ORIGIN OF ANTI-TUMOR IMMUNITY FAILURE IN MAMMALS

Kluwer Academic / Plenum Publishers
New York, Boston, Dordrecht, London, Moscow

ORIGIN OF ANTI-TUMOR IMMUNITY

FAILURE IN MAMMALS

Ivan Bubanovic
Medica Centre
Nis, Serbia and Montenegro

Translated by
Marija Rusimovic

ISBN 0-306-48629-6

233 Spring Street, New York, New York 10013

http//www.wkap.nl/

10 9 8 7 6 5 4 3 2 1

A C.I.P. record for this book is available from the Library of Congress.

Printed in the United States of America

"… sciences long ago recognized that observations are not superior to hypotheses in generating scientific progress nor are hypotheses superior to observations. Both are necessary."

David F. Horrobin
(1939-2003)

CONTENTS

INTRODUCTION xiii

Chapter 1 1
The Vertebrate Immune System

1.1 THE VERTEBRATE IMMUNE SYSTEM EVOLUTION 1
1.1.1 Macrophages 3
1.1.2 Lymphocytes and Lymphoid Organs 4
1.1.2.1 Origin of TCR(s) 9
1.1.3 Cytokines throughout Vertebrate Evolution 12
1.2 MHC MOLECULES – NATURE, FUNCTION AND EVOLUTION 17
1.2.1 MHC System in Mammals 18
1.2.1.1 The Structure 18
1.2.1.2 The Function 19
1.2.1.3 Non-Classical MHC Molecules (class Ib) 21
1.2.2 The MHC System in Non-mammals 22
1.2.3 Ontogeny of MHC Molecules Expression 24
1.2.4 The Evolution of MHC Molecules 25
1.2.5 Mechanisms of MHC Molecules Variability 28
1.2.5.1 Viruses like Inductors of MHC Variability 30
1.2.5.2 The Heterozygote Advantage Hypothesis 31
1.2.5.3 The Moving Target Hypothesis 34
1.2.5.4 Shifting MHC Presentation Holes 35
1.2.5.5 Shifting T-Cell Recognition Holes 35
1.2.6 Variability of TAP, LMP and Other Immunological Genes 36
1.2.7 Regulation of MHC Genes Transcription 37

1.2.7.1 Cytokines which modulate expression of MHC class I molecules 39
1.2.7.2 Cytokines which modulate expression of MHC class II molecules 40
1.3 AUTO-IMMUNITY - A BY PRODUCT OF ADOPTIVE IMMUNITY 41
1.3.1 Sex Hormones and Auto-immunity 44
1.3.2 Evolutionary Pressure of Auto-immunity 46
REFERENCES 48

Chapter 2 57
Alloimmunity and Pregnancy

2.1 ALLOIMMUNITY 57
2.1.1 Allorecognition 58
2.1.1.1 Dichotomy of Direct and Indirect Allorecognition 59
2.1.1.2 Secondary (auto-immune-like) Alloimmune Response 61
2.1.2 Xenoreactivity 61
2.1.3 Alloimmunity in Vertebrates 63
2.2 ALLOIMMUNITY AND VIVIPARITY 66
2.2.1 Evolution of Viviparity 69
2.2.1.1 Viviparity in Cartilagofish 69
2.2.1.2 Viviparity in Reptiles 70
2.2.1.3 Viviparity in Mammals 73
2.2.1.4 Expression of MHC molecules on Different Types of Placenta in Mammals 75
2.2.2 Evolutionary Pressure of Alloimmunity 78
REFERENCES 81

Chapter 3 85
Anti-tumor Immunity Failure in Mammals

3.1 MECHANISMS OF ANTI-TUMOR IMMUNITY 85
3.1.1 Antigen Processing/Presenting Machinery 86
3.1.2 Antigen Recognition by TCR 90
3.1.3 DSs Maturation/Activation 91
3.1.3.1 Heat Shock Proteins (HSP) 92
3.1.3.2 Role and Expression of Co-Stimulatory Molecules 94
3.1.3.3 DCs and Th1/Th2 Dichotomy 96
3.1.4 Th1 Type and Th2 Type of Anti-tumor Immune Response 98
3.2 ARE TUMORS IMMUNOGENIC? 100
3.2.1 Tumor-Associated/Specific Antigens 101

