protection of immune gene diversity in wild dogs. This study emphasizes the importance of immune genome research in advancing our understanding of the impact of dog health, evolutionary biology, and domestication on immune system function.

Keywords Canid; Canine immunogenomics; Domestication; Immune system; Major histocompatibility complex (MHC)

1 Introduction

Canid immunogenomics is a burgeoning field that explores the genetic underpinnings of the immune system in canids, including domestic dogs and their wild relatives such as wolves and foxes (vonHoldt et al., 2011). This area of study leverages high-throughput sequencing technologies to decode the complex genetic variations that contribute to immune responses and disease susceptibility in these species. Structural variations (SVs), copy number variations (CNVs), and epigenetic modifications are among the key genomic elements investigated to understand how they influence immune function (Koch et al., 2016; Wang et al., 2018).

Domestication has profoundly impacted the canine immune system, primarily through selective breeding and adaptation to human environments. Studies have shown that domesticated dogs exhibit significant genomic differences from their wild counterparts, including variations in genes associated with immune responses. For instance, structural variations specific to dogs have been linked to genes involved in energy metabolism, neurological processes, and immune systems, suggesting that these changes were crucial for adapting to new diets and living conditions during domestication (Zhao, 2018). Additionally, methylation patterns and CNVs have been found to differ significantly between dogs and wolves, further highlighting the role of domestication in shaping the canine immune system (Ramírez et al., 2014; Serres-Armero et al., 2017).

This study reviews the current research status of canine immunogenomics, including domesticated dogs and their wild relatives, providing a comparative perspective for better understanding the genetic and epigenetic mechanisms of immune response in canine animals. It focuses on the effects of domestication on the canine immune system, explores various genomic elements, including SVs, CNVs, and epigenetic modifications, and their roles in immune function. The aim of this study is to provide insights into the evolutionary dynamics of the canine immune system by synthesizing recent research findings and to identify areas for future research.

2 Genetic Basis of the Canine Immune System

2.1 Overview of the canine immune system

The canine immune system, like that of other vertebrates, is composed of innate and adaptive components that work together to protect the host from pathogens (Chen, 2024). The innate immune system provides the first line of defense through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), which detect pathogen-associated molecular patterns (PAMPs) and initiate immediate immune responses (Vaure and Liu, 2014; Vijay, 2018). The adaptive immune system, on the other hand, involves the major histocompatibility complex (MHC) molecules that present antigens to T cells, facilitating a more specific and long-lasting immune response (Migalska et al., 2019).

2.2 Major histocompatibility complex (MHC) in canines

The *MHC* genes are crucial for the adaptive immune response in canines, encoding proteins that present foreign antigens to T cells. These genes exhibit high polymorphism, which is believed to be maintained by pathogen-mediated selection (Bartocillo et al., 2021). In canines, MHC class I molecules, such as DLA-88*50801, have been structurally characterized to reveal diverse peptide-binding modes, which are essential for recognizing a wide array of pathogens (Xiao et al., 2016). Studies on raccoon dogs, a non-model canid species, have shown that MHC class I genes are subject to positive selection and balancing selection, indicating their evolutionary adaptation to pathogen pressures.

2.3 Toll-like receptors (TLRs) and pathogen recognition

TLRs are a family of PRRs that play a pivotal role in the innate immune system by recognizing PAMPs and initiating immune responses (Figure 1) (Fitzgerald and Kagan, 2020). In canines, TLRs such as TLR2, TLR4, and TLR5 are involved in recognizing bacterial components and other pathogens (Quéméré et al., 2015). These receptors are highly polymorphic, which allows for a broad recognition spectrum and adaptability to various pathogens (Minias et al., 2021). The expression and functionality of TLR4, for instance, vary across different species, including dogs, which has implications for vaccine development and therapeutic interventions. The evolutionary dynamics of TLRs in canines suggest that these receptors are under continuous selection pressure to maintain their diversity and functionality in pathogen recognition (Quéméré et al., 2021).

