Immunology of Animal Reproduction

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by

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2013

NIPA

New India Publishing Agency

Pitam Pura, New Delhi-110 088

Published by

Sumit Pal Jain for

New India Publishing Agency
101, Vikas Surya Plaza, CU Block, L.S.C. Mkt.,
Pitam Pura, New Delhi-110 088, (India)
Phone : 011-27341616, Fax : 011-27341717
Mobile : 09717133558
E-mail : info@nipabooks.com
Web : www.nipabooks.com

ISBN : 978-93-81450-72-7

Laser Type Setting and Printed at : Jai Bharat Printing Press, Delhi.-110032

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No. VC/CRP-Foreword/2012-13 Date 19-10-2012

Foreword

It gives me immense pleasure to write foreword for the book titled "Immunology of Animal Reproduction" authored by Prof. Y. Hari Babu, Director of Instruction (PGS), Karnataka Veterinary, Animal and Fisheries Sciences University, Bidar. Immunology is a fascinating subject and reproductive immunology further enlightens and arouses interest to know the unknown things in animal reproductive immunology. There is lot of importance in human reproductive immunology and sufficient literature is available and also there exists sufficient awareness. But, animal reproduction vis-a-vis with immunology is concerned, it is just gaining momentum and scattered information is available through deep search. By going through the book, I could able to find sufficient information is provided and presented very precisely in this book.

The book will help in designing strategies to combet genital infection and reproductive failures due to immunological etiology. This book will be useful to researchers/gynecologists/veterinarians involved in basic or applied research in the discipline of reproductive immunology and Veterinary Gynecology. The book has been written in a more concise with neat presentation, effective illustrations and figures.

With great pleasure, I recommend this book as a ready material, for students, teachers, scientists and persons associated with reproduction and immunology.

(C. Renukaprasad)
Vice-Chancellor

Preface

Reproductive immunology is a hybrid discipline involving reproduction on one side and immunology on the other side. Efficient reproduction is the greatest biological problem for the livestock production. Immunology is a powerful tool for studying normal fertility and infertility. In the field of reproductive immunology, one major issue is to explore the successful gestation of the histocompatible foetus in the uterus of an immunological competent mother, major immunological causes that interfere with the conception rate in animals. This book, shows how immunology relates to fertility or infertility in the bovines and other livestock.

It is with immense pleasure that this book, "Immunology of Animal Reproduction" is brought out. There has been veritable explosion in human reproductive immunology- a subject which occupies a prime position in human reproduction. The impetus for this book evolved from a recognized need for a comprehensive note to provide the basic understanding of the complex description of the immunology of animal reproduction which is otherwise to scanty available information. A little information is available on different sources especially websites. But comprehensive and up-to-date information needed by the scientists, teachers, students of undergraduate and postgraduate in biology, veterinary and veterinarians in general is found to be the need of the hour. Considering the necessity, I thought of bringing a text with comprehensive information in a simpler way.

The book is intended to the students involved in the study of microbiology, immunology, and animal reproduction as an introduction to more extensive studies. An overview of immunology is provided in the book to refer immediately any basic information needed, for further understanding of the subject dealt in this book. The chapters covered

may provide the structural component for the basic understanding of the reproductive immunology in animals.

It is designed to complement, but not to compete with the few excellent texts already available with regard to human reproduction. The book is profusely illustrated with figures and tables. The concise nature of the book and the simple and clear treatment of the topics, it is hopefully will prove to be useful to all. Criticism and suggestions for improvement of the book will be greatly appreciated.

Author

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Chapter - 1

Introduction

Reproduction is one of the most serious biological problems that markedly influence the efficiency of livestock production. Immunology is a powerful tool for studying both normal fertility and infertility of farm animals. Reproductive immunology is in turn is an important tool for unlocking normal fertility problems and various forms of infertility or reproductive disorders. Although the immune and reproduction systems have been considered independent of each other, the cooperation of both the systems is crucial for initiation and maintenance of mammalian pregnancy. Therefore, reproductive immunology has now become a mature discipline and a major theme during advances in the field of reproductive immunology is to explain the successful gestation of the histcompatable mammalian embryos within the uterus of its immunologically competent mother.

Immune responses play an important role in various reproductive processes, including ovulation, menstruation and parturition. Clearly, during pregnancy, when the mother must accept a semi-allogeneic foetus, immune responses also play a very important role which was first recognized by Medawar in 1953, when the concept of the foetal allograft was presented in order to explain the immunological relationship between mother and foetus. Since then, the immunology of pregnancy has been the leading subject within reproductive immunology research.

