MECHANISM OF TUMOUR RESISTANCE IN SALMONELLA-IMMUNIZED MICE

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TABLE OF CONTENTS

ABSTRACT xiii
SIGNED STATEMENT xv
ACKNOWLEDGEMENTS xvi
ABBREVIATIONS USED IN THIS THESIS xvii

CHAPTER ONE
TUMOUR RESISTANCE INDUCED BY INFECTION WITH INTRACELLULAR BACTERIAL PARASITES

1.1 The role of immune responses in controlling the growth of tumours 1
1.2 The induction of non-specific tumour resistance by infection with microbial pathogens 4
1.3 Resistance to intracellular bacterial parasites 5
1.3.1 The carrier state 5
1.3.2 Requirement for activated macrophages to control IBP infections 6
1.3.3 Sensitized thymus-derived lymphocytes induced during IBP infections mediate macrophage activation 9
1.3.4 The life span and migratory characteristics of the lymphocytes generated during IBP infections 10
1.3.5 Newly formed protective lymphoblasts accumulate at sites of inflammation 12
1.4 The characteristics of tumour resistance induced by IBP 14
1.5 Biochemical markers for activated macrophages 17
1.6 The mechanism of macrophage activation in vitro 19
1.6.1 Role of soluble factors (MAF) 19
1.6.2 Macrophages must internalize MAF to be activated 20
1.6.3 Different macrophage subpopulations vary in sensitivity to MAF 21
1.6.4 The role of lipopolysaccharides in macrophage activation by MAF 22
### Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6.5</td>
<td>23</td>
</tr>
<tr>
<td>1.6.6</td>
<td>25</td>
</tr>
<tr>
<td>1.6.7</td>
<td>26</td>
</tr>
<tr>
<td>1.7</td>
<td>28</td>
</tr>
<tr>
<td>(a)</td>
<td>29</td>
</tr>
<tr>
<td>(b)</td>
<td>29</td>
</tr>
<tr>
<td>(c)</td>
<td>29</td>
</tr>
<tr>
<td>(d)</td>
<td>29</td>
</tr>
<tr>
<td>1.8</td>
<td>30</td>
</tr>
<tr>
<td>1.9</td>
<td>31</td>
</tr>
<tr>
<td>1.9.1</td>
<td>31</td>
</tr>
<tr>
<td>1.9.2</td>
<td>33</td>
</tr>
<tr>
<td>1.10</td>
<td>34</td>
</tr>
<tr>
<td>1.10.1</td>
<td>34</td>
</tr>
<tr>
<td>1.10.2</td>
<td>35</td>
</tr>
<tr>
<td>1.10.3</td>
<td>37</td>
</tr>
<tr>
<td>1.11</td>
<td>38</td>
</tr>
<tr>
<td>1.11.1</td>
<td>38</td>
</tr>
<tr>
<td>1.11.2</td>
<td>39</td>
</tr>
<tr>
<td>1.11.3</td>
<td>41</td>
</tr>
<tr>
<td>1.11.4</td>
<td>43</td>
</tr>
<tr>
<td>1.11.5</td>
<td>43</td>
</tr>
<tr>
<td>1.12</td>
<td>47</td>
</tr>
<tr>
<td>1.12.1</td>
<td>47</td>
</tr>
<tr>
<td>1.12.2</td>
<td>49</td>
</tr>
<tr>
<td>1.12.3</td>
<td>50</td>
</tr>
<tr>
<td>1.13</td>
<td>53</td>
</tr>
<tr>
<td>1.14</td>
<td>54</td>
</tr>
</tbody>
</table>
CHAPTER TWO
MATERIALS AND METHODS

