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Animal Contributions to Immunology: An Opinion

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Abstract: Animal models are invaluable to studies aiming to improve the well-being of human beings, particularly in the science of immunology. Traditionally, mice models have been used for both immunology research and teaching. Scientists worldwide have proposed other animal models that can contribute to the study of immunology. The objective of this opinion paper is to identify the contributions of invertebrate and vertebrate animals to the science of immunology. Immune features are categorized into nine major groups according to how they contribute, as follows: in vitro investigations, in vivo investigation, for development, as models, in discoveries, in the study of evolution, for therapeutics, for protection, and in the study of specific phenomena. A detailed description of the immune system and its evolutionary development is provided. Piscan, anuran, avian, and lapin immune models are suggested based on our research and those of others as alternatives to the traditional mice model.

Keywords: animal, contribution, immunology, models, mice.

动物对免疫学的贡献：意见

摘要：动物模型对于旨在改善人类福祉的研究非常宝贵，尤其是在免疫学方面。传统上，小鼠模型已用于免疫学研究和教学。世界各地的科学家提出了其他有助于免疫学研究的动物模型。本意见书的目的是确定无脊椎动物和脊椎动物对免疫学科学的贡献。免疫功能根据其贡献方式分为九大组，如下：体外研究、体内研究、开发、模型、发现、进化研究、治疗、保护和研究的具体现象。提供了免疫系统及其进化发展的详细描述。根据我们的研究和其他人的研究，建议使用皮斯坎、蚺、禽类和拉宾免疫模型作为传统小鼠模型的替代品。

关键词：动物、贡献、免疫学、模型、小鼠。

1. Introduction

In biological classification, there are five kingdoms, and the largest of these is Animalia [1]. Animalia is made up of invertebrates and vertebrates. These two groups are further divided into higher and lower forms [2],[3], which are divided into a number of specific animal groups [1], [4]. These groups can serve a wide range of functions that are valuable to scientific discovery, particularly in the field of immunology [5], [6], [7], [8], [9].The objective of this opinion paper is to shed light on the contribution of specific members of these animal groups to the science of immunology and suggest new immune models as alternatives to the mice model [10].

2. Theme

The immune features of the lower and higher forms of invertebrates and vertebrates can be divided into general and specific [4], [8], [9]. These features are either specific structures and/or specific mechanisms unique to an animal group. Features discovered in a specific group may be applicable to other groups. Thus far, nine broad areas of contribution to the science of immunology have been identified in Animalia. The discussion of each contribution includes a brief description of the immune feature, its unique immune characteristics, and suggestions for alternative models for the specific contribution [10]. Thus, the following three hypotheses were proposed:

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1. Animals are valuable for immunological teaching and research.

2. Specific animal groups are valid human immunity models.

3. The cells and body fluids of animals can serve as supporting materials for immunological investigations.

3. Contributions

Animals are indispensable for both teaching and research in the field of immunology, with both invertebrates and vertebrates making important contributions. Mice have traditionally been the model of choice for immunology. Recently, there has been an increase in the number of studies worldwide proposing other animal models, such as farm animals, rabbits, fish, and amphibians [11], [12], [14], [15], [16], [17]. Many of these models may be valuable contributors to immunology science (Table 1).

Table 1 Animal contributions to immunology [5], [6], [7]

Contribution	Study nature	Entities	Use
Investigation	In-vitro	BSA Fetal calf serum Sheep red cells	Antigen Cellular immune test E rosett formation Antigen carrier
Investigation	In-vivo	Test immune system	Hypersensitivity Autoimmunity Mitogenicity
Development	In-vivo	Test immune system	Vaccines Therapeutic sera
Models	In-vivo	Test immune system	Immunity to infection
Discovery	In-vivo	Thymus Bursa of Fabricius	Structural immunology
Evolution	In-vivo	Representative of each animal group	Evolutionary and developmental immunology
Therapeutics	In-vivo	Antitoxins Antiveinins standard globulin	Immunotherapy
Protection	In-vivo	Microbial toxinosis	Mouse protection test
Phenomena	In-vivo	Arthus reaction Jhon Moote reaction Anaphyl Axis anergy	Building up models Detection of molecular mechanisms
Simulations	In-vivo	Animal-Human	Immune simulations

4. Specific Immune Features

Each invertebrate and vertebrate animal group has both general and specific immune features. General features refer to those that are expressed in all or most of the members of the group, such as phagocytosis, self and non-self recognition, and graft rejection, while specific features belong to fewer members or individuals within the group, such as melano-macrophage centers in fish [9], [18]. These features are listed in Tables 2 and 3.