Major Histocompatibility Complex (MHC) is a group of extremely polymorphic genes. The gene products of MHC are the main targets for organ rejection and destruction of allotransplants. Transcripts of MHC genes have been detected as early as zygote in mice (Sprinks *et al.*, 1993)

and at blastocyst stage in cattle (Low *et al.*, 1990). Since the embryo expresses MHC molecules of paternal origin, which can be recognized by immune system of the mother, it can be considered as a "natural allograft ". Though the mammalian uterus is capable of destroying the tissue grafts like skin allografts (Hansen *et al.*, 1986), allogeneic conceptus is not being rejected by maternal immune system. Medawar (1953) hypothesized three possibilities for the immunologic tolerance of maternal immune system for allogeneic foetal antigens. His first hypothesis was that the foetus is anatomically separated from the mother; in the second, he proposed that the foetus is antigenically immature and therefore could not stimulate the maternal immune system; in the third hypothesis, he suggested that the maternal immune system is relatively inert during pregnancy. Over the years, each of Medawar's hypotheses has been challenged, and new insights have begun to emerge about the maternal-foetal relationship.

The role of the maternal immune system during pregnancy has focused mainly on the aspect of immune tolerance to the invading trophoblast and, therefore, foetus. While this is a critical aspect of reproductive immunology, It is also important to consider the function of the maternal Immune system in the promotion of implantation and maintenance of pregnancy.

One of the most intriguing puzzles in modern immunology involves the "paradox of pregnancy," in which immunologic tolerance to paternally derived foetal antigens is achieved despite an apparently adequate maternal defense against infection. With 50% of its genetic material derived from its father, the foetus's susceptibility to rejection by the maternal immune system is similar to the susceptibility of a transplanted organ. Evidence indicates that the maternal immune system may tolerate foetal antigens by suppressing cell-mediated immunity while retaining normal humoral immunity. These changes are known to occur locally at the maternal-foetal interface but may also affect systemic immune responses to infection. Although pregnant women are not immunosuppressed in the classic sense, immunologic changes of pregnancy may induce a state of increased susceptibility to certain intracellular pathogens, including viruses, intracellular bacteria, and parasites.

Pregnancy success remains a fascinating phenomenon to immunologists as it defies the immunological rules of rejection. Although it was previously thought that the maternal immune system does not see the foetus, it is now well documented that foetal cells reach the maternal body and encounter host immune ceils. Natural tolerance mechanisms following this interaction remain to be fully elucidated.

Pregnancy has provided a number of challenging problems for immunology, the first of which comes with the recognition that the foetus is antigenically alien to mother conversely the relationship of the mother to the foeus is potentially the same as that in which a graft-versus-host reaction might be expected. To resolve this dilemma, it was originally argued that the foetus occupied an immunologically privileged site. Privileged sites such as the eye are certainly known and privilege presumably refers to anatomical locations free from humoral and cellular attack. On the face of it, both pre and post-implementation states would be unlikely to qualify for this form of immunological exemption. It was this immune exemption of the developing embryo that captured an attention as a model in the search for a more appropriate form of immunosupression than was available some 25 years ago.

The extent to which pregnancies in domestic animals sometimes become compromised by failure of the maternal immune system to be properly regulated is unknown (Hansen, 2000). There is lack of knowledge on reproductive and immune interactions in domestic animals. The complete information on the immuno-physiology of pregnancy in farm animals allows a more focused, rational and potentially more effective approaches to prevent pregnancy losses. The other promising application of reproductive immunology is to enhance the uterine defense mechanisms. It may help to develop the pharmocological methods for treating endometritis and pyometra that are based on enhancement of uterine immune function with least use of antibiotics.

The role of the maternal immune system during pregnancy has focused mainly on the aspect of immune tolerance to the invading trophoblast and, therefore, foetus. While this is a critical aspect of reproductive immunology, it is also important to consider the function of the maternal immune system in the promotion of implantation And maintenance of pregnancy. This review will focus on Decidual macrophages and their role on apoptosis and cell clearance during pregnancy.

A fundamental feature of the immune system is to protect the host from pathogens. This function depends upon the innate immune system's capacity to coordinate cell migration for surveillance and to recognize and respond to invading microorganisms. During normal pregnancy, the human decidua contains a high number of immune cells, such as macrophages, natural killer (NK) cells and regulatory T cells (Treg). Seventy percent of decidual leukocytes are NK cells, 20–25% are macrophages and 1.7% are dendritic cells. From the adaptive immune

system, B cells are absent, but T lymphocytes constitute about 3-10% of the decidual immune cells. During the first trimester, NK cells, dendritic cells and macrophages infiltrate the decidua and accumulate around the invading trophoblast cells. Deletion of either macrophages, NK cells or dendritic cells (DC) has deleterious effects. Elegant studies have shown that in the absence of NK cells, trophoblast cells are not able to reach the endometrial vascularity leading to termination of the pregnancy. These studies suggest that uNK cells are critical for trophoblast invasion in the uterus. Similarly, depletion of DCs prevented blastocyst implantation and decidual formation. Indeed, this study suggests that uDC are necessary for decidual formation and may affect the angiogenic response by inhibiting blood vessel maturation.