2.1 Mice
2.2 Bacteria
2.3 Immunization of mice with L1RX
2.4 Preparation of L1RX antigen extract
2.5 Lipopolysaccharide
2.6 Anti-Thy 1.2 antiserum
2.7 Media for preparation and culture of cell suspensions
2.8.1 Hanks’ Balanced Salt Solution
2.8.2 Tissue culture media
2.9 Composition of gaseous phases for buffering in vitro cell cultures
2.10 Trypan blue for injection into mice
2.11 Cell counting
2.12 Differential Counting
2.13 Tumour Cell Lines
2.14 Immunization of mice with allogeneic tumour cells
2.15 Peritoneal Cells
2.16 Preparation of spleen and lymph node cell suspensions
2.17 Splenic lymphocytes
2.18 Blast cells
2.18.1 For use in in vitro cytotoxicity assays, cold target inhibition assays and cell binding assays
2.18.2 For use in IL2 assay
2.19 Adherence of PC to Plastic
2.20 Preparation of PC which do not adhere to nylon wool
2.21 Preparation of PC which do not adhere to glass wool
2.22 Fractionation of PC on Percoll density gradients
2.22.1 Discontinuous density gradients
2.22.2 Continuous density gradients
2.23 Removing polymorphonuclear cells from cell suspensions
2.24 Radiolabelling of Cells
2.24.1 Labelling cells with $^{125}$I
   (i) In vivo
   (ii) In vitro
2.24.2 Labelling cells with $^{51}$Cr
2.24.3 Labelling cells with $^{3}$H-ThR
2.25 The measurement of anti-tumour activity In vivo
2.25.1 Clearance of $^{125}$I-EAT cells from the peritoneal cavity
2.25.2 Whole body retention of $^{125}$I
2.26 In vitro cytotoxicity assay
2.27 Cold Target Inhibition of In vitro cytotoxicity
2.29 Killing of Tumour Cells Across Cell impermeable Membranes
2.29 Cell-binding assay
2.30 Sugars used in an attempt to inhibit P3 cytotoxicity
2.31 Testing lymphoid cells for the ability to release lymphokines
2.31.1 Induction of lymphokine release
2.31.2 Assays for lymphokines in culture supernatants
2.31.3 Interleukin 2 assays
2.31.4 Macrophage Activation Factor
2.32 Preparation of lymphokine standards
2.32.1 Macrophage Activation Factor
2.32.2 Preparation of Interleukin 2 standard

CHAPTER THREE
CHARACTERIZATION OF THE EFFECTOR CELLS RESPONSIBLE FOR TUMOUR RESISTANCE IN SALMONELLA ENTERIDITIS ILRX IMMUNIZED MICE

3.1 Introduction
3.2. The effect of trypan blue on the clearance of $^{125}$I-EAT from mice immunized with S. enteritidis llix 83

3.2.1 Short-term ip immunized mice 84

3.2.2 Long-term iv immunized mice recalled with llix antigen ip 85

3.2.3 Long-term ip immunized mice. 85

3.3. The cytolytic activity of PC from trypan blue-treated llix-immunized mice 85

3.3.1 Short-term llix immunized mice 86

3.3.2 Recalled, long-term iv-immunized mice 87

3.4 The in vitro activity of cytotoxic lymphocytes from allo-immunize mice injected with trypan blue 87

3.5 The cytotoxic activity of PC from short-term immunized mice after pretreatment in vitro with trypan blue 88

3.6 The in vitro cytotoxic activity of PC in the presence of trypan blue 89

3.7 Characterization of cytotoxic peritoneal cells 90

3.7.1 Adherence to Plastic 91

3.7.2 Adherence to nylon wool 92

3.8 Bouyant density fractionation of PC on discontinuous gradients 93

3.8.1 PC from recalled, iv immunized mice 94

3.8.2 PC from short-term ip immunized mice 94

3.9 Bouyant density fractionation of PC using continous gradients 95

3.10 Summary and conclusions 96

CHAPTER FOUR
THE INTERACTION OF ACTIVATED MACROPHAGES WITH NORMAL AND NEOPLASTIC CELLS

4.1 Introduction. 57

4.2 The effect of varying the effector to target cells ratio on in vitro cytotoxicity 101
4.3 The role of soluble factors in the lysis of tumour cells by PC from lirX-immunized mice

4.3.1 The effect of low cell density on in vitro cytolysis

4.3.2 Separation of tumour cells and PC by cell impenetrable membranes

4.4 The effect of antibody on the cytolysis of $^{51}$Cr-P815 cells by cytotoxic PC

4.5 Con A activated splenic blast cells as targets for tumoricidal PC

4.5.1 Summary of experiments using $^{51}$Cr-blast cells as target cells

4.5.2 Criticism of previous studies using Con A blast cells as target cells

4.5.3 $^{125}$I-blast cells are not lysed by PC from lirX-immunized mice

4.6 The inhibition of cytolysis by unlabelled tumour cells

4.7 Con A activated-blast cells as cold target inhibitors of cytolysis

4.7.1 Con A blast cells do not inhibit the lysis of $^{51}$Cr-P815 cells

4.7.2 The lysis of $^{51}$Cr-P815 cells by Con A blast cells is due to cytotoxic cells

4.7.3 Con A blast cells do not inhibit lysis of $^{51}$Cr-EAT cells

4.8 The ability of activated macrophages from lirX-immunized mice to bind tumour cells

4.8.1 The effect of varying the concentration of P815 cells on binding to activated macrophage monolayers

4.8.2 The effect of varying the number of adherent cells on the binding of P815 cells

4.8.3 The effect of antibody on the binding of P815 cells to activated macrophages
4.8.4 Binding of P815 cells to normal macrophages and to macrophages obtained at different times after immunization