3 Impact of Domestication on Immune Genes

3.1 Evolutionary changes in immune genes during domestication

Domestication has significantly influenced the evolution of immune genes in canids. Structural variations (SVs) in the genome, such as insertions, deletions, and translocations, have been identified as key factors in the domestication process. These SVs are particularly enriched in genes associated with immune systems, indicating that immune function has been a critical area of adaptation during domestication (Wang et al., 2018). For instance, the insertion of a new copy of the *AKR1B1* gene in dogs, which is highly expressed in the small intestine and liver, suggests an enhanced ability for de novo fatty acid synthesis and antioxidant activity, likely in response to dietary changes during the agricultural revolution.

3.2 Adaptation to human-influenced environments

The adaptation of canids to human-influenced environments has also shaped their immune systems. The shift from wild habitats to human-dominated landscapes exposed domestic dogs to a new range of pathogens, necessitating changes in their immune responses. This is evident in the increased expression of immune-related genes and the presence of structural variations that enhance immune function. Additionally, the European roe deer, which has expanded into agricultural landscapes, shows that exposure to new pathogens can drive the evolution of immune genes, such as toll-like receptors (TLRs), which continue to evolve dynamically in response to pathogen-mediated positive selection (Quéméré et al., 2015).

3.3 Genetic bottlenecks and immune gene diversity

Domestication has also led to genetic bottlenecks, which have had a profound impact on immune gene diversity. Small population sizes during domestication and strong artificial selection for specific traits have increased the number of deleterious genetic variants in domestic dogs compared to their wild counterparts, such as gray wolves (Marsden et al., 2015). This is reflected in the higher ratio of amino acid-changing heterozygosity to silent heterozygosity in dogs, indicating a higher genetic load. The bottlenecks associated with domestication and breed formation have reduced the efficiency of natural selection, leading to an accumulation of deleterious variants in regions of the genome implicated in selective sweeps. This highlights the importance of maintaining large population sizes to prevent the accumulation of deleterious variants and preserve immune gene diversity.

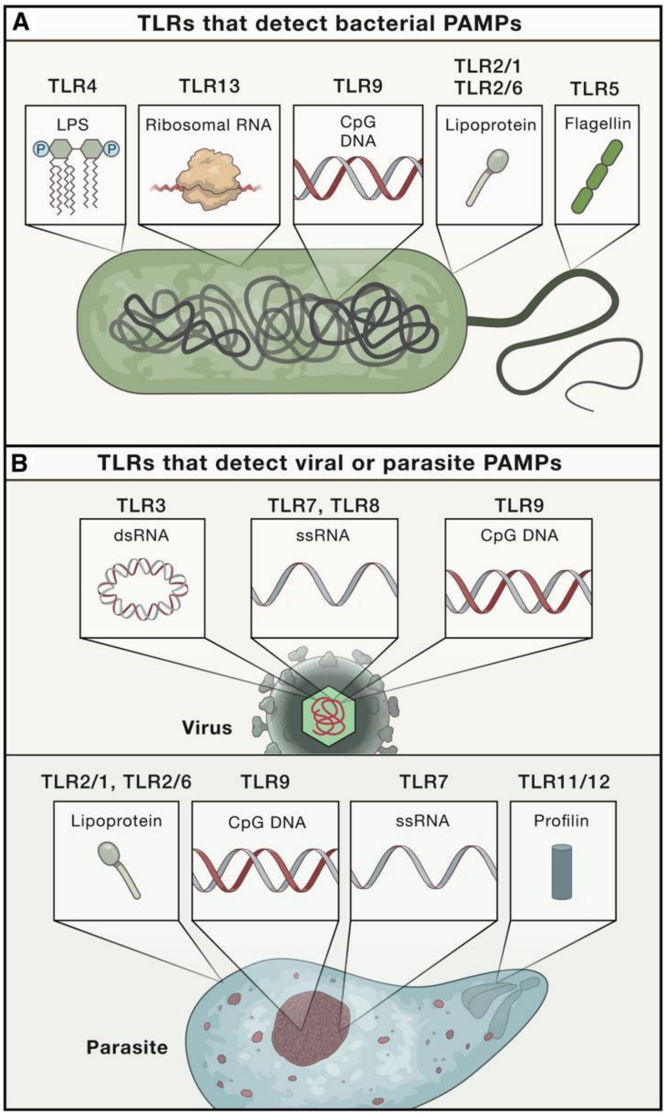

Figure 1 Multiple TLR family members can detect PAMPs on individual microorganisms (Adopted from Fitzgerald and Kagan, 2020)