3.2.1.1 Carcinoembryonic Antigen (CEA) and Alpha-fetoprotein (AFP) 103
3.2.1.2 Differentiation Antigens (DA) 103
3.2.1.3 Viral Antigens (VA) 104
3.2.1.4 Oncogenic Fusion Proteins (OFP) 104
3.3 BASIC MECHANISMS OF ANTI-TUMOR IMMUNITY FAILURE IN MAMMALS 105
3.3.1 Altered Expression of MHC Molecules and Tumor Antigens by Tumor Cells 105
3.3.1.1 Expression of HLA-G on Tumor Cells as a Mechanism of Immunosurveillance 107
3.3.2 Altered Expression of Co-stimulatory and Adhesion Molecules by Tumor Cells and APCs 108
3.3.3 Downregulation of Anti-tumor Immune Response by Cytokines 110
3.3.4 Th1/Th2 Immunity and Tumor Escape 112
3.3.5 Downregulation of Immune Response by Molecules Other than Cytokines 114
3.3.6 Anti-tumor Immunity Failure by Apoptosis and/or Anergy Induction 115
3.3.6.1 Extrathymic Lymphocyte Maturation and Selection 117
3.3.6.2 Failure of Blood-thymus Barrier 120
3.3.7 Immunomodulatory Role of Prostaglandine 123
REFERENCES 126

Chapter 4 135
Immunosurveillance Mechanisms of the Fetoplacental Unit

4.1 "SEMINAL PRIMING" AND SUCCESSFUL PREGNANCY 135
4.1.1 Role of TGF-β in "Seminal Priming" 138
4.2. DECIDUA AND TROPHOBLAST 138
4.2.1 Decidual Immunocompetent Cells 139
4.2.1.1 Decidual NK Cells 140
4.2.1.2 Class Ib MHC Molecules and Activity of Decidual Immune Cells 142
4.2.1.3 Decidual T Cells 144
4.2.1.4 Decidual Macrophages 148
4.2.1.5 Cytokine Network of the Decidua 150
4.2.2 The Trophoblast 153
4.2.2.1 Trophoblast Expression of MHC Molecules 154
4.2.3 Pregnancy and Cytokines 155
4.2.3.1 IL-10 156

4.2.3.2 TGF-β 158
4.2.3.3 IL-4 159
4.2.3.4 IL-6 160
4.2.3.5 IL-2 161
4.2.3.6 IL-12 162
4.2.3.7 IL-15 163
4.2.3.8 IL-18 163
4.2.3.9 IFN-γ 164
4.2.3.10 TNF-α and β 165
4.2.4 Activity of Trophoblast TAP Machinery 167
4.3. PROSTAGLANDINE 168
4.3.1 Immunomodulatory Role of Prostaglandine 169
4.4. SEX HORMONES AND IMMUNITY IN PREGNANCY 170
4.4.1 Progesterone 170
4.4.1.1 Progesterone Induced Blocking Factor (PIBF) 173
4.4.2 Estrogens 174
4.5. IMMUNOMODULATORY PROTEINS 175
4.6 ANTI-TROPHOBLAST IMMUNITY FAILURE BY APOPTOSIS AND/OR ANERGY INDUCTION 176
4.6.1 Extrathymic Lymphocyte Maturation (eTLM) and Selection 179
4.6.2 Failure of Blood-thymus Barrier 180
4.7 EVOLUTIONARY SOLUTIONS OF VIVIPARITY IN MAMMALS 181
REFERENCES 184

Chapter 5 195
Tumors in Mammals and Non-mammalian Classes of Vertebrates

5.1. COMPARATIVE ONCOLOGY 195
5.1.1 Genetic Properties of Tumors in Vertebrates 199
5.1.1.1 Oncogenes 201
5.1.2 Phenomenon of Cell Socialization in Embryogenesis vs. Oncogenesis 202
5.1.3 Selection of Tumor Cells as Micro-evolutionary Process of Tumor Development 204
5.1.4 Factors Influencing Oncogenesis in Vertebrates 207
5.1.4.1 Age 207
5.1.4.2 Temperature 208
5.1.4.3 Gender 208
5.1.4.4 Chemical Carcinogens 209
5.1.4.5 Radiation 210
5.1.4.6 Viruses 210

5.2. TUMORS IN NON-MAMMALIAN CLASSES OF VERTEBRATES 211
5.2.1 Tumors in Cartilagofish 212
5.2.2 Tumors in Bonefish 213
5.2.3 Tumors in Amphibians 216
5.2.4 Tumors in Reptiles 218
5.2.5 Tumors in Birds 221
5.2.6 Some Important Conclusions 223
5.3. ANTI-TUMOR IMMUNITY AS AUTO-IMMUNITY 225
5.4. PREGNANCY AS A "SUCCESSFUL" TUMOR 228
5.4.1 Immunological Properties in Successful vs. Unsuccessful Pregnancy 230
5.4.2 Immunological Properties in Pregnancy and Tumor Microenvironment 231
5.5. EVOLUTION OF THE HYPOTHESIS 232
5.5.1 Origin of Anti-tumor Immunity Failure in Vertebrates 235
REFERENCES 241