4.9 The lysis of tumour cells bound to adherent cytotoxic PC

4.9.1 Experimental design

4.9.2 The effect of varying the number of $^{51}$Cr-P815 cells

4.9.3 The effect of varying the number of macrophages

4.10 The binding of normal cells to activated macrophage monolayers

4.11 The binding of Con $\lambda$-activated blast cells to normal macrophages

4.12 Attempts to reconcile the differences between the results obtained from binding and cold target inhibition experiments

4.12.1 The effect of unlabelled P815 cells on the viability of $^{51}$Cr-blast cells co-cultured with PC from LiX-immunized mice

4.12.2 Con A blast cells do not induce the release of cytotoxic factors from PC

4.12.3 The binding of Con A blast cells to macrophage monolayers is short-lived

4.13 The effect of simple sugars on the cytolysis of P815 cells by PC

4.14 Summary and conclusions

CHAPTER FIVE
THE LIFE SPAN OF LYMPHOCYTES MEDIATING THE RECALL OF TUMOUR RESISTANCE IN LONG-TERM LiX-IMMUNIZED MICE

5.1 Introduction

5.2 Dependence of in vivo cytotoxicity on the number of spleen cells transferred

5.3 Systemic transfer of the ability to recall tumour resistance
5.4 The functional life span of 11RX sensitized lymphocytes after systemic transfer
5.5 The functional life span of sensitized lymphocytes after local transfer
5.5.1 Experiment 1: Decay of spleen cell activity after ip transfer
5.5.2 Experiment 2: Direct comparison of the decay of lymphocyte function after iv and ip transfer
5.5.3 Experiment 3: Comparison of the decay of spleen cell activity in recipients and donors
5.6 Summary and conclusions

CHAPTER SIX
Lymphokine Release during 11RX Infection

6.1 Introduction
6.2 The release of Interleukin 2 by 11RX-sensitized lymphoid cells
6.3 Requirement for T cells in the release of IL2
6.4 The anatomical distribution of lymphocytes releasing IL2 at various times after 11RX immunization
6.5 Is the inactivity of LN and spleen cells due to the lack of antigen presenting cells?
6.5.1 Ability of normal PC to present antigen
6.5.2 Effect of adding normal PC on the ability of lymphoid cell suspensions to release IL2
   (i) Lymph node cells
   (ii) Spleen cell suspensions
6.6 Is the lack of IL2 secretion due to suppression
6.7 Preliminary attempts to detect MAF release
6.7.1 Activation of PC from long-term 11RX-immunized mice
6.7.2 Activation of macrophages by conditioned culture media
6.8 Development of an assay for MAF in culture supernatants
6.9 T cells are required for the release of MAF

6.10 The cytostatic activity of lymphokine-treated macrophages

6.11 Variability of the MAF assay

6.11.1 Lack of reproducibility of MAF assays using SHP

6.12 Effect of varying time of incubation with pp1 PC with conditioned culture supernatants

6.13 Effect of adding LPS and prolonging incubation time prior to harvesting

6.14 Cytotoxic activity of lymphokine-treated macrophages is consistently detected using long-term assays

6.15 Some cell populations appear to have cytotoxic activity when long-term assays are sampled with cell harvester

Experiment 1

Experiment 2

Experiments 3-5

6.16 The effect of delaying the addition of target cells on the cytotoxic activity of lymphokine-activated macrophages

6.17 The relationship between cytostasis and cytotoxicity

6.18 The relationship between IL2 and MAF release by lymphoid cells at different times after immunization with LILX

6.19 Summary and conclusions

CHAPTER SEVEN

THE MECHANISM OF TUMOUR RESISTANCE IN LILX IMMUNIZED MICE

7.1 Introduction

7.2 The nature of the effector cells responsible for tumour resistance in LILX immunized mice.

7.2.1 The effect of trypan blue on cytotoxicity

7.2.2 Fractionation of cytotoxic PC on Percoll density gradients
7.2.3 Fractionation of cytotoxic PC into adherent and non-adherent subpopulations

7.2.4 The relative contribution of activated macrophages and NK cells to tumour resistance induced by L1210 infections

7.3 The requirement for cell contact in the lysis of tumour cells by PC

7.4 Effect of antibody on the cytolytic activity of PC

7.5 Relationship of the ability of activated macrophages to bind and lyse tumour cells

7.6 The susceptibility of Con A blast cells to lysis by activated macrophages

7.7 The recognition of tumour cells by activated macrophages

7.7.1 The results of cold target inhibition studies

(a) Activated macrophages recognize structures which are present on all types of tumour cells

(b) Activated macrophages do not interact with dividing T cells in the same way as they do with tumour cells

(c) Possible reasons why the findings of cold target inhibition experiments differ from those of Hamilton and Fishman