4 Comparative Immunogenomics of Wild and Domestic Canids

4.1 Immune gene diversity in wild canids

Wild canids, such as wolves, coyotes, and foxes, exhibit significant immune gene diversity, which is crucial for their survival in diverse and often challenging environments. For instance, studies have shown that wild canids like the gray wolf (*Canis lupus*) and the red fox (*Vulpes vulpes*) possess a wide array of immune genes that enable them to respond effectively to various pathogens (Vinkler et al., 2023). The genetic diversity in these species is shaped by both historical and contemporary evolutionary forces, including genetic drift and pathogen-mediated selection. For example, toll-like receptors (TLRs) in wild canids continue to evolve dynamically, reflecting ongoing adaptation to pathogen pressures.

4.2 Immunogenomic variations in domestic breeds

Domestic dog breeds exhibit distinct immunogenomic variations compared to their wild counterparts. The domestication process has led to structural variations (SVs) in the genome, which have significant implications for immune system function. For example, domestic dogs have been found to possess specific SVs, such as insertions and deletions, that are enriched in genes related to immune responses (Wang et al., 2018). Additionally, copy number variations (CNVs) in domestic dogs show significant differences from those in wild canids, with certain CNVs being associated with immune response genes (Serres-Armero et al., 2017). Despite the population bottlenecks during domestication, domestic dogs maintain a similar proportion of CNV loci as wild canids, suggesting selective pressures favoring these variations.

4.3 Host-pathogen co-evolution in wild vs. domestic canids

The co-evolution of hosts and pathogens has led to distinct immunogenomic landscapes in wild and domestic canids (Canuti et al., 2022). In wild canids, the continuous exposure to a wide range of pathogens drives the evolution of diverse immune genes, enabling these animals to adapt to new and emerging infectious diseases (Quéméré et al., 2015). For instance, the red fox has shown susceptibility to SARS-CoV-2, highlighting the ongoing interaction between wild canids and novel pathogens (Porter et al., 2022). In contrast, domestic dogs have undergone significant genomic changes due to human-mediated selection, which has influenced their immune system. The domestication process has introduced new immune challenges, such as those related to close contact with humans and other domestic animals, leading to unique immunogenomic adaptations.

5 Case Study: Immune Adaptations in Sled Dogs

5.1 Unique immune gene profiles in sled dog breeds

Sled dogs, such as the Alaskan malamute and Siberian husky, exhibit unique immune gene profiles that have evolved to support their demanding lifestyles in harsh environments. These breeds have been subject to both natural and artificial selection pressures, leading to distinct genetic adaptations. For instance, structural variations (SVs) in the dog genome, including insertions, deletions, and translocations, have been linked to immune system functions (Figure 2) (Wang et al., 2018). These SVs are enriched in genes associated with energy metabolism and immune responses, which are crucial for sled dogs that endure extreme cold and physical exertion (Zhao, 2018).