Table 2 Immune features of invertebrates [4], [8], [9]

Features
Phagocytosis
Self- non-self recognition
Specific memory
Haemagglutinins resembling antibodies
Higher forms show cell-mediated immune reactions
Higher forms show the emergence of the circulatory system
IL-1, TNF in coelomate and echinoderms
Tunicates, the emergence of MHC, lymphoid like cells, stem cells
Arthropods, complement
D. melanogaster ,Toll like receptor

Table 3 Immune features of vertebrates [4], [8], [9]

Features
Self- non-self recognition
Phagocytosis
Graft versus host reaction
MHC
Lymphoid system
Antibodies
Cytokines
Thymus in fish
First lymph node and GALT appearance in amphibian

5. Group-Wise Contributions

The following lists some group-wise contributions:

Insects: first Toll-like receptor discovered in *D. melanogaster*.

Tunicates: first appearance of single-structured major histocompatibility complex (MHC).

Jawless fish: first immunoglobulin to appear in this group.

Cartilaginous fish: rise of B and T lymphocyte compartments.

Bony fish: first melanomacrophage centers to appear (this is still a characteristic in this group); zebrafish is

analogous to the mice model in immunotoxicity models.

Amphibia: typical lymph node, thymus, gut-associated lymphoid tissue (GALT), and bone marrow.

Birds: chickens were first to be used in bacterin preparation of Pasteurella.

Birds: bursa of Fabricius first to be discovered in birds, separate T and B cells in the immune system, multi-lobed thymus in the neck region.

Mammals: lapin used as an immune model for microbial and nonmicrobial diseases

Mammals, ovine: B cells activated in their lymph nodes.

Mammals, bovine: from the udder of the cow to human vaccines. Bovine thymus extract used as therapeutic for autoimmune diseases.

Mammals, equines: preparation of therapeutic antitoxins for toxin-induced human diseases.

6. Evolution of Immune System Compartments [4], [8], [19]

6.1. MHC

MHC class I genes are found in all major jawed vertebrates. High levels of polymorphism and genetic diversity are characteristic of most classical MHC genes. Single-structured MHC has been identified in Tunicates. Bony fish possess polymorphic MHC. Amphibians have been described as having clear-cut MHC, while mammals have diverse MHC.

6.2. Complement

Specific glycoprotein molecules that mediate self and non-self recognition have been found in corals and sponges. Molluscs have a sort of alternative complement pathway, and cartilaginous fish have a classical complement pathway. Birds have an evident complement system that differs from that of mammals, and mammals have three well-developed and rather complicated pathways in their complement system.

6.3. Immunoglobulin

Immunoglobulin structure begins to appear as a four-chain unit in jawless fish. Cartilaginous fish have IgM, IgW, and IgNAR immunoglobulin. Bony fish also have IgM and IgD-like immunoglobulin. Amphibians possess IgD, IgY, and IgK immunoglobulin, and reptiles have IgM and IgY. Birds have IgM, IgY, and IgA. Mammals express diverse isotype structures, such as IgM, IgG, IgA, IgD, and IgE.

6.4. Cytokines

Coelenterata and echinoderms have the cytokines IL1 and TNF, bony fish have IL2 and IFNs, and mammals have an array of cytokine types.

6.5. Lymphoid Cells

Lymphoid-like cells have been noted in Tunicates, and lymphoid cells have been identified in jawless fish. Both B and T cells have been identified in cartilaginous fish, and developed lymphoid cells, in a functional sense, have been found in both birds and mammals.

6.6. Mononuclear Cell System

D. melanogaster cells bear TLR surface cell marker. Bony fish in their innate immune cell system have melano-macrophage formation.

6.7. Phagocytosis

Animals belonging to the very beginning creatures of the invertebrates have been shown to perform a phagocytic activity such as that of Protozoa. Phagocytosis as a process, immunology literature considered it as a crude way for differentiation of self-non-self. By discovering Toll-like receptors on the surface of leukocytes, it became evident that it is a semi-specific way to differentiate the self. In all known animal groups, starting from protozoa up to higher groups of mammals, the man performs phagocytosis.