INDEX 249

Introduction

The history of science has shown the majority of hypotheses to be wrong. Sharp scientific criticism and strictly controlled experimental studies reject most of the hypotheses, leaving behind only a small number of assumptions and ideas. Nevertheless, each logical assumption should have its rightful place on the scientific "battlefield" supposed to assess its validity and determine its final fate. Even when a hypothesis is wrong, it still finds its place in the entire efforts of the humankind towards attaining the scientific truth. Namely, the wrong hypotheses serve largely to illuminate the way towards the correct ones or, at least, to show which way not to follow. Correct or not, ideas and hypotheses are necessary for the progress of science. They epitomize the efforts of human thought to elucidate nature without experimental verification and in the circumstances of scant data availability. Finally, hypotheses and ideas represent a symbiotic creation of our knowledge and imagination, the two most impressive appearances in the evolution of humans.

It is thoroughly unknown whether Charles Darwin was indeed familiar with the phenomenon of similarity between microcosm and macrocosm claimed by many philosophers and physicists to be convincing and fascinating. Whatever his knowledge might have been in this regard, the possibility that Darwin's approach to defining the phenomena in biology is applicable to both planetary and cellular levels is fairly real. Namely, many physiological and pathological phenomena like those found in immunology and oncology, such as various forms of immune tolerance and immunomodulation, clonal selection of immune and tumor cells, modification of subset relationships between immune cells in tissues and organs, rest on the basic postulates of Darwinism, i.e. randomness of change, negative and positive selection, set-up of ecological niches, and the like.

The body of any animal can be viewed as a society or “ecosystem” whose individual members are cells, reproducing by cell division and organized into collaborative assemblies or tissues. In this “ecosystem”, the cells are born, live and die under various forms of selection pressure like territorial limitation, population size, source of nutrients provided, infectious agents, etc. The body is a highly organized society of cells whose main task is the maintenance of homeostasis of the whole organism. The failure of control mechanisms which make the cell the unit of society, marking the beginning of its “asocial” behaviour, is most frequently a malignant alteration. This process is not abrupt, nor is it based on the single event. It is, rather, a long-term process characterized mainly by mutation, competition and natural selection operating within the population of cells. The basic mechanisms controlling the cell sociability represent the first defence line against the altered cells, while the second line of defence is supposed to be made up of the immune system cells. Speaking in Darwinian terms, within the “ecosystem” of organism, cells of the immune system operate as “predators” of the altered and mutated cells or cells infected by the intracellular parasites.

The biological phenomena whose mechanisms are, at present, explored and largely understood, certainly had their own evolution. Searching for the origin and details of the evolution of “advanced solutions” as well as selection pressures that might justify their emergence and existence, we often fail to see that many such phenomena are, in fact, co-evolutionary by-products of “evolutionary innovations”. In other words, the evolutionary emergence of “advanced solutions” is sometimes, if not always, accompanied by certain by-products and by the co-evolution of compensatory mechanisms acting as a counterbalance to these.

An example of the evolution of “advanced solutions” is the evolution of adoptive immunity, and co-evolution of auto-immunity and alloimmunity. Alongside with the diversification of the mechanisms of adoptive immunity, auto-immunity and alloimmunity gain attribute of the evolutionary by-products and become sources of selection pressure. To that effect, alloimmunity could be a source of very strong selection pressure in mammals, simply because it is directly connected with the reproductive efficacy. At the same time, new forms of selection pressure that are connected with adoptive immunity gave rise to new mechanisms controlling killer machinery of the immune system. Finally, the last in a line of by-products in the processes of evolutionary “modelling” and “re-modelling” of vertebrate immune system can be called the failure of anti-tumor immunity.

As my intention has been to include only those critical points related to the origin as well as parallelism between immunoregulatory/suppressive mechanisms in pregnancy and tumor sufferers, I set out to write this

publication presuming that the majority of readers are already familiar with the fundamentals of medicine, biology, immunology, immunopathology, oncology, mammalian reproduction and vertebrate evolution. To that effect, this publication is free of descriptions otherwise found in most textbooks. Naturally, the book is intended for all readers showing interest. If, upon reading this subject matter, the interest of readers grows into practical work in the fields of reproductive or tumor immunology, or something even greater, the author's satisfaction would be complete, and the objective of the entire publication fulfilled.

Finally, I recommend the articles cited throughout the text to all those readers who would like to expand their knowledge regarding the evolution of the immune system, alloreactivity, immune recognition, various forms of immune tolerance, reproductive and tumor immunology, as well as comparative immunology and oncology.

Author, 2004

ibubanovic@yahoo.com