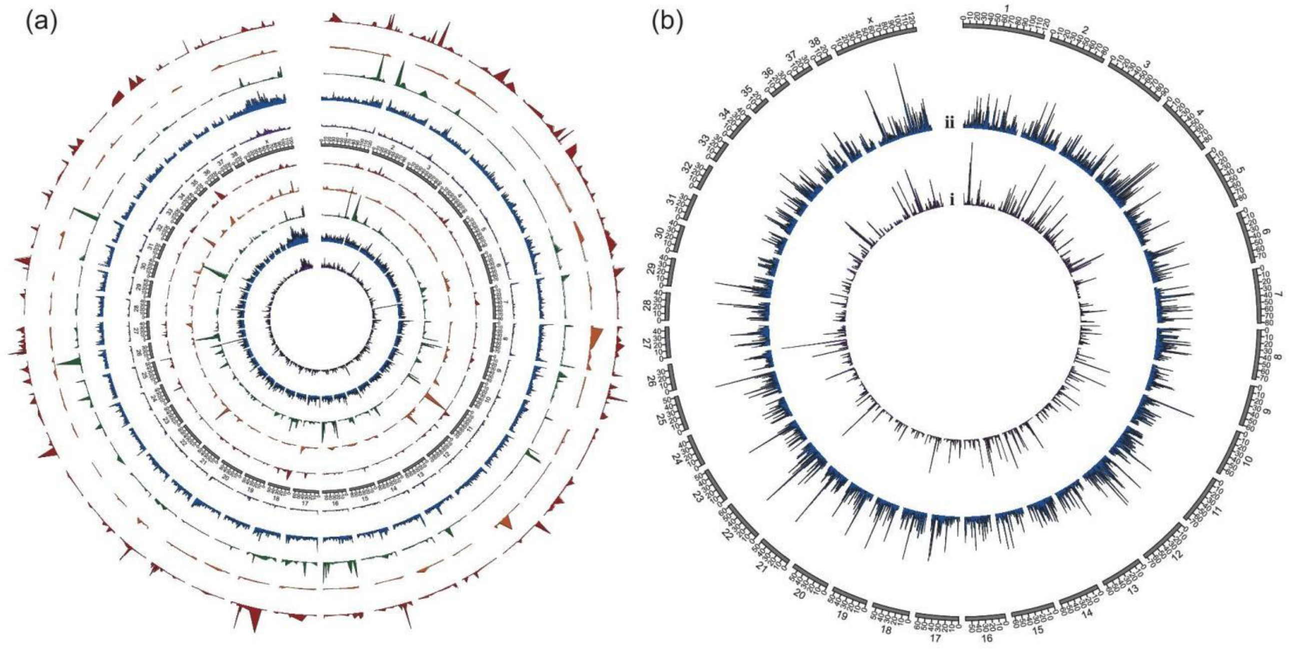

Figure 2 Structural variation in the dog genome (Adopted from Wang et al., 2018)

Image caption: (a) Circle diagram showing SVs detected by the dog-dhole alignment (yellow) and the dog-wolf alignment (black). (b) SVs in the dog genome by identified by multiz alignment. Each ring from the inner ring outwards represents translocations, insertions, deletions, repeats and inversions, respectively (Adopted from Wang et al., 2018)

5.2 Pathogen resistance in sled dogs

Sled dogs have also developed enhanced resistance to various pathogens, a trait that is vital for their survival in environments where they are exposed to a wide range of infectious agents. Studies on other canid species, such as the raccoon dog, have shown that major histocompatibility complex (MHC) genes play a significant role in pathogen resistance through high allelic diversity and positive selection (Bartocillo et al., 2021). Similar mechanisms are likely at play in sled dogs, where pathogen-driven selection has shaped their immune gene repertoire. Additionally, the identification of positively selected genes linked to immunity in other dog populations, such as African dogs, suggests that sled dogs may possess unique genetic adaptations that confer resistance to specific pathogens (Liu et al., 2018).

5.3 Lessons from sled dogs for understanding canine immunogenomics

The study of sled dogs provides valuable insights into canine immunogenomics and the broader implications of domestication on immune system evolution. The genetic adaptations observed in sled dogs highlight the role of structural variations and positive selection in shaping immune responses. These findings underscore the importance of considering both natural and artificial selection pressures in the study of domesticated species (Pilot et al., 2016; Serres-Armero et al., 2021). Furthermore, the unique immune profiles of sled dogs can inform research on other canid species and contribute to our understanding of the genetic basis of disease resistance and environmental adaptation in domestic dogs (Wilbe et al., 2010; Vinkler et al., 2023).

6 Future Directions in Canine Immunogenomics

6.1 Emerging technologies for immunogenomic research

The field of canine immunogenomics is rapidly evolving with the advent of new technologies. High-quality draft genomes of various canid species, such as the gray wolf and dhole, have provided insights into structural variations (SVs) that are crucial for understanding phenotypic evolution, disease susceptibility, and environmental adaptations in dogs (Wang et al., 2018). Whole genome re-sequencing and the development of fine-scale genomic maps of segmental duplications (SDs) have enabled the identification of copy number variations (CNVs) that play significant roles in sensory perception, immune response, and metabolic processes. Additionally, the Dog10K Consortium aims to sequence 10 000 canid genomes, which will capture the genetic diversity underlying phenotypic and geographical variability, further advancing our understanding of canine immunogenomics (Ostrander et al., 2019).

