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Effect of specific anti-human leukaemia immunotoxins on the colony formation by human haematopoietic progenitors and by human leukaemia cells

C. K. TEBBI,*† D. CHERVINSKY* & B. K. SEON‡ *Department of Pediatrics, †Adolescent Unit and ‡Department of Molecular Immunology, Roswell Park Memorial Institute, Buffalo, New York, USA

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SUMMARY

The specific cytotoxic activity of anti-human T cell leukaemia immunotoxins (IT) was investigated for their effects on *in vitro* colony formation of leukaemic cells and normal haematopoietic progenitors, i.e., CFU-GM, CFU-E and CFU-GEMM. These IT were prepared by conjugating ricin A chain with the monoclonal antibodies SN1 and SN2. These antibodies define two unique human T cell leukaemia antigens. This study reveals that while these IT are only marginally cytotoxic to normal haematopoietic progenitors, they strongly suppress colony formation of human T leukaemia cells. The latter suppression is augmented by the presence of 10 mM NH_4Cl which results in total suppression. The present results indicate the therapeutic usefulness of these IT for *in vitro* eradication of leukemia cells in the bone marrow of patients with T cell leukaemia. Potentially, such a purged bone marrow can be used in autologous transplantation in leukaemia patients.

Keywords immunotoxins ricin A chain monoclonal antibodies human leukaemia CFU assay

INTRODUCTION

Tumour cells can be specifically killed *in vitro* by complement fixing, cytolytic anti-tumour antibodies. Complete specific eradication of tumour cells *in vitro*, however, may well be better accomplished by using immunotoxins, i.e., the covalent conjugates of anti-tumour antibodies with toxins or with toxin subunits (reviewed in Olsnes & Pihl, 1982; Moolten, Schreiber & Zajdel, 1982; Neville & Youle, 1982; Raso, 1982; Thorpe & Ross, 1982; Jansen *et al.*, 1982; Vitetta *et al.*, 1983). Of the toxins, diphtheria toxin and its fragments have been studied by many investigators and such studies have provided much information important in understanding the mechanism of cell killing by toxins (reviewed in Uchida, 1982). However, the prevalence of anti-diphtheria toxin antibodies in the human population renders this toxin and its fragment undesirable for clinical use. More recently, therefore, much attention has been given to plant toxins, e.g., ricin and abrin, and their subunits. The ricin molecule consists of two subunits, an A and a B chain, which are linked by a disulfide bond (reviewed in Olsnes & Pihl, 1982). The B chain is a lectin which is specific for galactose residues present on the surface of a wide variety of cells. The binding of the ricin B chain to mammalian cells allows the entry of the ricin A chain into the cytoplasm where the A chain acts on the 60S subunit of the ribosome to cause irreversible inhibition of protein synthesis and cell death. Isolated ricin B chain binds to cell surfaces but it is non-toxic while isolated ricin A chain (RA) is not

Correspondence: Dr Ben K. Seon, Department of Molecular Immunology, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263, USA.

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