Study on immunology of reproduction helps in understanding

a) Immune deficiency responsible for the interruption of pregnancy can help to treat to enable the method to repair the foetus.

b) Lead to the production of contraceptive vaccines which might prevent pregnancy.

c) Lead to cure for certain autoimmune diseases and cancer.

d) Immunological approaches for augmentation of fertility in animals.

e) Prevent abortions, rejecting of Grafts.

The immune regulation of pregnancy is still conundrum.The local immune system in the endometrium and its changes during implantattion is thought to be the key feature of nature allowing acceptance of an allogeneic graft in the form of an embryo.Beyond the trilling field of reproductive immunology, implantation is a naturally occuring complex model system to study a broad spectrum of cellular intractions resulting in immunological phenomena like peripheral tolerence,regulation of cytokine production,directed homing of immune cells via interaction with adhesion molecules and immune control of invasive cell growth.

Immune system plays a key role in normal reproduction of both sexes. Further, the same immune system can play a devastating role in infertility. Reproductive immunology is an exciting, ever-growing area of inquiry having applications both in basic reproductive biology and in practical areas of fertility management.

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Chapter - 2

Overview of Immune Response

1. TYPES AND GRADES OF IMMUNITY

The immune response, which has inherited the character of memory, as evinced by rapidity and specificity of the responses on the second exposure to antigen, was cleared the minds of scientists especially bacteriologists who could find certain cells especially lymphocytes to play a major role in immune response.

The fact that the blood also contains soluble protective substances both heat stable which were later known as antibody and heat labile, later called as the complement system. These two were regarded as totally separate phenomenon in the beginning years. Eventually the distinctions between specific and non-specific responses were understood.

There are two types of immunity

i) Non-specific (Innate, natural or native) immunity

ii) Specific (Acquired) immunity.

i) Non-specific (Innate, natural or native) immunity : As its name implies, this type of immune response has no specificity and shows no increase on subsequent exposure (i.e. no memory develops) as it does in specific immunity. This is the first line of defense mechanism against any microorganisms or their produces or effects, various non-specific immune barriers include like physical barrier (skin, mucous membranes, epithelia), biological barrier (Inflammation, phagocytosis), chemical barrier (enzymatic action, interferons, complement etc.) and general barrier (fever).

ii) Specific (Acquired immunity) : Once the non-specific immunity is breached, then specific immunity is activated to protect the host. Several immunological mechanisms are involved. These aspects happen through production of specialized proteins called antibodies or through the sensitized lymphocytes.

Naturally acquired active immunity : When an individual contacts the antigen in daily routine activities or gets the infection, then the antibodies or the sensitized lymphocytes are produced indicate the naturally acquired active immunity.

Naturally acquired passive immunity : When an animal is pregnant, the antibodies that the dam/mother has are transferred to the foetus through the placenta and as such the young ones or calves will be immune for certain period after birth because of these maternal antibodies. Certain other antibodies can pass through the mother to the young ones through the first secretions, also called as colostrum. Hence feeding of the colostrum (first milk) to the young ones is a must to ascertain certain amount of immunity to the young ones. This type of immunity lasts for the short period i.e. from few weeks to few months.

Artificially Acquired Active Immunity : When an animal is vaccinated against any vaccine or any inactivated bacterial toxins, immunity is developed.

Artificially Acquired Passive Immunity : When the antibodies are produced in any animal or *in vitro*, then this type of immunity is developed. Antisera or antitoxins developed in other animals, when given to the animal in acute stage, and then the immunity is developed, even though for a short period.

2. DEVELOPMENT OF IMMUNE SYSTEM : HUMORAL AND CELL MEDIATED RESPONSES

The field of immunology primarily includes the study of the natural resistance to pathogen and of the immune system. The immune system can recognise virutally any foreign material which enters the host organism; it will produce an appropriate response against the foreign substance. From the evolutionary point of view, the immune system is very old. Its bane property - the recognition of "non-self" and "self" - can be found in the simplest multicellular organisms.

The immune system is a diffuse organ which weighs about 1000 g in adults. It is composed of approximately 10^{12} lymphocytes and accessory cells, which include macrophages, polymorphonuclear