6.2 Integrating immunogenomics with canine health management

Integrating immunogenomic data with canine health management can lead to improved disease prevention and treatment strategies. For instance, the identification of the dog erythrocyte antigen (DEA) 1 blood group in both domestic and non-domestic canids has implications for blood transfusion practices, ensuring compatibility and reducing the risk of transfusion reactions (Charpentier et al., 2020). Moreover, understanding the genetic basis of immune responses, such as the role of natural killer (NK) cells in cancer immunotherapy, can inform the development of targeted treatments for dogs with naturally occurring cancers (Gingrich et al., 2018). The creation of a canine PD-L1 antibody and a caninized PD-L1 mouse model exemplifies how immunogenomic research can translate into effective immunotherapies for both canine and human cancers (Oh et al., 2023).

6.3 Conservation and genetic management of wild canid populations

Conservation efforts for wild canid populations can benefit significantly from immunogenomic research. The study of structural variations and CNVs in wild canids, such as gray wolves, can reveal genetic adaptations that are essential for their survival and inform conservation strategies (Serres-Armerong et al., 2017). Additionally, the identification of novel genetic variants, such as the distinct lineage of canine distemper virus (CDV) circulating among domestic dogs in India, highlights the importance of monitoring and managing disease outbreaks in wild canid populations to prevent cross-species transmission and ensure their long-term viability (Bhatt et al., 2019). Integrating immunogenomic data with conservation practices can help maintain genetic diversity and resilience in wild canid populations.

7 Concluding Remarks

The review of canid immunogenomics has highlighted several key findings regarding how domestication has shaped the canine immune system. Comparative studies of natural killer (NK) cells in dogs have shown that canine NK cells exhibit distinct transcriptional profiles under various conditions and are more similar to human NK cells than to those of mice, providing valuable insights for translational *NK* studies. Research on zoonotic intestinal helminths has revealed that these parasites modulate the canine immune system by altering T cell responses and preventing dendritic cell maturation, which helps in understanding the immune evasion strategies of these parasites. The study of the canine transmissible venereal tumor (CTVT) has uncovered specific genomic aberrations that enable its long-term persistence and adaptation, shedding light on the mechanisms of clonal transmissibility and immune evasion. Additionally, the evolution of MHC class I genes in raccoon dogs has demonstrated the role of pathogen-driven positive selection and long-term balancing selection in maintaining allelic diversity, which is crucial for immunological fitness.

The findings from these studies have several implications for future research. The similarity between canine and human NK cells suggests that dogs could serve as a valuable model for studying human NK cell biology and developing NK cell-based immunotherapies. The immunomodulatory effects of zoonotic helminths on the canine immune system highlight the need for further investigation into parasite-host interactions and the development of novel therapeutic strategies to manage parasitic infections. The insights gained from the study of CTVT can inform research on other transmissible cancers and contribute to the development of targeted therapies that can disrupt the mechanisms of immune evasion and clonal propagation. The extensive allelic diversity of MHC class I genes in raccoon dogs underscores the importance of studying non-model canid species to understand the evolutionary pressures shaping immune gene diversity and to identify potential targets for enhancing disease resistance.

The evolution of the canine immune system has been profoundly influenced by domestication, pathogen interactions, and genetic diversity. Domestication has likely led to selective pressures that have shaped immune responses to better suit the environments and lifestyles of domestic dogs. The interaction with various pathogens, including viruses, bacteria, and parasites, has driven the evolution of immune genes, such as MHC class I, to enhance pathogen recognition and immune response. The study of canid immunogenomics not only provides insights into the adaptive mechanisms of the canine immune system but also offers valuable models for understanding human immunology and developing novel therapeutic approaches. Future research should continue to explore the genetic and environmental factors that influence immune function in canids, with the goal of improving health outcomes for both dogs and humans.

Acknowledgments

We would like to thank Professor Meng for his/her invaluable guidance, insightful suggestions, and continuous support throughout the development of this study.

Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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