1. Reutilization of label

2. The use of "normal" cell lines

3. Possible differences in the way various tumour cells interact with macrophages

4. Competition may not involve tumour-binding receptors on macrophages

7.7.2 The results of cell binding experiments

(a) Activated macrophages bind tumour cells and dividing and non-dividing lymphocytes with similar efficiency

(b) The binding of Con A blast cells to activated macrophages is transient
(c) Does binding of tumour cells and blast cells to activated macrophages require the same receptor? 198

7.1.3 The role of carbohydrates in the recognition of tumour cells by activated macrophages 199

7.8 Characterization of lymphocytes induced by immunization with ILR X 200

7.9 The functional life-span of lymphocytes mediating the recall of tumour resistance in ILR X immunized mice. 201

7.9.1 Short-lived lymphocytes are detected after iv transfer of spleen cells 202

7.9.2 Long-lived lymphocytes are detected after ip transfer of spleen cells 203

7.9.3 Relative contribution of long-lived and short-lived lymphocytes in recall of tumour resistance 204

7.9.4 The possible role of long-lived non-recirculating peritoneal lymphocytes in recalling tumour resistance 205

7.10 The release of lymphokines by lymphoid cells from ILR X-immunized mice 207

7.10.1 Differences between macrophage activation in vitro by lymphokines and activation in vivo by ILR X infection 208

7.10.2 Spleen cells and LNC release little or no IL2 210

7.10.3 The possible action of suppressor cells in controlling the in vitro release of IL2 and MAF by PC early after ILR X infection 211

7.10.4 The relationship between the lymphocytes which release MAF in vitro and those which confer protection in vivo 213

7.11 Summary, conclusions and future directions 214

PUBLICATIONS 217

BIBLIOGRAPHY 218
The experiments reported in this thesis investigated the tumour resistance induced by immunization of (BALB/c × C3H)F₁ mice with a live vaccine of the intracellular bacterial parasite, Salmonella enteritidis 11RX (11RX). The aims were to define the cytotoxic effector cells, the mechanism by which they recognize tumour cells and to characterize the 11RX-sensitized T cells induced by 11RX infections which are involved in the generation of tumour resistance.

This study confirmed previous suggestions that activated macrophages are the principal cytotoxic cells present in the peritoneal cavity of 11RX-immunized mice. It was found that the lysis of tumour cells in vitro is dependent on contact between effector and target cells and that activated macrophages bind tumour cells more efficiently than do macrophages from normal mice. Unlabelled tumour cells could competitively and non-specifically inhibit the lysis of radioactively labelled tumour cells by peritoneal cells (PC) from 11RX-immunized mice.

Concanavalin A-activated splenic blast (blast) cells were compared to tumour cells for their ability to interact with activated macrophages. Blast cells were not lysed by PC from 11RX-immunized mice and did not inhibit the lysis of tumour cells in vitro. However, blast cells did bind to monolayers of activated macrophages and to a lesser degree to normal macrophages. The extent of blast cell binding to the two macrophage types was equal to that observed with tumour cells, unlike the adherence of tumour cells to activated macrophages, the bond between blast cells and activated macrophages was labile and dissociated with incubation in vitro suggesting that the two types of interactions were qualitatively different.
Spleen cells from LIRX-immunized mice could transfer to naïve recipients the ability to recall resistance to intraperitoneal (ip) tumour challenge upon ip injection of LIRX antigen extract. When the ip route was used to transfer spleen cells, high levels of ip tumour resistance could be recalled three weeks later.

Tumoricidal activity could be induced in inflammatory macrophages by culturing them in vitro with lymphoid cells from LIRX-immunized mice and LIRX antigen. The lymphokines, Interleukin 2 (IL2) and Macrophage Activation Factor (MAF) are released by LIRX-sensitized lymphoid cells when they are stimulated in vitro with LIRX antigen. Lymphoid cell populations differ in their ability to release these lymphokines and, furthermore, the ability to release MAF did not correlate directly with the release of IL2. Treatment of lymphoid cells with anti-3x 1.2 antibody and complement abolished their ability to release the two lymphokines.

From these observations the following conclusions were drawn. The tumour resistance induced in mice by LIRX immunization is effected mainly by activated macrophages and is mediated by LIRX-sensitized T cells which are long-lived. These sensitized T cells can activate tumoricidal macrophages by releasing MAF when stimulated with bacterial antigens. The sensitized T cells which release MAF may be different from those which release IL2.

Lysis of tumour cells by activated macrophages requires the binding of target cells by effector cells which is mediated by surface structures common to tumour cells. The binding structures present on normal dividing blast cells appear to be different from those present on tumour cells. This may explain why blast cells are not killed by LIRX-activated macrophages.