6.8. Lymphoid System

The lymph nodes forming the majority of the lymphoid system compartments starts as lymphoid cell foci in jawless fish. Thymus first appeared in cartilagenous fish. Lymph node structure, gut associate lymphoid tissue first appeared in amphibians with a characteristic open system compared to the closed system found in mammals. Lymph nodes containing germinal centers, bursa of Fabricius containing B cells, and separated B and T cell compartments were first seen in birds. Mammals have well developed systemic and mucosal lymphoid systems, as shown in Table 4.

Table 4 Evolution of lymphoid organs of vertebrates [9]

Cartilaginous fish	Bony Fish	Amphibia	Reptile	Birds	Mammals
GALT Epigonal Thymus spleen	GALT Head kidney Thymus spleen	GALT Thymus Spleen Bone Marrow	GALT Thymus Spleen	GALT, BF** Thymus Spleen Germinal centers	GALT Thymus Spleen Bone Marrow Lymph Node German Center

Note: BF** - Bursa of Fabricius

7. Models

7.1. Fish

Barbus cyprinus proved to be a valid piscan model for infection and immune modulation [13], [14]. Zabrafish were evaluated and proved to be valid as an immunotoxicity model [19]. Some workers have put

forward Zebrafish as an immune model analogous to that of mice [20].

7.2. Amphibia

It has been suggested that the anuran frog Rana sp. was suitable as a teaching immune model and as a probe for the mononuclear cell system [15], [16], [17]. The anuran A glial cells were found resident in the nervous system, having a stage-dependent morpho-type variation [21].

7.3. Avis

Post hatch chickens were used as test models for mapping T cell mitogenicity and found to be valid [22]. Therapeutic sera and vaccines were found to be of T cell mitogenic potential in a post-hatch chicken skin test model [23].

7.4. Lapin

Rabbits were evaluated and proved to be valid immune models for both microbial and non-microbial disease conditions [23], as well as an immune modulation model [24].

7.5. Vertebrate Carbohydrate-Binding Lectin

Representatives of the common living vertebrates have been elected and were assayed for the presence of carbohydrate-binding lectins as a probe for mapping vertebrate immunophylitic tree [25]. A comparative view to the model's validity for immunologic works is shown in Table 5.

Table 5 Immune animal modeling comparative view

Features	Mice	Rabbit*	Chicken	Frog	Fish
Lymphatic System	Closed	Closed	Closed	Open	Open
Bone marrow	+	+	+	+	-
Lymph nodes	+	+	+	+	-
Thymus	+	+	+	+	+
Spleen	+	+	+	+	+
Bursa of Fabricius	-	-	+	-	-
B cell, T cell, Macrophage	+	+	+	+	+
MHC, GVHR	+	+	+	+	+
Humoral & cellular immune responses	+	+	+	+	+
Immunoglobulin	Five isotypes	Five isotypes	Three isotypes	Three isotypes	Two to three isotypes
Immune model	General	General	Fairly common in vet studies	Phagocytosis Macrophage labeling in tissue Lymphography of use at once, need special environment	Immunization Immuno-toxicity Immune modulation limited by the eligibility of aquatic need

* Farm animal use as laboratory immune models limited by large size and economy
** BF bursa of Fabricius

8. Model Election Basis

From an academic point of view, all animal groups are of contributing value to immunology, though vertebrates have the major share. The researcher's preference, orientation, purpose, funding, and the availability of resources should be taken into account. Researchers oriented to biology and the medical field have focused on rabbits as a substitute for mice, while veterinary researchers have mainly focused on farm animals, avian, and piscan models rather than mice. The purpose of this discussion is to shift the researchers to other choices. Frog models can be helpful for teaching basic investigations on innate immune systems [26], [27].

9. Limitations to the Proposed Models

In the practical sense, there are some limitations that should be borne in mind when planning to use these proposed models. Fish have special aquaculture requirements. Not all laboratories that teach or conduct research in immunology could fulfill these. The same can be said of the aquaculture needs during the aquatic part of amphibian lifecycle and the open nature of the lymphoid system. Large vertebrate animals have their own limitations of use, including economy, reproductive nature, handling, and management.

10. Applied Values

The applied values of animal immune models can be summarized as follows:

1. Waiver models

2. Suitability of certain animal models for demonstration of hypersensitivity, such as with white rats

3. Specific immune phenomena need specific immune models like those of melano-macrophage centers in fish.

4. Academic research purposes

11. Conclusion

The immune features of both vertebrates and invertebrates were pinpointed. Nine major contributions were deduced on the basis of the mapped groups. Evolution of the various components of the immune system entities were matched. Representatives of some vertebrate groups were developed and evaluated as a waiver immune model from the traditional mice model [10].

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