Adoptive T cell immunotherapy of MSV-induced tumours in nude mice. Part II. Sequential analysis of serum immune complexes and blocking activity in reconstituted mice in relation to tumour biology

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In seven separate experiments, nude (nu/nu) mice carrying established murine sarcoma virus (MSV) tumours were reconstituted with syngeneic (+/+) immune splenic T cells. These immune protected mice were randomly divided to provide smaller groups for serial exsanguination. At various time points mice were individually bled and CIC concentration and blocking activity of each individual serum was determined. Control sera were obtained from nu/nu and adult +/+ mice inoculated with tumour cells only, and from nu/nu mice protected with normal +/+ spleen cells.

In all the mice studied, CIC and blocking appeared to be mutually independent parameters throughout the MSV tumour course. On the other hand, in immune protected mice considered alone or together with the control groups, CIC and time after tumour cell inoculation, but not tumour size, were significantly correlated. A significant relationship between blocking and tumour size was also established, although this only applied to immune protected mice. However, analysis of the combined data from sequentially bled immune protected mice in relation to different phases of tumour behaviour, did not support the notion that blocking, and more particularly the persistence of CIC, contribute to tumour regrowth and dissemination.

Abbreviations

Blocking inhibition by test sera of cell mediated cytotoxicity in vitro
CIC circulating immune complexes
MSV Moloney strain of murine sarcoma virus
NK natural killing by non-immune lymphocytes
ClqSPA Clq solid phase assay
EDTA ethylene diaminetetracetic acid

Introduction

In previous studies [27] we demonstrated that adoptive transfer of immune, but not normal, T cells to nude mice rendered them capable of rejecting otherwise progressively growing MSV tumours. The protection conferred was influenced by several factors including the dose, the time interval between immunization and transfer, and the timing of the adoptive cell transfer in relation to tumour cell challenge. Even if immunotherapy was delayed until primary tumours were well established, it still resulted in a high (≥70 per cent) tumour rejection rate. The unexpected finding in mice apparently ‘cured’ of their primary tumour was secondary tumour development. This occurred after varying tumour-free intervals,
usually presenting as tumour recurrences at the original primary site either on their own or together with distant metastases.

Previous work has shown that sera from animals bearing progressively growing tumours (progressor sera) inhibit tumour specific cytotoxicity in vitro [10, 17]. Admixture of progressor sera with sera from animals who have rejected the primary lesion [10], or with antisera reacting with tumour specific antigens [17], abrogates this blocking of target cell killing. It has been suggested [10, 14] that these data reflect the presence of blocking CIC in antigen excess in the progressor sera, which are converted to non-blocking CIC in antibody excess in the serum mixtures.

We have therefore studied CIC profiles and serum blocking activity in immune protected nude mice, attempting to relate these parameters to each other and to different phases of tumour growth, particularly with respect to their causal involvement in tumour reappearance and metastatic spread.

**Materials and methods**

**Mice**

BALB/c nu/nu mice, 6–8 weeks of age, and of at least 11 backcross generations, and SPF neonatal and adult +/+ BALB/c mice were obtained from the ICRF Animal Unit, Mill Hill, London NW7.

**Tumour induction and adoptive transfer**

The experimental protocol is outlined in figure 1. Complete details of the MSV-induced tumour, recipient animals and procedures used are as described previously [27].

![Figure 1. Protocol for adoptive immunotherapy and serial assessment of CIC and serum blocking activity.](image-url)